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## (54) Title: ANTI-RON ANTIBODIES

(57) Abstract: Monoclonal antibodies that bind and inhibit activation of human RON (Recepteur d' Origine Nantais) are disclosed. The antibodies can be used to treat certain forms of cancer that are associated with activation of RON.

## ANTI-RON ANTIBODIES

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application Serial No. 61/466,679, filed March 23, 2011, and U.S. Provisional Application Serial No. 61/361,808, filed July 6, 2010; the contents of each application are hereby incorporated by reference in their entirety.

## FIELD OF THE INVENTION

[0002] The field of the invention is molecular biology, immunology and oncology. More particularly, the field is therapeutic antibodies.

## BACKGROUND

[0003] Recepteur d' Origine Nantais (RON), also known as Macrophage Stimulating Protein Receptor (MSP R, or MST1-R), is a member of the MET family of receptor tyrosine kinases that binds the ligand known as Macrophage Stimulating Protein (MSP). RON is composed of a 40 kDa extracellular a chain and a 150 kDa transmembrane $\beta$ chain. The $\beta$ chain is responsible for the intrinsic kinase activity, and the extracellular portions of the two chains function together as the ligand binding domain (Wagh et al., 2008, ADV. CANCER RES. 100:1-33).
[0004] MSP binding to RON activates multiple downstream signaling pathways and mediates multiple cellular activities. RON pathway dysregulation is involved in inflammatory response, wound healing and liver regeneration. RON signaling can sustain tumor growth, survival, motility, invasion and angiogenesis in certain malignancies. The RON protein exists in several splice variants, some of which are tumorigenic in animal models of cancer. One such splice variant is delta 160 RON, which lacks exons 5 and 6 (Lu et al., 2007, CANCER LETT. 257:157-164).
[0005] When activated by ligand binding, RON activates the PI3K/AKT pathway and the MAPK pathway. RON also affects cells through interactions with other receptors, e.g., c-Met, integrins and EGFR. To date, no activating mutations in RON exons have been reported. Alternative splicing and overexpression appear to be the main mechanisms for constitutive
activation of the receptor. Several small molecule inhibitors have been reported that inhibit multiple receptor tyrosine kinases, including RON, examples of which include EXCEL-2880, (Qian et al, 2009, CANCER RES. 69:8009-8016) and BMS-77607 (Schroeder et al, 2009 J. MED CHEM. 52:1251-1254). A dual c-met/RON inhibitor has also been reported, Amgen compound I (Zhang et al, 2008, CANCER RES. 68:6680-6687). A recent publication describes a selective RON small molecule inhibitor (Raeppel et al, 2010 bIOORG MED CHEM LETT 20:2745-9). Several antibodies that inhibit human RON activity have been reported (Huet et al., US 2009/0226442; Pereira et al., US 2009/0136510; Zhu et al., WO 2006/020258; Pereira et al., WO 2005/120557; and commercial antibody MAB691, R\&D Systems, Minneapolis, MN ).
[0006] Naturally occurring antibodies are multimeric proteins that contain four polypeptide chains (FIG. 1). Two of the polypeptide chains are called heavy chains (H chains), and two of the polypeptide chains are called light chains ( $\mathbf{L}$ chains). The immunoglobulin heavy and light chains are connected by an interchain disulfide bond. The immunoglobulin heavy chains are connected by interchain disulfide bonds. A light chain consists of one variable region (VLin FIG. 1) and one constant region (CLin FIG. 1). The heavy chain consists of one variable region (VHin FIG. 1) and at least three constant regions $\left(\mathrm{CH}_{1}, \mathrm{CH}_{2}\right.$ and $\mathrm{CH}_{3}$ in FIG. 1). The variable regions determine the specificity of the antibody. Each variable region comprises three hypervariable regions also known as complementarity determining regions (CDRs) flanked by four relatively conserved framework regions (FRs). The three CDRs, referred to as CDRi, $\mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$, contribute to the antibody binding specificity. Naturally occurring antibodies have been used as starting material for engineered antibodies, such as chimeric antibodies and humanized antibodies.
[0007] Although antibodies that bind RON are known in the art, there is still a need for improved RON antibodies that can be used as therapeutic agents.

## SUMMARY

[0008] The invention is based, in part, upon the discovery of a family of antibodies that specifically bind human RON. The antibodies contain RON binding sites based on the CDRs of the antibodies. The antibodies can be used as therapeutic agents. When used as therapeutic agents, the antibodies are engineered, e.g., humanized, to reduce or eliminate an immune response when administered to a human patient.
[0009] The antibodies prevent or inhibit the activation of (i.e., neutralize) human RON. In some embodiments, the antibodies prevent RON from binding to its ligand, MSP, thereby neutralizing RON activity. In certain embodiments, the antibodies prevent RON activation without inhibiting RON binding to MSP. The antibodies can be used to inhibit the downstream signaling of the breast tumor cell line T47D. Furthermore, when administered to a mammal, the antibodies can inhibit or reduce tumor growth in the mammal.
[0010] These and other aspects and advantages of the invention will become apparent upon consideration of the following figures, detailed description, and claims. As used herein, "including" means without limitation, and examples cited are non-limiting.

## DESCRIPTION OF THE DRAWINGS

[0011] The invention can be more completely understood with reference to the following drawings.
[0012] FIG. 1 (prior art) is a schematic representation of a typical naturally-occurring antibody.
[0013] FIG. 2 is a sequence alignment showing the amino acid sequence of the complete immunoglobulin heavy chain variable region of antibodies 07F01, 12B11, 17F06, 18H09 and 29B06. The amino acid sequences for each antibody are aligned against one another, and $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$, are identified in boxes. The unboxed sequences represent framework (FR). Alignment positioning (gaps) are based on Kabat numbering, rather than an alignment algorithm such as Clustal sequences.
[0014] FIG. 3 is a sequence alignment showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each of the immunoglobulin heavy chain variable region sequences in FIG. 2.
[0015] FIG. 4 is a sequence alignment showing the amino acid sequence of the complete immunoglobulin light chain variable region of antibodies 07F01, 12B11, 17F06, 18H09 and 29B06. The amino acid sequences for each antibody are aligned against one another, and $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$, are identified in boxes. The unboxed sequences represent framework (FR) sequences. Alignment positioning (gaps) are based on Kabat numbering, rather than an alignment algorithm such as Clustal sequences.
[0016] FIG. 5 is a sequence alignment showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each of the immunoglobulin light chain variable region sequences in FIG. 4.
[0017] FIG. 6 is a graph showing dose-response curves for inhibition of the MSP-RON binding interaction by antibodies 17F06(A), 07F01 (•), 12B11 ( $)$ ), 18H09 (•), and 29B06 (x), as measured by electrochemiluminescence assay.
[0018] FIG. 7 is a graph showing dose-response curves for inhibition of MSP-dependent phosphorylation of ERK by antibodies 17F06 (A), 07F01 (•), 12B11 (*), 18H09 (•), and 29B06 (x) by ELISA assay.
[0019] FIG. 8 is a histogram summarizing results from an experiment measuring inhibition of MSP induced HPAF-II cell migration by antibodies 07F01, 18H09, 29B06, 12B11, 17F06 and an IgG negative control (murine IgG) by transwell assay.
[0020] FIG. 9 is a graph summarizing data on inhibition of growth of a wild-type (wt) RON-dependent in vivo tumor model by antibodies 07F01 (•), 12B11 ( $)$ ), 18H09 ( $\quad$ ), 29B06 ${ }^{(*)}$, and a murine IgG control ( $\mathbf{0}$ ). The antibodies and IgG control were dosed at $20 \mathrm{mg} / \mathrm{kg}$ twice per week intraperitoneally.
[0021] FIG. 10 is a graph summarizing data on inhibition of growth of a delta 160 RONdependent in vivo tumor model by antibodies 17F06 (A), 07F01 (•), 12B11 ( $\downarrow$ ), 18H09 (■), 29B06 (*), and a murine IgG control (o). The antibodies and IgG control were dosed at 20 $\mathrm{mg} / \mathrm{kg}$ twice per week intraperitoneally.
[0022] FIG. 11 is a graph summarizing data on inhibition of growth of an NCI-H358 xenograft tumor model by antibody 29B06 (*) and a murine IgG control (o). The antibody and IgG control were dosed at $40 \mathrm{mg} / \mathrm{kg}$ (abbreviated as "mpk") three per week intraperitoneally.
[0023] FIG. 12A is a schematic diagram showing the amino acid sequences of the complete immunoglobulin heavy chain variable region of 07 F 01 (SEQ ID NO: 2) and the complete heavy chain variable regions denoted as Chimeric 07F01 C102S (SEQ ID NO: 133), Sh07F01 Hv3-48 (SEQ ID NO: 135), and Sh07F01 Hv3-48 D28T T60A L63V E65G (SEQ ID NO: 137). The amino acid sequences for each heavy chain variable region are aligned against one another, and Complementary Determining Sequences (CDR) (Kabat definition), $\mathrm{CDR}_{1}$, $\mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$, are identified in boxes. The unboxed sequences represent framework (FR) sequences.
[0024] FIG. 12B is a schematic diagram showing the amino acid sequences of the complete immunoglobulin heavy chain variable region of 29B06 (SEQ ID NO: 42) and the complete heavy chain variable regions denoted as Sh29B06_Hv4-59 (SEQ ID NO: 143), Hu29B06 Hv4-

59 (SEQ ID NO: 145), and Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F (SEQ ID NO: 147). The amino acid sequences for each heavy chain variable region are aligned against one another, and $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) are identified in boxes. The unboxed sequences represent framework (FR) sequences.
[0025] FIG. 13A is a schematic diagram showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) for each of the variable region sequences shown in FIG. 12A.
[0026] FIG. 13B is a schematic diagram showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) for each of the variable region sequences shown in FIG. 12B.
[0027] FIG. 14A is a schematic diagram showing the amino acid sequences of the complete light chain variable region of 07F01 (SEQ ID NO: 4) and the complete light chain variable regions denoted as HE L 07F01 Kvl-9 (SEQ ID NO: 139) and Sh07F01 Kvl-9 F1 (SEQ ID NO: 141). The amino acid sequences for each light chain variable region are aligned against one another, and $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) are identified in boxes. The unboxed sequences represent framework (FR) sequences.
[0028] FIG. 14B is a schematic diagram showing the amino acid sequences of the complete light chain variable region of 29B06 (SEQ ID NO: 44) and the complete light chain variable region denoted as Sh29B06 Kv2-28 (SEQ ID NO: 149). The amino acid sequences for each light chain variable region are aligned against one another, and $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) are identified in boxes. The unboxed sequences represent framework (FR) sequences.
[0029] FIG. 15A is a sequence alignment showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) for each of the variable region sequences shown in FIG. 14A.
[0030] FIG. 15B is a sequence alignment showing the $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences (Kabat definition) for each of the variable region sequences shown in FIG. 14B.
[0031] FIG. 16 is a histogram summarizing results from an experiment measuring inhibition of MSP induced HPAF-II cell migration by anti-RON antibodies Sh29B06-78 and Sh07F01-62, an IgG negative control (human IgG), and a no MSP control by transwell assay.
[0032] FIG. 17 is a histogram summarizing results from an experiment measuring inhibition of MSP induced HPAF-II cell invasion by anti-RON antibodies Sh29B06-78 and Sh07F01-62 and an IgG negative control (human IgG) at 0 and 1 nM MSP.
[0033] FIG. 18 is a graph summarizing data on inhibition of growth of an NCI-H358 xenograft tumor model by anti-RON antibodies mu07F01 (o), Sh07F01-62 (A), mu29B06 ( $\bullet$ ), RON8 (•), and Sh29B06-78 (•), and a human IgG control (+).
[0034] FIG. 19 depicts Western blots summarizing results from an experiment measuring RON receptor degradation by anti-RON antibodies mu07F01, Sh07F01-62, mu29B06, RON8, and Sh29B06-78.

## DETAILED DESCRIPTION

[0035] The anti-RON antibodies disclosed herein are based on the antigen binding sites of certain monoclonal antibodies that have been selected on the basis of binding and neutralizing the activity of human RON. The antibodies contain immunoglobulin variable region CDR sequences that define a binding site for human RON.
[0036] In view of the neutralizing activity of these antibodies, they are useful for modulating the growth and/or proliferation of certain types of cancer cells. When used as a therapeutic agent, the antibodies can be engineered to minimize or eliminate an immune response when administered to a human patient. In some embodiments, the antibodies are fused or conjugated to other moieties, such as effector molecules (e.g., other proteins or small molecule therapeutics), a detectable label or a toxin moiety. Various features and aspects of the invention are discussed in more detail below.
[0037] As used herein, unless otherwise indicated, the term "antibody" means an intact antibody (e.g., an intact monoclonal antibody) or antigen-binding fragment of an antibody (e.g., an antigen-binding fragment of a monoclonal antibody), including an intact antibody or antigen-binding fragment that has been modified, engineered or chemically conjugated, or that is a human antibody. Examples of antibodies that have been modified or engineered are chimeric antibodies, humanized antibodies, and multispecific antibodies (e.g., bispecific antibodies). Examples of antigen-binding fragments include Fab, Fab', F(ab') ${ }_{2}$, Fv, single chain antibodies (e.g., scFv), minibodies and diabodies. An antibody conjugated to a toxin moiety is an example of a chemically conjugated antibody.

## I. Antibodies That Bind RON

[0038] The antibodies disclosed herein comprise: (a) an immunoglobulin heavy chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{H}} \mathrm{i}-\mathrm{CDR}_{\mathrm{H}_{2}}-\mathrm{CDR}_{\mathrm{H}} 3$ and (b) an immunoglobulin light chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{L} 1}-\mathrm{CDR}_{\mathrm{L} 2}-\mathrm{CDR}_{\mathrm{L} 3}$, wherein the heavy
chain variable region and the light chain variable region together define a single binding site for binding human RON protein.
[0039] In some embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}-\mathrm{CDR} \mathrm{H}_{2}-\mathrm{CDR}_{\mathrm{H} 3}$ and (b) an immunoglobulin light chain variable region, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding human RON. A CDR ${ }_{H}{ }^{i}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 5 (07F01), SEQ ID NO: 51 (07F01), SEQ ID NO: 124 (Sh07F01 Hv3-48 D28T T60A L63V E65G), SEQ ID NO: 15 (12B11), SEQ ID NO: 53 (12B11), SEQ ID NO: 25 (17F06), SEQ ID NO: 55 (17F06), SEQ ID NO: 35 ( $\mathbf{1 8 H 0 9}$ ), SEQ ID NO: 57 ( $\mathbf{1 8 H 0 9 ) , ~ S E Q ~ I D ~ N O : ~} 45$ (29B06), SEQ ID NO: 59 (29B06), and SEQ ID NO: 126 (Sh29B06 Hv4-59, Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F); a CDR $_{\mathrm{H}_{2}}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6 (07F01), SEQ ID NO: 16 (12B11), SEQ ID NO: 26 (17F06), SEQ ID NO: 36 (18H09), SEQ ID NO: 46 (29B06), and SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G); and a $\mathrm{CDR}_{\mathrm{H} 3}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO:7 (07F01), SEQ ID NO: 17 (12B11), SEQ ID NO: 27 (17F06), SEQ ID NO: 37 (18H09), SEQ ID NO: 47 (29B06), and SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G). Throughout the specification a particular SEQ ID NO. is followed in parentheses by the antibody that was the origin of that sequence. For example, "SEQ ID NO: 5 (07F01)" means that SEQ ID NO: 5 comes from antibody 07F01.
[0040] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a $\mathrm{CDR}_{\mathrm{H}} \mathrm{i}$ comprising the amino acid sequence of SEQ ID NO: 5 (07F01), SEQ ID NO: 51 (07F01), or SEQ ID NO: 124 (Sh07F01 Hv3-48 D28T T60A L63V E65G); a $\mathrm{CDR}_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 6 ( $\mathbf{0 7 F 0 1 )}$ ) or SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and a $\mathrm{CDR}_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 7 (07F01) or SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G).
[0041] In some embodiments, the heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: $5(\mathbf{0 7 F 0 1})$, a CDR ${ }_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and a CDR ${ }_{\text {H3 }}$
comprising the amino acid sequence of SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G).
[0042] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 15 (12B11) or SEQ ID NO: 53 (12B11), a CDR ${ }_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 16 (12B11), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 17 (12B11).
[0043] In some embodiments, the heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 25 (17F06) or SEQ ID NO: 55 (17F06), a $\mathrm{CDR}_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 26 (17F06), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 27 (17F06).
[0044] In some embodiments, the heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 35 ( $\mathbf{1 8 H 0 9 )}$ or SEQ ID NO: 57 (18H09), a $\mathrm{CDR}_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 36 ( $\mathbf{1 8 H 0 9 )}$, and a CDR ${ }_{\text {H3 }}$ comprising the amino acid sequence of SEQ ID NO: 37 (18H09).
[0045] In some embodiments, the heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 45 (29B06), SEQ ID NO: 59 (29B06), or SEQ ID NO: 126 (Sh29B06 Hv4-59, Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), a $\mathrm{CDR}_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 46 (29B06), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 47 (29B06).
[0046] In some embodiments, the heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 45 (29B06) or SEQ ID NO: 126
(Sh29B06 Hv4-59, Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), a CDR ${ }_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 46 (29B06), and a $\mathrm{CDR}_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 47 (29B06).
[0047] Preferably, the $\mathrm{CDR}_{\mathrm{H}} \mathrm{i}, \mathrm{CDR}_{\mathrm{H} 2}$, and $\mathrm{CDR}_{\mathrm{H} 3}$ sequences are interposed between human or humanized immunoglobulin FRs. The antibody can be an intact antibody or an antigen-binding antibody fragment.
[0048] In some embodiments, the antibody comprises (a) an immunoglobulin light chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{L} 1}-\mathrm{CDR}_{\mathrm{L} 2}-\mathrm{CDR}_{\mathrm{L} 3}$, and (b) an immunoglobulin heavy chain variable region, wherein the IgG light chain variable region and the $\operatorname{IgG}$ heavy
chain variable region together define a single binding site for binding human RON. A CDR ${ }_{L 1}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 8 (07F01), SEQ ID NO: 18 (12B11), SEQ ID NO: 28 (17F06), SEQ ID NO: 38 ( $\mathbf{1 8 H 0 9 ) , ~ S E Q ~}$ ID NO: 48 (29B06), and SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl); a $\mathrm{CDR}_{\mathrm{L} 2}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9 (07F01), SEQ ID NO: 19 (12B11), SEQ ID NO: 29 (17F06), SEQ ID NO: 39 (18H09), SEQ ID NO: 49 (29B06), and SEQ ID NO: 131 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 FI); and a $\mathrm{CDR}_{\mathrm{L}_{3}}$ comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 10 (07F01), SEQ ID NO: 20 (12B11), SEQ ID NO:30 (17F06), SEQ ID NO: 40 (18H09), and SEQ ID NO: 50 (29B06).
[0049] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a CDR ${ }_{\mathrm{L}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 8 ( $\mathbf{0 7 F 0 1 )}$ ) or SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl), a CDR ${ }_{\text {L } 2}$ comprising the amino acid sequence of SEQ ID NO: 9 (07F01) or SEQ ID NO: 131 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl), and a CDR ${ }_{\text {L3 }}$ comprising the amino acid sequence of SEQ ID NO: 10 (07F01).
[0050] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl); a $\mathrm{CDR}_{\mathrm{L} 2}$ comprising the amino acid sequence of SEQ ID NO: 131 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl); and a CDR ${ }_{\text {L3 }}$ comprising the amino acid sequence of SEQ ID NO: 10 (07F01).
[0051] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 18 (12B11); a CDR ${ }_{\text {L2 }}$ comprising the amino acid sequence of SEQ ID NO: 19 (12B11); and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 20 (12B11).
[0052] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 28 (17F06); a CDR ${ }_{\text {L2 }}$ comprising the amino acid sequence of SEQ ID NO: 29 (17F06); and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 30 (17F06).
[0053] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 38
(18H09); $\mathrm{a} \mathrm{CDR}_{\mathrm{L} 2}$ comprising the amino acid sequence of SEQ ID NO: 39 (18H09); and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 40 (18H09).
[0054] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L}}$ I comprising the amino acid sequence of SEQ ID NO: 48 (29B06); a CDR ${ }_{\text {L2 }}$ comprising the amino acid sequence of SEQ ID NO: 49 (29B06); and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 50 (29B06).
[0055] Preferably, the $\mathrm{CDR}_{\mathrm{L}} \mathrm{I}, \mathrm{CDR}_{\mathrm{L} 2}$, and $\mathrm{CDR}_{\mathrm{L} 3}$ sequences are interposed between human or humanized immunoglobulin FRs. The antibody can be an intact antibody or an antigen-binding antibody fragment.
[0056] In some embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{H}^{\mathrm{i}}-\mathrm{CDR}}^{\mathrm{H} 2}-\mathrm{CDR}_{\mathrm{H} 3}$ and (b) an immunoglobulin light chain variable region comprising the structure $\mathrm{CDR}_{\mathrm{L}} \mathrm{I}-\mathrm{CDR}_{\mathrm{L} 2}-\mathrm{CDR}_{\mathrm{L} 3}$, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding human RON. The $\mathbf{C D R}_{\mathbf{H}} \mathbf{i}$ is an amino acid sequence selected from the group consisting of SEQ ID NO: 5 (07F01), SEQ ID NO: 51 (07F01), SEQ ID NO: 124 (Sh07F01 Hv3-48 D28T T60A L63V E65G), SEQ ID NO: 15 (12B11), SEQ ID NO: 53 (12B11), SEQ ID NO: 25 (17F06), SEQ ID NO: 55 (17F06), SEQ ID NO: 35 (18H09), SEQ ID NO: 57 (18H09), SEQ ID NO: 45 (29B06), SEQ ID NO: 59 (29B06), and SEQ ID NO: 126 (Sh29B06 Hv4-59, Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F); the $\mathrm{CDR}_{\mathrm{H} 2}$ is an amino acid sequence selected from the group consisting SEQ ID NO: 6 ( $\mathbf{0 7 F 0 1}$ ), SEQ ID NO: 16 (12B11), SEQ ID NO: 26 (17F06), SEQ ID NO: 36 (18H09), SEQ ID NO: 46 (29B06), and SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G); and the $\mathrm{CDR}_{\mathrm{H} 3}$ is an amino acid sequence selected from the group consisting of SEQ ID NO:7 (07F01), SEQ ID NO: 17 (12B11), SEQ ID NO: 27 (17F06), SEQ ID NO: 37 (18H09), SEQ ID NO: 47 (29B06), and SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G). The CDR $_{\mathrm{L}} \mathbf{i}$ is an amino acid sequence selected from the group consisting of SEQ ID NO: 8 (07F01), SEQ ID NO: 18 (12B11), SEQ ID NO: 28 (17F06), SEQ ID NO: 38 (18H09), SEQ ID NO: 48 (29B06), and SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl9 Fl ); the $\mathrm{CDR}_{\mathrm{L} 2}$ is an amino acid sequence selected from the group consisting of SEQ ID NO: 9 ( $\mathbf{0 7 F 0 1 )}$, SEQ ID NO: 19 (12B11), SEQ ID NO: 29 (17F06), SEQ ID NO: 39 (18H09), SEQ ID NO: 49 (29B06), and SEQ ID NO: 131 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl); and the $\mathrm{CDR}_{\mathrm{L} 3}$ is an amino acid sequence selected from the group consisting of SEQ ID NO: 10
(07F01), SEQ ID NO: 20 (12B11), SEQ ID NO: 30 (17F06), SEQ ID NO: 40 (18H09), and SEQ ID NO: 50 (29B06).
[0057] The antibodies disclosed herein comprise an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region. In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region selected from the group consisting of SEQ ID NO: 2 (07F01), SEQ ID NO: 12 (12B11), SEQ ID NO: 22 (17F06), SEQ ID NO: 32 (18H09), SEQ ID NO: 42 (29B06), SEQ ID NO: 133 (Chimeric 07F01 C102S), SEQ ID NO: 135 (Sh07F01 Hv3-48), SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), SEQ ID NO: 143 (Sh29B06 Hv4-59), SEQ ID NO: 145 (Hu29B06 Hv4-59), and SEQ ID NO: 147 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), and an immunoglobulin light chain variable region.
[0058] In other embodiments, the antibody comprises an immunoglobulin light chain variable region selected from the group consisting of SEQ ID NO: 4 ( $\mathbf{0 7 F 0 1 ) , ~ S E Q ~ I D ~ N O : ~} 14$ (12B11), SEQ ID NO: 24 (17F06), SEQ ID NO: 34 (18H09), SEQ ID NO: 44 (29B06), SEQ ID NO: 139 (HE L 07F01 Kvl-9), SEQ ID NO: 141 (Sh07F01 Kvl-9 Fl), and SEQ ID NO: 149 (Sh29B06 Kv2-28), and an immunoglobulin heavy chain variable region.
[0059] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region selected from the group consisting of SEQ ID NO: 2 ( $\mathbf{0 7 F 0 1 )}$, SEQ ID NO: 12 (12B11), SEQ ID NO: 22 (17F06), SEQ ID NO: 32 (18H09), SEQ ID NO: 42 (29B06), SEQ ID NO: 133 (Chimeric 07F01 C102S), SEQ ID NO: 135 (Sh07F01 Hv3-48), SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), SEQ ID NO: 143 (Sh29B06 Hv4-59), SEQ ID NO: 145 (Hu29B06 Hv4-59), and SEQ ID NO: 147 (Hu29B06 Hv4-59 D27G T30S M48I 167V Y78F), and an immunoglobulin light chain variable region selected from the group consisting of SEQ ID NO: 4 (07F01), SEQ ID NO: 14 (12B11), SEQ ID NO: 24 (17F06), SEQ ID NO: 34 (18H09), SEQ ID NO: 44 (29B06), SEQ ID NO: 139 (HE L 07F01 Kvl-9), SEQ ID NO: 141 (Sh07F01 Kvl-9 Fl), and SEQ ID NO: 149 (Sh29B06 Kv2-28).
[0060] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 ( $\mathbf{0 7 F 0 1 ) \text { , and an }}$ immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 (07F01).
[0061] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 12 (12B11), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (12B11).
[0062] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22 (17F06), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 24 (17F06).
[0063] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 32 ( $\mathbf{1 8 H 0 9}$ ), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 34 ( $\mathbf{1 8 H 0 9 ) .}$
[0064] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 42 (29B06), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 44 (29B06).
[0065] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 139 (HE L 07F01 Kvl-9).
[0066] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 147 (Hu29B06 Hv4-59

D27G T30S M48I I67V Y78F), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 149 (Sh29B06 Kv2-28).
[0067] In certain embodiments, the antibodies disclosed herein comprise an immunoglobulin heavy chain and an immunoglobulin light chain. In some embodiments, the antibody comprises an immunoglobulin heavy chain selected from the group consisting of SEQ ID NO: 93 (07F01), SEQ ID NO: 97 (12B11), SEQ ID NO: 101 (17F06), SEQ ID NO: 105 (18H09), SEQ ID NO: 109 (29B06), SEQ ID NO: 156 (Chimeric 07F01 C102S IgGl), SEQ ID NO: 160 (Chimeric 29B06 IgGI), SEQ ID NO: 164 (Sh07F01 Hv3-48 IgGI), SEQ ID NO: 166 (Sh07F01 Hv3-48 D28T T60A L63V E65G IgGI), SEQ ID NO: 172 (Sh29B06

Hv4-59 IgGl), SEQ ID NO: 174 (Hu29B06 Hv4-59 IgGI), and SEQ ID NO: 176 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgGl), and an immunoglobulin light chain.
[0068] In other embodiments, the antibody comprises an immunoglobulin light chain selected from the group consisting of SEQ ID NO: 95 (07F01), SEQ ID NO: 99 (12B11), SEQ ID NO: 103 (17F06), SEQ ID NO: 107 (18H09), SEQ ID NO: 111 (29B06), SEQ ID NO: 158 (Chimeric 07F01 Kappa), SEQ ID NO: 162 (Chimeric 29B06 Kappa), SEQ ID NO: 168 (HE L 07F01 Kvl-9 Kappa), SEQ ID NO: 170 (Sh07F01 Kvl-9 Fl Kappa), and SEQ ID NO: 178 (Sh29B06 Kv2-28 Kappa), and an immunoglobulin heavy chain.
[0069] In some embodiments, the antibody comprises (i) an immunoglobulin heavy chain selected from the group consisting of SEQ ID NO: 93 (07F01), SEQ ID NO: 97 (12B11), SEQ ID NO: 101 (17F06), SEQ ID NO: 105 (18H09), SEQ ID NO: 109 (29B06), SEQ ID NO: 156 (Chimeric 07F01 C102S IgGl), SEQ ID NO: 160 (Chimeric 29B06 IgGl), SEQ ID NO: 164 (Sh07F01 Hv3-48 IgGl), SEQ ID NO: 166 (Sh07F01 Hv3-48 D28T T60A L63V E65G IgGI), SEQ ID NO: 172 (Sh29B06 Hv4-59 IgGI), SEQ ID NO: 174 (Hu29B06 Hv4-59 IgGl), and SEQ ID NO: 176 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgGl), and (ii) an immunoglobulin light chain selected from the group consisting of SEQ ID NO: 95 (07F01), SEQ ID NO: 99 (12B11), SEQ ID NO: 103 (17F06), SEQ ID NO: 107 (18H09), SEQ ID NO: 111 (29B06), SEQ ID NO: 158 (Chimeric 07F01 Kappa), SEQ ID NO: 162 (Chimeric 29B06 Kappa), SEQ ID NO: 168 (HE L 07F01 Kvl-9 Kappa), SEQ ID NO: 170 (Sh07F01 Kvl-9 Fl Kappa), and SEQ ID NO: 178 (Sh29B06 Kv2-28 Kappa).
[0070] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 93 (07F01), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 95 (07F01).
[0071] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 97 (12B11), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 99 (12B11).
[0072] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 101 (17F06), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 103 (17F06).
[0073] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 105 (18H09), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 107 (18H09).
[0074] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 109 (29B06), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 111 (29B06).
[0075] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 166 (Sh07F01 Hv3-48 D28T T60A L63V E65G IgGI), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 168 (HE L 07F01 Kvl-9 Kappa).
[0076] In some embodiments, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 176 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgGI), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 178 (Sh29B06 Kv2-28 Kappa).
[0077] In certain embodiments, an isolated antibody that binds human RON comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence that is at least $70 \%, 75 \%, 80 \%, 85 \%, 90 \%, 95 \%, 98 \%$, or $99 \%$ identical to the entire variable region or the framework region sequence of SEQ ID NO: 2 (07F01), SEQ ID NO: 12 (12B11), SEQ ID NO: 22 (17F06), SEQ ID NO: 32 (18H09), SEQ ID NO: 42 (29B06), SEQ ID NO: 133 (Chimeric 07F01 C102S), SEQ ID NO: 135 (Sh07F01 Hv3-48), SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), SEQ ID NO: 143 (Sh29B06 Hv4-59), SEQ ID NO: 145 (Hu29B06 Hv4-59), or SEQ ID NO: 147 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F).
[0078] In certain embodiments, an isolated antibody that binds human RON comprises an immunoglobulin light chain variable region comprising an amino acid sequence that is at least $70 \%, 75 \%, 80 \%, 85 \%, 90 \%, 95 \%, 98 \%$, or $99 \%$ identical to the entire variable region or the framework region sequence of SEQ ID NO: 4 ( $\mathbf{0 7 F 0 1}$ ), SEQ ID NO: 14 ( $\mathbf{1 2 B 1 1 ) , ~ S E Q ~ I D ~ N O : ~}$ 24 (17F06), SEQ ID NO: 34 ( $\mathbf{1 8 H 0 9 ) , ~ S E Q ~ I D ~ N O : ~} 44$ (29B06), SEQ ID NO: 139 (HE L 07F01 Kvl-9), SEQ ID NO: 141 (Sh07F01 Kvl-9 Fl), or SEQ ID NO: 149 (Sh29B06 Kv228).
[0079] Homology or identity may be determined in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2,

ALIGN or Megalign (DNASTAR) software. BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin et al, (1990) PROC. NATL. ACAD. SCI. USA 87, 2264-2268; Altschul, (1993) J. MOL. EVOL. 36, 290-300; Altschul et al, (1997) NUCLEIC ACIDS RES. 25, 3389-3402, incorporated by reference) are tailored for sequence similarity searching. The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases see Altschul et al, (1994) NATURE GENETICS 6, 119-129 which is fully incorporated by reference. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff et al, (1992) PROC. NATL. ACAD. SCI. USA 89, 10915-10919, fully incorporated by reference). Four blastn parameters may be adjusted as follows: $\mathrm{Q}=10$ (gap creation penalty); $\mathrm{R}=10$ (gap extension penalty); wink=1 (generates word hits at every wink.sup.th position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings may be $\mathrm{Q}=9 ; \mathrm{R}=2$; wink $=1$; and gapw $=32$. Searches may also be conducted using the NCBI (National Center for Biotechnology Information) BLAST Advanced Option parameter (e.g.: -G, Cost to open gap [Integer]: default $=5$ for nucleotides/ 11 for proteins; -E, Cost to extend gap [Integer]: default = 2 for nucleotides/ 1 for proteins; -q, Penalty for nucleotide mismatch [Integer]: default $=-3$; -r , reward for nucleotide match [Integer]: default $=$ 1 ; -e, expect value [Real]: default $=10 ;-\mathrm{W}$, wordsize [Integer]: default $=11$ for nucleotides/ 28 for megablast/ 3 for proteins; -y, Dropoff (X) for blast extensions in bits: default $=20$ for blastn/ 7 for others; -X, X dropoff value for gapped alignment (in bits): default $=15$ for all programs, not applicable to blastn; and $-Z$, final X dropoff value for gapped alignment (in bits): 50 for blastn, 25 for others). ClustalW for pairwise protein alignments may also be used (default parameters may include, e.g., Blosum62 matrix and Gap Opening Penalty $=10$ and Gap Extension Penalty $=0.1$ ). A Bestfit comparison between sequences, available in the GCG
package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP $=8$ and $\mathrm{LEN}=2$.
[0080] In each of the foregoing embodiments, it is contemplated herein that immunoglobulin heavy chain variable region sequences and/or light chain variable region sequences that together bind human RON may contain amino acid alterations (e.g., at least 1,2 , $3,4,5$, or 10 amino acid substitutions, deletions, or additions) in the framework regions of the heavy and/or light chain variable regions.
[0081] In certain embodiments, the antibody binds human RON with a $\mathbf{K}_{D}$ of $1 \mathrm{nM}, 900$ $\mathrm{pM}, 750 \mathrm{pM}, 650 \mathrm{pM}, 600 \mathrm{pM}, 500 \mathrm{pM}, 400 \mathrm{pM}, 300 \mathrm{pM}, 250 \mathrm{pM}, 200 \mathrm{pM}, 150 \mathrm{pM}, 100 \mathrm{pM}$, 50 pM or lower. Unless otherwise specified, $\mathrm{K}_{\mathrm{D}}$ values are determined by surface plasmon resonance methods under the conditions described in Examples 5 and 14.
[0082] Antibody Sh29B06-78 binds human RON with a $\mathrm{K}_{\mathrm{D}}$ of $500 \mathrm{pM}, 250 \mathrm{pM}, 200 \mathrm{pM}$, $150 \mathrm{pM}, 100 \mathrm{pM}$ or lower as measured by surface plasmon resonance methods under the conditions described in Examples 5 and 14. In an exemplary embodiment, antibody Sh29B0678 binds human RON with a $\mathrm{K}_{\mathrm{D}}$ of 150 pM or lower as measured by surface plasmon resonance methods at $37^{\circ} \mathrm{C}$ under the conditions described in Examples 5 and 14.
[0083] Antibody SH07F01-62 binds human RON with a $\mathrm{K}_{\mathrm{D}}$ of $500 \mathrm{pM}, 400 \mathrm{pM}, 350 \mathrm{pM}$, $300 \mathrm{pM}, 250 \mathrm{pM}, 200 \mathrm{pM}, 150 \mathrm{pM}, 100 \mathrm{pM}$ or lower as measured by surface plasmon resonance methods under the conditions described in Examples 5 and 14. In an exemplary embodiment, antibody SH07F01-62 binds human RON with a $\mathrm{K}_{\mathrm{D}}$ of 250 pM to 350 pM or lower as measured by surface plasmon resonance methods at $37^{\circ} \mathrm{C}$ under the conditions described in Examples 5 and 14.
[0084] In certain embodiments, the antibodies inhibit human MSP binding to human RON. For example, the antibodies can have an $\mathrm{IC}_{50}$ (concentration at $50 \%$ of maximum inhibition) of about $5 \mathrm{nM}, 2 \mathrm{nM}, 1 \mathrm{nM}$ or lower, when assayed using the protocol described in Examples 8 and 15 .
[0085] Although the embodiments illustrated in the Examples comprise pairs of variable regions, pairs of full length antibody chains, or pairs of CDR1, CDR2 and CDR3 regions, one from a heavy chain and one from a light chain, a skilled artisan will recognize that alternative embodiments may comprise single heavy chain variable regions or single light chain variable regions, single full length antibody chains, or CDR1, CDR2 and CDR3 regions from one
antibody chain, either heavy or light. The single variable region, full length antibody chain or CDR1, CDR2 and CDR3 region of one chain can be used to screen for corresponding domains in another chain, the two chains capable of forming an antibody that binds antigen. The screening may be accomplished by phage display screening methods using, e.g., a hierarchical dual combinatorial approach disclosed in PCT Publ. No. WO92/01047. In this approach, an individual colony containing either a heavy or light chain clone is used to infect a complete library of clones encoding the other chain (light or heavy), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described.

## II. Production of Antibodies

[0086] Methods for producing antibodies, such as those disclosed herein, are known in the art. For example, DNA molecules encoding light chain variable regions and/or heavy chain variable regions can be chemically synthesized using the sequence information provided herein. Synthetic DNA molecules can be ligated to other appropriate nucleotide sequences, including, $e . g$., constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs encoding the desired antibodies. Production of defined gene constructs is within routine skill in the art. Alternatively, the sequences provided herein can be cloned out of hybridomas by conventional hybridization techniques or polymerase chain reaction (PCR) techniques, using synthetic nucleic acid probes whose sequences are based on sequence information provided herein, or prior art sequence information regarding genes encoding the heavy and light chains of murine antibodies in hybridoma cells.
[0087] Nucleic acids encoding desired antibodies can be incorporated (ligated) into expression vectors, which can be introduced into host cells through conventional transfection or transformation techniques. Exemplary host cells are E.coli cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and myeloma cells that do not otherwise produce IgG protein. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the immunoglobulin light and/or heavy chain variable regions.
[0088] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in E. coli, it is first cloned into an expression vector by positioning the engineered gene downstream from a
suitable bacterial promoter, e.g., Trp or Tac, and a prokaryotic signal sequence. The expressed secreted protein accumulates in refractile or inclusion bodies, and can be harvested after disruption of the cells by French press or sonication. The refractile bodies then are solubilized, and the proteins refolded and cleaved by methods known in the art.
[0089] If the engineered gene is to be expressed in eukayotic host cells, e.g., CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, IgG enhancers, and various introns. This expression vector optionally contains sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy or light chain to be expressed. The gene construct can be introduced into eukaryotic host cells using conventional techniques. The host cells express $\mathbf{V}_{\mathbf{L}}$ or $\mathbf{V} \mathbf{H}$ fragments, VL-VH heterodimers, $\mathbf{V H}-\mathrm{V}_{\mathrm{L}}$ or VL-VH single chain polypeptides, complete heavy or light immunoglobulin chains, or portions thereof, each of which may be attached to a moiety having another function (e.g., cytotoxicity). In some embodiments, a host cell is transfected with a single vector expressing a polypeptide expressing an entire, or part of, a heavy chain (e.g., a heavy chain variable region) or a light chain (e.g., a light chain variable region). In other embodiments, a host cell is transfected with a single vector encoding (a) a polypeptide comprising a heavy chain variable region and a polypeptide comprising a light chain variable region, or (b) an entire immunoglobulin heavy chain and an entire immunoglobulin light chain. In still other embodiments, a host cell is co-transfected with more than one expression vector (e.g., one expression vector expressing a polypeptide comprising an entire, or part of, a heavy chain or heavy chain variable region, and another expression vector expressing a polypeptide comprising an entire, or part of, a light chain or light chain variable region).
[0090] A polypeptide comprising an immunoglobulin heavy chain variable region or light chain variable region can be produced by growing a host cell transfected with an expression vector encoding such variable region, under conditions that permit expression of the polypeptide. Following expression, the polypeptide can be harvested and purified using techniques well known in the art, e.g., affinity tags such as glutathione-S-transferase (GST) and histidine tags.
[0091] A monoclonal antibody that binds human RON, or an antigen-binding fragment of the antibody, can be produced by growing a host cell transfected with: (a) an expression vector that encodes a complete or partial immunoglobulin heavy chain, and a separate expression vector that encodes a complete or partial immunoglobulin light chain; or (b) a single expression
vector that encodes both chains (e.g., complete or partial heavy and light chains), under conditions that permit expression of both chains. The intact antibody (or antigen-binding fragment) can be harvested and purified using techniques well known in the art, e.g., Protein A, Protein G, affinity tags such as glutathione-S-transferase (GST) and histidine tags. It is within ordinary skill in the art to express the heavy chain and the light chain from a single expression vector or from two separate expression vectors.

## III. Antibody Modifications

[0092] Methods for reducing or eliminating the antigenicity of antibodies and antibody fragments are known in the art. When the antibodies are to be administered to a human, the antibodies preferably are "humanized" to reduce or eliminate antigenicity in humans. Preferably, the humanized antibodies have the same or substantially the same affinity for the antigen as the non-humanized mouse antibody from which it was derived.
[0093] In one humanization approach, chimeric proteins are created in which mouse immunoglobulin constant regions are replaced with human immunoglobulin constant regions. See, e.g., Morrison et al., 1984, PROC. NAT. ACAD. SCI. 81:685 1-6855, Neuberger et al, 1984, NATURE 3 12:604-608; U.S. Patent Nos. 6,893,625 (Robinson); 5,500,362 (Robinson); and 4,8 16,567 (Cabilly).
[0094] In an approach known as CDR grafting, the CDRs of the light and heavy chain variable regions are grafted into frameworks from another species. For example, murine CDRs can be grafted into human FRs. In some embodiments, the CDRs of the light and heavy chain variable regions of an anti-RON antibody are grafted into human FRs or consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described in U.S. Patent Nos. 7,022,500 (Queen); 6,982,321 (Winter); 6, 180,370 (Queen); 6,054,297 (Carter); 5,693,762 (Queen); 5,859,205 (Adair); 5,693,76 1 (Queen); 5,565,332 (Hoogenboom); 5,585,089 (Queen); 5,530, 101 (Queen); Jones et al. (1986) NATURE 321:522525; Riechmann et al. (1988) NATURE 332: 323-327; Verhoeyen et al. (1988) SCIENCE 239: 1534-1536; and Winter (1998) FEBS LETT 430: 92-94.
[0095] In an approach called "SUPERHUMANIZATION ${ }^{\text {TM }}$," human CDR sequences are chosen from human germline genes, based on the structural similarity of the human CDRs to
those of the mouse antibody to be humanized. See, e.g., U.S. Patent No. 6,881,557 (Foote); and Tan et al, 2002, J.IMMUNOL. 169:1119-1125.
[0096] Other methods to reduce immunogenicity include "reshaping," "hyperchimerization," and "veneering/resurfacing." See, e.g., Vaswami et al., 1998, ANNALS OF ALLERGY, ASTHMA, \& IMMUNOL. 81:105; Roguska et al, 1996, PROT. ENGINEER 9:895-904; and U.S. Patent No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, e.g., in U.S. Patent No. 5,639,641 (Pedersen).
[0097] Another approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB ${ }^{\text {TM }}$ technology (Vaccinex, Inc., Rochester, NY), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of $\operatorname{IgG}$ heavy and light chains are said to be produced. See, e.g., U.S. Patent Nos. 6,706,477 (Zauderer); 6,800,442 (Zauderer); and 6,872,518 (Zauderer).
[0098] Another approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, CA). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope focused" library for antibody selection.
[0099] Another approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING ${ }^{\mathrm{TM}}$ technology, which is practiced commercially by XOMA (US) LLC. See, e.g., PCT Publication No. WO 93/11794 and U.S. Patent Nos. 5,766,886 (Studnicka); 5,770,196 (Studnicka); 5,821,123 (Studnicka); and 5,869,619 (Studnicka).
[0100] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.
[0101] In addition, it is possible to create fully human antibodies in mice. Fully human mAbs lacking any non-human sequences can be prepared from human immunoglobulin transgenic mice by techniques referenced in, e.g., Lonberg et al., NATURE 368:856-859, 1994; Fishwild et al, NATURE biotechnology 14:845-851, 1996; and Mendez et al, NATURE GENETICS 15:146-156, 1997. Human mAbs can also be prepared and optimized from phage
display libraries by techniques referenced in, e.g., Knappik et al., J. MOL. BIOL. 296:57-86, 2000; and Krebs et al, J. Immunol. Meth. 254:67-84 2001).
[0102] If the antibody is for use as a therapeutic, it can be conjugated to an effector agent such as a small molecule toxin or a radionuclide using standard in vitro conjugation chemistries. If the effector agent is a polypeptide, the antibody can be chemically conjugated to the effector or joined to the effector as a fusion protein. Construction of fusion proteins is within ordinary skill in the art.

## IV. Use of Antibodies

[0103] The antibodies disclosed herein can be used to treat various forms of cancer, e.g., non-small cell lung cancer, breast, ovarian, prostate, cervical, colorectal, lung, pancreatic, gastric, and head and neck cancers. The cancer cells are exposed to a therapeutically effective amount of the antibody so as to inhibit or reduce proliferation of the cancer cell. In some embodiments, the antibodies inhibit cancer cell proliferation by at least $40 \%, 50 \%, 60 \%, 70 \%$, $80 \%, 90 \%, 95 \%, 98 \%, 99 \%$, or $100 \%$.
[0104] In some embodiments, the antibody (e.g., 07F01, 29B06, 17F06, 18H09, 12B11, sh29B06, sh07F01) inhibits or reduces proliferation of a tumor cell by inhibiting binding of human RON to its ligand, MSP. In some embodiments, the antibody (e.g., 07F01, 29B06, 17F06, 18H09, 12B 11, sh29B06, sh07F01) inhibits or reduces proliferation of a tumor cell without inhibiting RON binding to MSP. The antibody (e.g., 07F01, 29B06, 17F06, 18H09, 12B 11, sh29B06, sh07F01) can also be used in therapy. The antibody (e.g., 07F01, 29B06, 17F06, 18H09, 12B11, sh29B06, sh07F01) can be used to inhibit tumor growth in a mammal (e.g., a human patient). In some embodiments, use of the antibody to inhibit tumor growth in a mammal comprises administering to the mammal a therapeutically effective amount of the antibody.
[0105] In certain embodiments, antibody Sh29B06-78 is used in therapy. For example, antibody Sh29B06-78 can be used for inhibiting or reducing proliferation of a tumor cell. Antibody Sh29B06-78 can also be used for inhibiting or reducing tumor growth in a mammal.
[0106] In other embodiments, antibody Sh07F01-62 is used in therapy. For example, antibody Sh07F01-62 can be used for inhibiting or reducing proliferation of a tumor cell. Antibody Sh07F01-62 can also be used for inhibiting or reducing tumor growth in a mammal.
[0107] Cancers associated with overexpression or inappropriate activation of RON include non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, and some forms of brain cancer, melanomas, and gastrointestinal cancers.
[0108] As used herein, "treat," "treating" and "treatment" mean the treatment of a disease in a mammal, e.g., in a human. This includes: (a) inhibiting the disease, i.e., arresting its development; and (b) relieving the disease, i.e., causing regression of the disease state.
[0109] Generally, a therapeutically effective amount of active component is in the range of $0.1 \mathrm{mg} / \mathrm{kg}$ to $100 \mathrm{mg} / \mathrm{kg}$, e.g., $1 \mathrm{mg} / \mathrm{kg}$ to $100 \mathrm{mg} / \mathrm{kg}, 1 \mathrm{mg} / \mathrm{kg}$ to $10 \mathrm{mg} / \mathrm{kg}$. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health of the patient, the in vivo potency of the antibody, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the dosage may be progressively increased during the course of treatment. Human dosage can be optimized, e.g., in a conventional Phase I dose escalation study designed to run from $0.5 \mathrm{mg} / \mathrm{kg}$ to $20 \mathrm{mg} / \mathrm{kg}$. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once every two weeks. A preferred route of administration is parenteral, e.g., intravenous infusion. Formulation of monoclonal antibodybased drugs is within ordinary skill in the art. In some embodiments, the antibody is lyophilized and reconstituted in buffered saline at the time of administration.
[0110] For therapeutic use, an antibody preferably is combined with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.
[0111] Pharmaceutical compositions containing antibodies, such as those disclosed herein, can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Examples of routes of administration are intravenous (IV), intradermal, inhalation, transdermal, topical, transmucosal, and rectal administration. A preferred route of administration for monoclonal antibodies is IV infusion. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.
[0112] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof.
[0113] Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

## EXAMPLES

[0114] The following Examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

## Example 1: Production of Human RON Extracellular Domain (ECD)

[0115] This Example describes the production of the antigen, hRON ECD protein. The use of the full length ECD as the immunogen, allowed for the selection of two classes of hybridomas: (a) those producing antibodies that interact with the ligand binding domain,
thereby inhibiting contact of the ligand to the receptor; and (b) those producing antibodies that bind outside the ligand binding domain, thereby inhibiting the receptor functions through mechanisms other than inhibition of ligand binding.
[0116] DNA encoding the extracellular domain of human RON (hRON ECD) (ref seq.

NM_002447) was amplified by PCR and subcloned using the Xmal/EcoRI restriction sites inframe into the pEE14.4 vector (Lonza, Basel, Switzerland) containing THXmFC
(Thrombin/His tag/ Factor Xa- AJ mouse IgG-Fc), to produce a fusion protein. The resulting clone was linearized using the Pvul enzyme (NEBiolabs, Cat. No. R0150), then electroporated into CHO KISVcells (Lonza). The electroporated cells were diluted in 200 ml CD CHO media (Gibco Cat. No. 10743-01 1). The next day, CD CHO media containing methionine sulfoximine (MSX) for a final concentration of $50 \mu \mathrm{M}$ was added to the cells. After four weeks, positive clones were selected by sandwich ELISA in which the immobilized antibody was commercial monoclonal anti-hRON antibody MAB691 (R\&D Systems), and the detection antibody was commercial polyclonal anti-hRON antibody AF691 (R\&D Systems). Positive clones were retransfected using Lipofectamine ${ }^{\mathrm{TM}} 2000$ in a standard protocol. Cells were aliquoted into four separate shaker flasks and selected using $50 \mathrm{uM}, 100 \mathrm{uM}, 200 \mathrm{uM}$, and 400 uM MSX. After two weeks of selection, the individual flasks were checked for hRON-ECD protein expression by ELISA. The highest selection pressure, $400 \mu \mathrm{M}$ MSX, yielded good protein expression and was chosen for scale-up and purification. Cells were grown for 2 weeks at $37^{\circ} \mathrm{C}$ in BelloCell Bottles (Bellco Glass, Vineland, NJ) at a concentration of 2-2.5 $\mathrm{xlO}^{6}$ cells $/ \mathrm{ml}$ in CD CHO media, with a final concentration of $80 \mu \mathrm{M}$ MSX for protein production. The resulting cells were spun down in 500 ml conical tubes for 15 minutes. The supernatant was filtered using vacuum filtration using a 0.45 micron filter and then a 0.22 micron filter. The protein was then batch bound to ProSepA beads (Millipore) at $4^{\circ} \mathrm{C}$ overnight with rotation after adjusting the pH to 7.5. The beads were washed with IX PBS and loaded onto disposable protein A affinity columns (Bio-Rad Econo-Pac columns; Bio-Rad cat. No. 732-1010). The beads were washed with 10 column volumes (CV) of glycine binding buffer ( 3 M glycine $\mathrm{ph} 9.0,1 \mathrm{M} \mathrm{NaCl}$ ). The protein was then eluted off the column using $5-10 \mathrm{CV}$ of 200 mM glycine pH 2.5 acid elution buffer. The samples were then neutralized using 1.3 mL of 1.0 M Tris pH 8.0 neutralization buffer concentrated using Vivaspin concentrators (Sartorius Stedim Biotech).

## Example 2: Anti-RON Antibodies

[0117] This Example describes the production of anti-hRON monoclonal antibodies. Immunizations, fusions, and primary screens were conducted at Maine Biotechnology Services Inc. (Portland, ME), following the Repetitive Immunization Multiple Sites (RIMMS) protocol. Five AJ mice and five Balb/c mice were immunized with recombinant human RON extracellular domain (hRON-ECD). Two Balb/c mice with sera displaying the highest antiRON activity by Enzyme Linked Immunosorbent Assay (ELISA) were chosen for subsequent fusion. Spleens and lymph nodes from the appropriate mice were harvested. B-cells were harvested and fused with a myeloma line. Fusion products were serially diluted onto forty 96well plates to near clonality.
[0118] Approximately 4,000 supernatants from the cell fusions were screened by ELISA for binding to recombinant hRON-ECD. A total of 158 supernatants containing antibodies against RON were further characterized by in vitro biochemical and cell-based assays, as described below. A panel of hybridomas was selected, subcloned and expanded. Hybridoma cell lines were transferred to BioXCell (West Lebanon, NH) for antibody expression and purification by affinity chromatography on Protein G resin, under standard conditions.

## Example 3: Screening Assays

[0119] A biochemical assay was carried out to identify antibodies that inhibit ligand binding. A cell-based assay was carried out to identify antibodies that inhibit MSP induced phosphoERK downstream signaling of the receptor. Antibodies that inhibited RON mediated cellular signaling were selected for further characterization regardless of whether they blocked ligand binding in the neutralization assay.
[0120] The biochemical neutralization assay measures inhibition of MSP binding to hRON by antibodies in hybridoma supernatants, using electrochemiluminescence (ECL). MA2400 96-well high binding plates (Meso Scale Discovery) were coated with $25 \mu i$ of $0.42 \mu \mathrm{~g} / \mathrm{mL}$ hRON SEMA + PSI (an N-terminal portion of the ECD of hRON; R\&D Systems) in PBS for one hour at room temperature with agitation. The plates were washed four times with PBS + $0.1 \%$ Tween-20 (PBST), and blocked with $150 \mu i ̈$ ï of charcoal-stripped fetal bovine serum (FBS) (Gibco). The hybridoma supernatant were added and incubated for 45 minutes at room temperature. After incubation, $5 \mu$ ï of MSP ( $3 \mu \mathrm{~g} / \mathrm{mL}$ ) in charcoal stripped FBS was added to each well, and incubated for 45 minutes. The plate was washed four times with PBST, and 25
$\mu_{i ̈}$ of $1 \mu \mathrm{~g} / \mathrm{mL}$ biotinylated anti-MSP antibody (R\&D Systems) was added to the plates for one hour at room temperature with agitation. The plates were washed four times with PBST, and incubated with $25 \mu$ ï of $1 \mu \mathrm{~g} / \mathrm{mL}$ ST-streptavidin (Meso Scale Discovery) for one hour at room temperature with agitation. The plates were washed four times with PBST, and $150 \mu$ ï read buffer (Meso Scale Discovery) was added to each well before the plates were analyzed on a Sector Imager 2400 (Meso Scale Discovery) instrument. Antibodies 07F01, 18H09 and 29B06 each blocked MSP binding to hRON SEMA + PSI in this neutralization assay.
[0121] In the cell-based assay, antibodies in the hybridoma supernatant were tested for inhibition of MSP-induced phosphorylation of ERK, which is a RON downstream signaling molecule. T47D cells were cultured in 96-well plates in RPMI $1640+10 \%$ FBS + insulin. Medium was removed, and cells were incubated in serum-free medium for 24 hours. Hybridoma supernatants containing RON antibodies were added to the cells at a dilution of 1:4 in -serum-free medium, and incubated for one hour at $37^{\circ} \mathrm{C}$. MSP ( 5 nM ) was added to the wells and incubated for 15 minutes. Medium was removed, and cells were fixed in 4\% paraformaldehyde (PFA) in PBS. Total ERK and phospho-ERK were measured according to the vendor's instructions (R\&D Systems, DY1018). Antibodies 07F01, 12B11, 17F06, 18H09 and 29B06 each inhibited MSP induced ERK phosphorylation in T47D cells.
[0122] As discussed herein (see Examples 8 and 9), antibodies 07F01, 12B11, 17F06, 18H09 and 29B06 each inhibited MSP induced ERK phosphorylation in T47D cells, while only antibodies 07F01, 18H09 and 29B06 each blocked MSP binding to hRON SEMA +PSI in the neutralization assay. This suggests that antibodies 12B11 and 17F06 do not neutralize binding of MSP to the hRON SEMA+PSI domain, neutralize binding of MSP to RON in the context of the full RON extracellular domain, or function by a mechanism other than blocking MSP binding to RON.

## Example 4: Antibody Sequence Analysis

[0123] The light chain isotype and heavy chain isotype of each monoclonal antibody in Example 2 was determined using the IsoStrip ${ }^{\text {TM }}$ Mouse Monoclonal Antibody Isotyping Kit according the kit vendor's instructions (Roche Applied Science, Indianapolis, IN). All antibodies were found to be kappa or lambda light chain and $\operatorname{IgGl}$ or $\operatorname{IgG} 2$ a heavy chain.
[0124] The heavy and light chain variable regions of the mouse monoclonal antibodies were sequenced using 5' RACE (Rapid Amplification of cDNA Ends). Total RNA was
extracted from each monoclonal hybridoma cell line using the RNeasy ${ }^{\circledR}$ Miniprep kit according to the kit vendor's instructions (Qiagen, Valencia, CA). Full-length first strand cDNA containing 5' ends was generated using either the GeneRacer ${ }^{\text {TM }}$ Kit (Invitrogen, Carlsbad, California) or SMARTer ${ }^{\text {TM }}$ RACE cDNA Amplification Kit (Clontech, Mountain View, CA) according to the kit vendor's instructions using random primers for 5' RACE.
[0125] The variable regions of the light (kappa or lambda) and heavy (IgGlor IgG2b) chains were amplified by PCR, using KOD Hot Start Polymerase (EMD Chemicals, Gibbstown, NJ), Expand High Fidelity PCR System (Roche Applied Science), or Advantage 2 Polymerase Mix (Clontech) according to the kit vendor's instructions. For amplification of 5' cDNA ends in conjunction with the GeneRacer ${ }^{\text {TM }}$ Kit, the GeneRacer ${ }^{\text {TM }} 5$ ' Primer, 5' cgactggagcacgaggacactga 3' (SEQ ID NO: 112) (Invitrogen) was used as a 5' primer. For amplification of 5 ' cDNA ends in conjunction with the SMARTer ${ }^{\text {TM }}$ RACE cDNA Amplification Kit , the Universal Primer Mix A primer (Clontech), a mix of: 5' CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT 3' (SEQ ID NO: 113) and 5' ctaatacgactcactataggac 3' (SEQ ID NO: 114), was used as a' primer. Heavy chain variable regions were amplified using the above $5^{\prime}$ primers and a $3^{\prime}$ IgGl constant region specific primer, 5' tatgcaaggcttacaaccaca 3' (SEQ ID NO: 115), or a 3' IgG2a constant region specific primer, $5^{\prime}$ agGacaggacttgattgtggg $3^{\prime}$ (SEQ ID NO: 116). Kappa chain variable regions were amplified with the above $5^{\prime}$ primers and a $3^{\prime}$ kappa constant region specific primer, 5' ctcattcctattgangctcttgacait 3' (SEQ ID NO: 117). Lambda chain variable regions were amplified with the above 5' primers and a mix of 3' lambda constant region specific primers, 5 ' GCACGGGACAAACTCTTCTC 3' (SEQ ID NO: 118) and 5' CACAGTGTCCCCTTCATGTG 3' (SEQ ID NO: 119).
[0126] Individual PCR products were isolated by agarose gel electrophoresis and purified using the Qiaquick ${ }^{\circledR}$ Gel Purification kit according to the kit vendor's instructions (Qiagen). The PCR products were subsequently cloned into the $\mathrm{pCR}{ }^{\circledR} 4 \mathrm{Blunt}$ plasmid or $\mathrm{pCR} 2.1^{\circledR} \mathrm{TOPO}$ plasmid using the Zero Blunt ${ }^{\circledR}$ TOPO ${ }^{\circledR}$ PCR Cloning Kit or the TOPO ${ }^{\circledR}$ TA Cloning Kit, respectively, according to the kit vendor's instructions (Invitrogen) and transformed into DH5$\alpha$ bacteria (Invitrogen) through standard molecular biology techniques. Plasmid DNA isolated from transformed bacterial clones was sequenced using M13 Forward
(5' GTAAAACGACGGCCAGT 3') (SEQ ID NO: 120) and M 13 Reverse primers
(5' CAGGAAACAGCTATGACC $3^{\prime}$ ) (SEQ ID NO: 121) by Beckman Genomics (Danvers, MA),
using standard dideoxy DNA sequencing methods to identify the sequence of the variable region sequences. The sequences were analyzed using Vector NTI software (Invitrogen) and the IMGT/V-Quest web server (imgt.cines.fr) to identify and confirm variable region sequences.
[0127] The nucleic acid sequences encoding and the protein sequences defining variable regions of the murine monoclonal antibodies are shown below (amino terminal signal peptide sequences are not shown). CDR sequences (Kabat definition) are indicated by bold font and underlining in the amino acid sequences.
[0128] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 07F01
Antibody (SEQ ID NO: 1)

| 1 | gaggtgaagc ttctcgagtc tggaggtggc ctggtgcagc cgggtggatc cctgaaactc |
| ---: | :--- |
| 61 | tcctgtgcag cctcaggatt cgattttagt agacactgga tgagttgggt ccggctggct |
| 121 | ccagggaaag ggctagaatg gatcgcagaa attaatccag atagcagaac gataaactat |
| 181 | acgccatctc taaaggagaa attcatcatc tccagagaca acgccaaaaa ttcgctgttt |
| 241 | ctgcaaatga acagagtgag atctgaggac |
| 301 | agaattcatt |
| 361 | tea |

[0129] Protein Sequence Defining the Heavy Chain Variable Region of the 07F01
Antibody (SEQ ID NO: 2)

```
evkllesggg lvqpggslkl scaasgfdfs rhwmswvrla pgkglewiae inpdsrtiny
tpslke kfiii srdnaknslf lqmnrvrsed talyycarrv rihyygamdc wgqgtsvtvs
121 s
```

[0130] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 07F01
Antibody (SEQ ID NO: 3)

[0131] Protein Sequence Defining the Kappa Chain Variable Region of the 07F01
Antibody (SEQ ID NO: 4)

```
1 divltqsqki vstsvgarvs vtckasqnvg sslvwyqqkp gqspktliys asf rysgvpd
6 1 ~ r f t g s g s g t d ~ f t l t i s n v q s ~ e d l a d y f c c j g ~ y n n y p l t ~ f g a ~ g t k l e l k
```

[0132] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 12B 11
Antibody (SEQ ID NO: 11)

| 1 | gaggtgcagt | tagtggagtc | tgggggaggc |
| ---: | :--- | :--- | :--- |
| 61 | tcctgtgcag | cctctggatt | cactttcagt |
| 121 | ccggagaaga | ggctggagtg | ggtcgcagga |
| 181 | ccagacactg | tgaagggacg | attcaccatc |
| 241 | ctgcaaatga | gcggtctgag | gtctgaggac |
| 301 | tactatggtg | ttaactttga | ctactggggc |


| ttagtgaagc | ctggagggtc | cctgaaactc |
| :--- | :--- | :--- |
| acctatgcca | tgtcttggat | tcgccagact |
| atcactaatg | gtggtagttt | cacctactat |
| tccagagaca | atgccaggaa | catcctatac |
| acggccatgt | attattgtgc | aagacagggt |
| caaggcacca | ctctcacagt | ctcctca |

[0133] Protein Sequence Defining the Heavy Chain Variable Region of the 12B11
Antibody (SEQ ID NO: 12)

| 1 evqlvesggg | lvkpggslkl | scaasgftfs | tyamswirgt | pekrlewvag | itnggsf tyy |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 61 pdtvkg rfti | srdnarnily | lqmsglrsed | tamyycarcjg | yygunf dywg | qgttltvss |

[0134] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 12B 11
Antibody (SEQ ID NO: 13)

| 1 | gatgctgtga | tgacccaaac | tccactctcc | ctgcctgtca | gtcttggaga tcaagcctcc |  |
| ---: | :--- | :--- | :--- | :--- | :--- | :--- |
| 61 | atctcttgca | ggtctagtca | gagccttgaa | aacagtaacg | gaaacactta | tttgaactgg |
| 121 | tacctccaga | accaggcca | gtctccacag | ctcctgatct | acagggtttc | caaccgattt |
| 181 | tctggggtcc | cagacaggtt | cagtggtagt | ggatcaggga | cagatttcac | actgaaaatc |
| 241 | atcagagtgg | aggctgagga | tttgggactt | tatttctgcc | tccaagttac | acatgtcccg |
| 301 | cacacgttcg | gaggggggac | caactggaa | ttaaa |  |  |

[0135] Protein Sequence Defining the Kappa Chain Variable Region of the 12B11
Antibody (SEQ ID NO: 14)

| 1 davmtqtpls | lpvslgdqas | iscrssqsle | nsngntylnw | ylqkpgqspq | lliyrvsnrf |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 61 sgvpdrfsgs | gsgtdftlki | irveaedlgl | Y folqvthvp | htfgggtkle | lk |

[0136] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 17F06
Antibody (SEQ ID NO: 21)

| 1 | gaagtgaagc | tggtggagtc | ggggggaggc | ttagtgaagc | ctggagcgtc | tctgaaactc |
| ---: | :--- | :--- | :--- | :--- | :--- | :--- |
| 61 | tcctgtgcag | cctctggatt | cattttcagt | tcctatggca | tgtcttgggt | tcgccagact |
| 121 | tcagacaaga | ggctggagtg | ggtcgcttcc | attagtagtg | gtggtggtac | cacctactat |
| 181 | ctagacactg | taagggccg | attcaccatc | tccagagaga | atgccaagga | caccctgtac |
| 241 | ctgcaaatga | gtggtctgaa | gtctgaagac | acggccttgt | attactgtac | aagaggccaa |
| 301 | tggttactaa | agtttgctta | ctggggccaa | gggactctgg | tcactgtctc | tgca |

[0137] Protein Sequence Defining the Heavy Chain Variable Region of the 17F06
Antibody (SEQ ID NO: 22)

| 1 evklvesggg | lvkpgaslkl | scaasgfifs | sygmswvrqt | ewvas | issgggttyy |
| :---: | :---: | :---: | :---: | :---: | :---: |
| ldtvkg rfti | srenakdtly | lqmsglksed | talyyctrg_ | wllkfaywg | gtlvtvsa |

[0138] Nucleic Acid Sequence Encoding the Lambda Chain Variable Region of the 17F06
Antibody (SEQ ID NO: 23)
1 caacttgtgc tcactcagtc atcttcagcc tctttctccc tgggagcctc agcaaaactc
61 acgtgcacct tgagtagtca
121 ctcaacactacg tacaccattg
ctaatggtatgt
181
gggattcctg
ctatcata
[0139] Protein Sequence Defining the Lambda Chain Variable Region of the 17F06
Antibody (SEQ ID NO: 24)

```
qlvltqsssa sfslgasakl tctlssqhtt ytiewyqqlp lkppkyvmel kkdgshstgv
6 1 ~ g i p d r f s g s s ~ s g a d r y l t i s ~ n i q p e d e a i y ~ i c g v g e t i e d ~ q f v y v ~ f g g g t ~ k v t v l
```

[0140] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 18 H 09
Antibody (SEQ ID NO: 31)

[0141] Protein Sequence Defining the Heavy Chain Variable Region of the 18H09
Antibody (SEQ ID NO: 32)

| 1 | evqlqesgps |
| ---: | :--- |
| 61 pslksrisit | rdtsknqfyl |

[0142] Nucleic Acid Sequence Encoding the Lambda Chain Variable Region of the 18H09
Antibody (SEQ ID NO: 33)
1 caggctgttg tgactcagga atctgcactc accacatcac ctggtgaaac agtcacactc
61 acttgtcgct caagtgccgg ggctgttaca actagtaact ttgccaactg ggtccaagaa
121 aaaccagatc atttattcac tggtctaata ggtgatacca acatccgagc tccaggtgtt
181 cctgccagat tctcaggctc cctgattgga gacaaggctg ccctcaccat cacaggggca
241 cagactgagg atgaggcaat atatttctgt gctctttggt acagcaacca ttactgggtg
301 ttcggtggag gaaccaaact gactgtccta
[0143] Protein Sequence Defining the Lambda Chain Variable Region of the 18H09
Antibody (SEQ ID NO: 34)

[0144] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 29B06

## Antibody (SEQ ID NO: 41)


[0145] Protein Sequence Defining the Heavy Chain Variable Region of the 29B06
Antibody (SEQ ID NO: 42)

```
evqlqesgps lvkpsqtlsl tcsvtgdsit sgywnwirkf pgnkleymgy_ isysgktyyn
6 1 ~ p s l k s r i ~ s i t ~ r d t s k n h y y l ~ q l i s v t a e d t ~ a t y y c a r ~ s k y ~ d y a m d y w g q g ~ t s v t v s s ~
```

[0146] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 29B06
Antibody (SEQ ID NO: 43)

[0147] Protein Sequence Defining the Kappa Chain Variable Region of the 29B06
Antibody (SEQ ID NO: 44)

| 1 divltqspas | lavslgqrat iscraseivd | n fgisfmnwf | qqkpgqppkl | $\underline{1}$ iyaasnqgs |
| :---: | :---: | :---: | :---: | :---: |
| 61 gvparfsgsg | sgtdfslnih pveeddtamy | faqgskevpp | tfgggtklei | k |

[0148] The amino acid sequences defining the immunoglobulin heavy chain variable regions for the antibodies produced in Example 2 are aligned in FIG. 2. Amino terminal signal peptide sequences (for expression/secretion) are not shown. $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ (Kabat definition) are identified by boxes. FIG. 3 shows an alignment of the separate $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each antibody.
[0149] The amino acid sequences defining the immunoglobulin light chain variable regions of the antibodies in Example 2 are aligned in FIG. 4. Amino terminal signal peptide sequences (for expression/secretion) are not shown. $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$ and $\mathrm{CDR}_{3}$ are identified by boxes.

FIG. 5 shows an alignment of the separate $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each antibody.
[0150] Table 1 shows the SEQ ID NO. of each sequence discussed in this Example.

Table 1

| S E.Q. II) NO. | Nucleic Acid or Protein |
| :---: | :---: |
| 1 | 07FC) 1 Heavy Chain Variable Region - nucleic acid |
| 2 | 07FC) 1 Heavy Chain Variable Region - protein |
| 3 | 07FC) 1 Light (kappa) Chain Variable Region - nucleic acid |
| 4 | 07FC) 1 Light (kappa) Chain Variable Region - protein |
| 5 | 07FC) 1 Heavy Chain CDRi |
| 6 | $07 \mathrm{FC}) 1$ Heavy Chain CDR ${ }_{2}$ |
| 7 | $07 \mathrm{FC}) 1$ Heavy Chain $\mathrm{CDR}_{3}$ |
| 8 | 07FC) 1 Light (kappa) Chain CDRi |
| 9 | 07FC) 1 Light (kappa) Chain CDR ${ }_{2}$ |
| 10 | $07 \mathrm{FC}) 1$ Light (kappa) Chain $\mathrm{CDR}_{3}$ |
| 11 | 12B]l 1 Heavy Chain Variable Region - nucleic acid |
| 12 | 12B]l 1 Heavy Chain Variable Region - protein |
| 13 | 12B] 1 Light (kappa) Chain Variable Region - nucleic acid |
| 14 | 12B]l 1 Light (kappa) Chain Variable Region -protein |
| 15 | 12B]II Heavy Chain CDRi |
| 16 | 12B]l I Heavy Chain CDR 2 |
| 17 | 12B]l I Heavy Chain CDR ${ }_{3}$ |
| 18 | 12B]L 1 Light (kappa) Chain CDRi |
| 19 | 12B]1 1 Light (kappa) Chain CDR 2 |
| 20 | 12B]l 1 Light (kappa) Chain $\mathrm{CDR}_{3}$ |
| 21 | 17FC)6 Heavy Chain Variable Region - nucleic acid |
| 22 | 17FC)6 Heavy Chain Variable Region - protein |
| 23 | 17FC)6 Light (lambda) Chain Variable Region - nucleic acid |
| 24 | $17 \mathrm{FC}) 6$ Light (lambda) Chain Variable Region - protein |
| 25 | 17FC)6 Heavy Chain CDRi |
| 26 | 17FC)6 Heavy Chain CDR 2 |
| 27 | $17 \mathrm{FC}) 6$ Heavy Chain $\mathrm{CDR}_{3}$ |
| 28 | 17FC)6 Light (lambda) Chain CDRi |
| 29 | ${ }_{17 \mathrm{FC}) 6}$ Light (lambda) Chain $\mathrm{CDR}_{2}$ |
| 30 | $17 \mathrm{FC}) 6$ Light (lambda) Chain $\mathrm{CDR}_{3}$ |
| 31 | 18H(99 Heavy Chain Variable Region - nucleic acid |
| 32 | 18H()9 Heavy Chain Variable Region - protein |
| 33 | 18H(39 Light (lambda) Chain Variable Region - nucleic acid |
| 34 | 18H(39 Light (lambda) Chain Variable Region - protein |
| 35 | 18H(39 Heavy Chain CDRi |
| 36 | 18H(39 Heavy Chain CDR 2 |
| 37 | 18H(39 Heavy Chain CDR 3 |
| 38 | 18H(39 Light (lambda) Chain CDRi |
| 39 | 18H(39 Light (lambda) Chain CDR 2 |
| 40 | 18H(39 Light (lambda) Chain $\mathrm{CDR}_{3}$ |
| 41 | 29B(36 Heavy Chain Variable Region - nucleic acid |
| 42 | 29B(36 Heavy Chain Variable Region - protein |
| 43 | 29B(36 Light (kappa) Chain Variable Region - nucleic acid |
| 44 | 29B(36 Light (kappa) Chain Variable Region - protein |


| $\mathrm{S} \mathrm{EO} \mathrm{II}) \mathrm{NO}$ | Mucleic Acid or Protein |
| :---: | :---: |
| 45 | 29B06 Heavy Chain CDR^ |
| 46 | 29B06 Heavy Chain CDR ${ }_{2}$ |
| 47 | 29B06 Heavy Chain $\mathrm{CDR}_{3}$ |
| 48 | 29B06 Light (kappa) Chain CDRi |
| 49 | 29B06 Light (kappa) Chain $\mathrm{CDR}_{2}$ |
| 50 | 29B06 Light (kappa) Chain $\mathrm{CDR}_{3}$ |

[0151] Mouse monoclonal antibody heavy chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 2.

Table 2

| Kabl |  |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { RHWMS } \\ & \text { (SEQ ID NO: 5) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { EINPDSRTINYTPSLKE } \\ & \text { (SEQ ID NO: 6) } \end{aligned}$ | $\begin{aligned} & \hline \text { RVRIHYYGAMDC } \\ & \text { (SEQ ID NO: 7) } \\ & \hline \end{aligned}$ |
| 12B11 | $\begin{array}{\|l\|} \hline \text { TYAMS } \\ \text { (SEQ ID NO: } 15 \text { ) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { GITNGGSFTYYPDTVKG } \\ & \text { (SEQ ID NO: 16) } \\ & \hline \end{aligned}$ | QGYYGVNFDY (SEQ ID NO: 17) |
| 17F06 | $\begin{array}{\|l\|} \hline \text { SYGMS } \\ \text { (SEQ ID NO: 25) } \\ \hline \end{array}$ | $\begin{array}{\|l} \hline \begin{array}{l} \text { SISSGGGTTYYLDTVKG } \\ \text { (SEQ ID NO: 26) } \end{array} \\ \hline \end{array}$ | $\begin{aligned} & \text { GQWLLKFAY } \\ & \text { (SEQ ID NO: 27) } \end{aligned}$ |
| 18H09 | $\begin{array}{\|l\|} \hline \begin{array}{l} \text { SDYWN } \\ \text { (SEQ ID NO: 35) } \end{array} \\ \hline \end{array}$ | $\begin{array}{\|l} \hline \text { YISYSGSTYYNPSLK } \\ \text { (SEQ ID NO: 36) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { THILTIAY } \\ & \text { (SEQ ID NO: 37) } \\ & \hline \end{aligned}$ |
| 29B06 | $\begin{array}{\|l} \hline \text { SGYWN } \\ \text { (SEQ ID NO: 45) } \end{array}$ | YISYSGKTYYNPSLKS (SEQ ID NO: 46) | $\begin{aligned} & \text { SKYDYAMDY } \\ & \text { (SEQ ID NO: } 47 \text { ) } \end{aligned}$ |
| Chethe |  |  |  |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { GFDFSRH } \\ & \text { (SEQ ID NO: 51) } \end{aligned}$ | $\begin{aligned} & \hline \text { NPDSRT } \\ & \text { (SEQ ID NO: 52) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { RVRIHYYGAMDC } \\ & \text { (SEQ ID NO: 7) } \\ & \hline \end{aligned}$ |
| 12B11 | $\begin{array}{\|l} \hline \text { GFTFSTY } \\ \text { (SEQ ID NO: 53) } \\ \hline \end{array}$ | $\begin{array}{\|l} \hline \text { TNGGSF } \\ \text { (SEQ ID NO: 54) } \\ \hline \end{array}$ | $\begin{array}{\|l} \hline \text { QGYYGVNFDY } \\ \text { (SEQ ID NO: 17) } \\ \hline \end{array}$ |
| 17F06 | $\begin{array}{\|l\|} \hline \text { GFIFSSY } \\ \text { (SEQ ID NO: } 55 \text { ) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { SSGGGT } \\ & \text { (SEQ ID NO: 56) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { GQWLLKFAY } \\ & \text { (SEQ ID NO: 27) } \end{aligned}$ |
| 18H09 | $\begin{array}{\|l} \hline \text { GDSITSD } \\ \text { (SEQ ID NO: 57) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { SYSGS } \\ & \text { (SEQ ID NO: 58) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { THILTIAY } \\ & \text { (SEQ ID NO: 37) } \\ & \hline \end{aligned}$ |
| 29B06 | $\begin{aligned} & \hline \text { GDSITSG } \\ & \text { (SEQ ID NO: 59) } \end{aligned}$ | SYSGK (SEQ ID NO: 60) | $\begin{aligned} & \text { SKYDYAMDY } \\ & \text { (SEQ ID NO: } 47 \text { ) } \end{aligned}$ |

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Table 2 Cont.

| MMat |  |  |  |
| :---: | :---: | :---: | :---: |
|  | (DR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \begin{array}{l} \text { GFDFSRHW } \\ \text { (SEQ ID NO:61) } \end{array} \end{aligned}$ | $\begin{aligned} & \text { INPDSRTI } \\ & \text { (SEQ ID NO: } 62 \text { ) } \end{aligned}$ | ARRVRIHYYGAMDC (SEQ ID NO: 63) |
| 12B11 | $\begin{aligned} & \hline \text { GFTFSTYA } \\ & \text { (SEQ ID NO: 64) } \end{aligned}$ | $\begin{aligned} & \hline \text { ITNGGSFT } \\ & \text { (SEQ ID NO: } 65 \text { ) } \\ & \hline \end{aligned}$ | ARQGYYGVNFDY (SEQ ID NO: 66) |
| 17F06 | $\begin{aligned} & \text { GFIFSSYG } \\ & \text { (SEQ ID NO: 67) } \end{aligned}$ | $\begin{aligned} & \hline \text { ISSGGGTT } \\ & \text { (SEQ ID NO: 68) } \end{aligned}$ | TRGQWLLKFAY (SEQ ID NO: 69) |
| 18H09 | $\begin{aligned} & \hline \text { GDSITSDY } \\ & \text { (SEQ ID NO: 70) } \end{aligned}$ | $\begin{aligned} & \hline \text { ISYSGST } \\ & \text { (SEQ ID NO: 71) } \\ & \hline \end{aligned}$ | ARTHILTIAY (SEQ ID NO: 72) |
| 29B06 | $\begin{aligned} & \text { GDSITSGY } \\ & \text { (SEQ ID NO: } 73 \text { ) } \end{aligned}$ | $\begin{aligned} & \text { ISYSGKT } \\ & \text { (SEQ ID NO: } 74 \text { ) } \end{aligned}$ | ARSKYDYAMDY (SEQ ID NO: 75) |

[0152] Mouse monoclonal antibody Kappa light chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 3.

Table 3

| Kabat/Chotha |  |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { KASQNVGSSLV } \\ & \text { (SEQ ID NO: } 8 \text { ) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { SASFRYS } \\ & \text { (SEQ ID NO: 9) } \end{aligned}$ | QQYNNYPLT (SEQ ID NO: 10 ) |
| 12B11 | $\begin{aligned} & \text { RSSQSLENSNGNTYLN } \\ & \text { (SEQ ID NO: 18) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { RVSNRFS } \\ & \text { (SEQ ID NO: 19) } \end{aligned}$ | $\begin{aligned} & \text { LQVTHVPHT } \\ & \text { (SEQ ID NO: 20) } \end{aligned}$ |
| 17F06 | $\begin{aligned} & \hline \text { TLSSQHTTYTIE } \\ & \text { (SEQ ID NO: 28) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { LKKDGSHSTGV } \\ & \text { (SEQ ID NO: 29) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { GVGETIEDQFVYV } \\ & \text { (SEQ ID NO: 30) } \\ & \hline \end{aligned}$ |
| 18H09 | $\begin{aligned} & \text { RSSAGAVTTSNFAN } \\ & \text { (SEQ ID NO: 38) } \end{aligned}$ | DTNIRAP (SEQ ID NO: 39) | ALWYSNHYWV (SEQ ID NO: 40) |
| 29B06 | RASEIVDNFGISFMN (SEQ ID NO: 48) | AASNQGS (SEQ ID NO: 49) | QQSKEVPPT (SEQ ID NO: 50) |
| MMcT |  |  |  |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { QNVGSS } \\ & \text { (SEQ ID NO: 76) } \end{aligned}$ | SAS | QQYNNYPLT <br> (SEQ ID NO: 10) |
| 12B11 | QSLENSNGNTY (SEQ ID NO: 77) | RVS | $\begin{aligned} & \text { LQVTHVPHT } \\ & \text { (SEQ ID NO: 20) } \end{aligned}$ |
| 17F06 | $\begin{aligned} & \text { SQHTTYT } \\ & \text { (SEQ ID NO: 78) } \end{aligned}$ | $\begin{aligned} & \hline \text { LKKDGSH } \\ & \text { (SEQ ID NO: 79) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { GVGETIEDQFVYV } \\ & \text { (SEQ ID NO: 30) } \\ & \hline \end{aligned}$ |
| 18H09 | $\begin{aligned} & \text { AGAVTTSNF } \\ & \text { (SEQ ID NO: } 80 \text { ) } \end{aligned}$ | DTN | ALWYSNHYWV (SEQ ID NO: 40) |
| 29B06 | EIVDNFGISF <br> (SEQ ID NO: 81) | AAS | QQSKEVPPT <br> (SEQ ID NO: 50) |

[0153] To create the complete heavy or kappa chain antibody sequences, each variable sequence above is combined with its respective constant region. For example, a complete heavy chain comprises a heavy variable sequence followed by the murine IgGl or IgG2a heavy chain constant sequence, a complete kappa chain comprises a kappa variable sequence followed by the murine kappa light chain constant sequence, and a complete lambda chain comprises a lambda variable sequence followed by the murine lambda IGLCl or IGLC2 light chain constant sequence.
[0154] Nucleic Acid Sequence Encoding the Murine IgGl Heavy Chain Constant Region
(SEQ ID NO: 82)

| 1 | gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac |
| ---: | :--- |
| 61 | tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc |
| 121 | tggaactctg gatccetgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac |
| 181 | ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc |
| 241 | acctgcaacg ttgcccaccc ggccagcagc |
| 301 | gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc |
| 361 | cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg |
| 421 | gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag |
| 481 | gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc |
| 541 | agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc |
| 601 | aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg |
| 661 | aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc |
| 721 | agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg |
| 781 | aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct |
| 841 | tacttcgtct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc |
| 901 | acctgctctg tgttacatga gggcctgcac |

[0155] Protein Sequence Defining the Murine IgGl Heavy Chain Constant Region (SEQ
ID NO: 83)

| 1 | akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt wnsgslssgv htfpavlqsd |
| ---: | :--- |
| 61 | lytlsssvtv psstwpsetv tcnvahpass tkvdkkivpr dcgckpcict vpevssvfif |
| 121 | ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve vhtaqtqpre eqfnstfrsv |
| 181 | selpimhqdw lngkefkcrv nsaafpapie ktisktkgrp kapqvytipp pkeqmakdkv |
| 241 | sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs yfvysklnvq ksnweagntf |
| 301 | tcsvlheglh nhhtekslsh spgk |

[0156] Nucleic Acid Sequence Encoding the Murine IgG2a Heavy Chain Constant Region
(SEQ ID NO: 84)

akttapsvyp lapvcgdttg ssvtlgclvk gyfpepvtlt wnsgslssgv htfpavlqsd 61 lytlsssvtv tsstwpsqsi tcnvahpass tkvdkkiepr gptikpcppc kcpapnllgg 121 psvfifppki kdvlmislsp ivtcvvvdvs eddpdvqisw fvnnvevhta qtqthredyn 181 stlrvvsalp iqhqdwmsgk efkckvnnkd lpapiertis kpkgsvrapq vyvlpppeee 241 mtkkqvtltc mvtdfmpedi yvewtnngkt elnykntepv Idsdgsyfmy sklrvekknw 301 vernsyscsv vheglhnhht tksfsrtpgk

[0157] Protein Sequence Defining the Murine IgG2a Heavy Chain Constant Region (SEQ
ID NO: 85)
481 tttgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac 541 agtactctcc gggtggtcag tgccctcccc atccagcacc aggactggat gagtggcaag 601 gagttcaaat gcaaggtcaa caacaaagac ctcccagcgc ccatcgagag aaccatctca 661 aacccaaag ggtcagtaag agctccacag gtatatgtct tgcctccacc agaagaagag 721 atgactaaga aacaggtcac tctgacctgc atggtcacag acttcatgcc tgaagacatt 781 tacgtggagt ggaccaacaa cgggaaaaca gagctaaact acaagaacac tgaaccagtc 841 ctggactctg atggttctta cttcatgtac agcaagctga gagtggaaaa gaagaactgg 901 gtggaaagaa atagctactc ctgttcagtg gtccacgagg gtctgcacaa tcaccacacg 961 actaagagct tctcccggac tccgggtaaa
[0158] Nucleic Acid Sequence Encoding the Murine Kappa Light Chain Constant Region
(SEQ ID NO: 86)
1 cgggctgatg ctgcaccaac tgtatccatc ttcccaccat ccagtgagca gttaacatct
61 ggaggtgcct cagtcgtgtg cttcttgaac aacttctacc ccaaagacat caatgtcaag
121 tggaagattg atggcagtga acgacaaaat ggcgtcctga acagttggac tgatcaggac
181 agcaaagaca gcacctacag catgagcagc accctcacgt tgaccaagga cgagtatgaa
241 cgacataaca gctatacctg tgaggccact cacaagacat caacttcacc cattgtcaag
301 agcttcaaca ggaatgagtg t
[0159] Protein Sequence Defining the Murine Kappa Light Chain Constant Region (SEQ
ID NO: 87)

1 radaaptvsi fppsseqlts ggasvvcfln nfypkdinvk wkidgserqn gvlnswtdqd 61 skdstysmss tltltkdeye rhnsytceat hktstspivk sfnrnec
[0160] Nucleic Acid Sequence Encoding the Murine Lambda (IGLCl) Light Chain
Constant Region (SEQ ID NO: 88)
1 ggccagccia agtcttcgcc atcagtcacc ctgtttccac cttcctctga agagctcgag
61 actaacaagg ccacactggt gtgtacgatc actgatttct acccaggtgt ggtgacagtg
121 gactggaagg tagatggtac ccctgtcact cagggtatgg agacaaccca gccttccaaa
181 cagagcaaca acaagtacat ggctagcagc tacctgaccc tgacagcaag agcatgggaa
241 aggcatagca gttacagctg ccaggtcact catgaaggtc acactgtgga gaagagtttg
301 tcccgtgctg actgttcc
[0161] Protein Sequence Defining the Murine Lambda (IGLCl) Light Chain Constant
Region (SEQ ID NO: 89)

1 gqpksspsvt lfppsseele tnkatlvcti tdfypgvvtv dwkvdgtpvt qgmettqpsk 61 qsnnkymass yltltarawe rhssyscqvt heghtveksl sradcs

# [0162] Nucleic Acid Sequence Encoding the Murine Lambda (IGLC2) Light Chain 

## Constant Region (SEQ ID NO: 90)

ggtcagccca agtccactcc cactctcacc
gaaaacaaag ccacactggt gtgtctgatt tccaactttt ccccgagtgg tgtgacagtg
gcctggaagg caaatggtac acctatcacc cagggtgtgg acacttcaaa tcccaccaaa
gagggcaaca agttcatggc cagcagcttc ctacatttga catcggacca gtggagatct
cacaacagtt ttacctgtca agttacacat gaaggggaca ctgtggagaa gagtctgtct
cctgcagaat gtctc
[0163] Protein Sequence Defining the Murine Lambda (IGLC2) Light Chain Constant
Region (SEQ ID NO: 91)

```
l gqpkstptlt vfppsseelk enkatlvcli snfspsgvtv awkangtpit qgvdtsnptk
61 egnkfmassf lhltsdqwrs hnsftcqvth egdtveksls paecl
```

[0164] The following sequences represent the actual or contemplated full length heavy and light chain sequence (i.e., containing both the variable and constant regions sequences) for each antibody described in this Example. Signal sequences for proper secretion of the antibodies (e.g., signal sequences at the 5 ' end of the DNA sequences or the amino terminal end of the protein sequences) are not shown in the full length heavy and light chain sequences disclosed herein and are not included in the final secreted protein. Also not shown are stop codons for termination of translation required at the 3 ' end of the DNA sequences. It is within ordinary skill in the art to select a signal sequence and/or a stop codon for expression of the disclosed full length IgG heavy chain and light chain sequences. It is also contemplated that the variable region sequences can be ligated to other constant region sequences to produce active full length IgG heavy and light chains.
[0165] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgGl Constant Region) of 07F01 (SEQ ID NO: 92)
gaggtgaagc ttctcgagtc tggaggtggc ctggtgcagc cgggtggatc cctgaaactc
tcctgtgcag cctcaggatt cgattttagt agacactgga tgagttgggt ccggctggct
ccagggaaag ggctagaatg gatcgcagaa attaatccag atagcagaac gataaactat
acgccatctc taaaggagaa attcatcatc tccagagaca acgccaaaaa ttcgctgttt
ctgcaaatga acagagtgag atctgaggac acagcccttt attactgtgc aagacgggta
agaattcatt actacggcgc tatggactgc tggggtcaag gaacctcagt caccgtctcc
tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact
aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg
acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct
gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc
gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc
agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc
ttcccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt
gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg
gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca
gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg
cacaggtgta
cctgcatgat a agccagcgga
tctacagcaa ctgtgttaca tgagggct gtaaa
[0166] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain
[0169] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgGl Constant Region) of 12B11 (SEQ ID NO: 96)


| 421 | atggtgaccc | ct |
| :---: | :---: | :---: |
| 481 | aactctggat | ccctgtccag |
| 541 | tacactctga | gcagctcagt |
| 601 | tgcaacgttg | cccaccoggc |
| 661 | tgtggttgta | agccttgcat |
| 721 | ccaaagccca | aggatgtgct |
| 781 | gacatcagca | aggatgatcc |
| 841 | cacacagctc | agacgcaacc |
| 901 | gaacttccca | tcatgcacca |
| 961 | agtgcagctt | tccetgcccc |
| 1021 | gctccacagg | tgtacaccat |
| 1081 | ctgacctgca | tgataacaga |
| 1141 | gggcagccag | cggagaacta |
| 1201 | ttcgtctaca | gcaagctcaa |
| 1261 | tgctctgtgt | tacatgaggg |
| 1321 | cctggtaaa |  |

ggtcaagggc t cggtgtgcac gactgtcccc cagcagcacc atgtacagtc caccattact cgaggtccag ccgggaggag ggactggctc catcgagaaa tccacctccc cttcttccct caagaacact tgtgcagaag cctgcacaac
tatttccctg accttcccag tccagcacct aaggtggaca ccagaagtat ctgactccta ttcagctggt cagttcaaca aatggcaagg accatctcca aaggagcaga gaagacatta cagcccatca agcaactggg caccatactg
agccagtgac agtgacctgg ctgtcctgca gtctgacctc ggcccagcga gaccgtcacc agaaaattgt gcccagggat catctgtctt catcttcccc aggtcacgtg tgttgtggta ttgtagatga tgtggaggtg gcactttccg ctcagtcagt agttcaaatg cagggtcaac aaaccaaagg cagaccgaag tggccaagga taaagtcagt ctgtggagtg gcagtggaat tggacacaga tggctcttac aggcaggaaa tactttcacc agaagagcct ctcccactct
[0170] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain
Variable Region and IgGl Constant Region) of 12B11 (SEQ ID NO: 97)
lvkpggslkl
srdnarnily apgsaaqtns sstwpsetvt Itpkvtcvvv ngkefkcrvn gqpaenyknt q pgk
tyamswirqt pekrlewvag itnggsftyy tamyycarqg yygvnfdywg qgttltvssa yfpepvtvtw nsgslssgvh tfpavlqsdl kvdkkivprd cgckpcictv pevssvfifp fswfvddvev htaqtqpree qfnstfrsvs tisktkgrpk apqvytippp keqmakdkvs qpimdtdgsy fvysklnvqk snweagntft
[0171] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa
Chain Variable Region and Constant Region) of 12B 11 (SEQ ID NO: 98)

[0172] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain
Variable Region and Constant Region) of 12B 11 (SEQ ID NO: 99)

[^0]
## [0173] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy

Chain Variable Region and IgG2A Constant Region) of 17F06 (SEQ ID NO: 100)

1 caacttgtgc tcactcagtc 61 acgtgcacct 121 ctcaagcctc 181 gggattcctg 241 aacatccagc 301 caatttgtgt 361 actcccactc 421 ctggtgtgtc 481 ggtacaccta 541 atggccagca 601 tgtcaagtta
tggtggagtc cctctggatt ggctggagtg taaagggccg gtggtctgaa agtttgctta catcggtcta gatgcctggt tgtccagtgg gctcagtgac acccggcaag cctgtcctcc tccctccaaa tggtggatgt aagtacacac tcagtgccct tcaacaacaa taagagctcc tcactctgac acaacgggaa cttacttcat actcctgttc ggactccggg
ggggggaggc
cattttcagt
ggtcgcttcc
attcaccatc
gtctgaagac
ctggggccaa
tccactggcc
caagggttat
tgtgcacacc
tgtaacctcg
cagcaccaag
atgcaaatgc
gatcaaggat
gagcgaggat
agctcagaca
ccccatccag
agacctccca
acaggtatat
$c t g c a t g g t c ~$
$a a c a g a g c t a ~$
gtacagcaag
agtggtccac
taaa
ttagtgaagc tcctatggca attagtagtg tccagagaga acggccttgt gggactctgg cctgtgtgtg ttccctgagc ttcccagctg agcacctggc gtggacaaga ccagcaccta gtactcatga gacccagatg caaacccata caccaggact gcgcccatcg gtcttgcctc acagacttca aactacaaga ctgagagtgg gagggtctgc
ctggagcgtc tctgaaactc tgtcttgggt tcgccagact gtggtggtac cacctactat atgccaagga caccctgtac attactgtac aagaggccaa tcactgtctc tgcagccaaa gagatacaac tggctcctcg cagtgacctt gacctggaac tcctgcagtc tgacctctac ccagccagtc catcacctgc aaattgagcc cagagggccc acctcttggg tggaccatcc tctccctgag ccccatagtc tccagatcag ctggtttgtg gagaggatta caacagtact ggatgagtgg caaggagttc agagaaccat ctcaaaaccc caccagaaga agagatgact tgcctgaaga catttacgtg acactgaacc agtcctggac aaaagaagaa ctgggtggaa acaatcacca cacgactaag
[0174] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG2A Constant Region) of 17F06 (SEQ ID NO: 101)
lvkpgaslkl scaasgfifs srenakdtly lqmsolksed pvcgdttgss stwpsqsitc vlmislspiv hqdwmsgkef tdfmpediyv eglhnhhttk
lqmsglksed talyyctrgq vtlgclvkgy fpepvtltwn nvahpasstk vdkkieprgp tcvvvdvsed dpdvqiswfv kckvnnkdlp ewtnngktel nykntepvld s sfsrtpgk

| sygmswvrqt | sdkrlewvas | issgggttyy |
| :--- | :---: | :--- |
| talyyctrgq | wllkfaywgq | gtlvtvsaak |
| fpepvtltwn | sgslssgvht | fpavlqsdly |
| vdkkieprgp | tikpcppckc | papnllggps |
| dpdvqiswfv | nnvevhtaqt | qthredynst |
| apiertiskp | kgsvrapqvy | vlpppeeemt |
| nykntepvld | sdgsyfmysk | lrvekknwve |

issgggttyy gtlvtvsaak fpavlqsdly papnllggps qthredynst lrvekknwve
[0175] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Lambda
Chain Variable Region and Constant Region (IGLC2)) of 17F06 (SEQ ID NO: 102)
 ggacactgtg gagaagagtc tgtctcctgc agaatgtctc

| tgggagcctc | agcaaaactc |
| :--- | :--- |
| aatggtatca | gcaactgcca |
| gaagccacag | cacaggtgt |
| atcgctacct | taccatttcc |
| tgggtgagac | aattgaggac |
| tcctaggtca | gcccaagtcc |
| tcaaggaaaa | caaagccaca |
| cagtggcctg | gaaggcaaat |
| ccaaagaggg | caacaagttc |
| gatctcacaa | cagttttacc |
| tgtctcctgc | agaatgtctc |

tgggagcctc agcaaaactc aatggtatca gcaactgcca gaagccacag cacaggtgtt tcgctacct taccatttcc aattgaggac gcccaagtcc caaagccaca gaaggcaaat
[0176] Protein Sequence Defining the Full Length Light Chain Sequence (Lambda Chain
Variable Region and Constant Region (IGLC2)) of 17F06 (SEQ ID NO: 103)


Ikppkyvmel kkdgshstgv qfvyvfgggt kvtvlgqpks gtpitqgvdt snptkegnkf
[0177] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy
Chain Variable Region and IgGl Constant Region) of 18H09 (SEQ ID NO: 104)

1 gaggtgcagc
61 acctgttatg
121 ccaggaaata
181 ccatctctca
241 cggttgaatt
301 cttacgattg 361 cccccatctg 421 ctgggatgcc 481 tccctgtcca 541 agcagctcag 601 gcccacccgg 661 aagccttgca 721 aaggatgtgc 781 aaggatgatc 841 cagacgcaac 901 atcatgcacc 961 ttccctgccc 1021 gtgtacacca 1081 atgataacag 1141 gcggagaact 1201 agcaagctca 1261 ttacatgagg
tcaggagt cactggcga aacttgagta aaagtcgaat ctgtgactac cttactgggg tctatccact tggtcaaggg gcggtgtgca tgactgtccc ccagcagcac tatgtacagt tcaccattac ccgaggtcca cccgggagga aggactggct ccatcgagaa ttccacctcc acttcttccc acaagaacac atgtgcagaa gcctgcacaa
aggacctagc ctccatcacc catgggatat ctccatcact tgaggacaca ccaagggact ggcccetgga ctatttccct caccttccca ctccagcacc caaggtggac cccagaagta tctgactcct gttcagctgg gcagttcaac caatggcaag aaccatctcc caaggagcag tgaagacatt tcagcccatc gagcaactgg ccaccatact
ctcgtgaaac cttctcagac tctgtccctc agtgattact ggaattggat ccggaaattc atcagctaca gtggtagcac ttactacaat cgagacacat ccaagaacca gttctacctt gccacatatt actgtgcaag aacccatata ctggtcactg tctctgcagc caaaacgaca tctgctgccc aaactaactc catggtgacc gagccagtga cagtgacctg gaactctgga gctgtcctgc agtctgacct ctacactctg tggcccagcg agaccgtcac ctgcaacgtt aagaaaattg tgcccaggga ttgtggttgt tcatctgtct tcatcttccc cccaaagccc aaggtcacgt gtgttgtggt agacatcagc tttgtagatg atgtggaggt gcacacagct agcactttcc gctcagtcag tgaacttccc gagttcaaat gcagggtcaa cagtgcagct aaaaccaaag gcagaccgaa ggctccacag atggccaagg ataaagtcag tctgacctgc actgtggagt ggcagtggaa tgggcagcca atggacacag atggctctta cttcgtctac gaggcaggaa atactttcac ctgctctgtg gagaagagcc tctcccactc tcctggtaaa
[0178] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgGl Constant Region) of 18H09 (SEQ ID NO: 105)
1
61 pvqlqesgps $\quad$ l
vkpsqtls rdtsknqfyl saaqtnsmvt wpsetvtcnv kvtcvvvdis efkcrvnsaa tvewqwngqp ekslshspgk
tcyvtgdsit sdywnwirkf pgnkleymgy rlnsvttedt atyycarthi ltiaywgqgt Igclvkgyfp epvtvtwnsg ahpasstkvd k kddpevqfsw fvddvevhta fpapiektis ktkgrpkapq vytipppkeq m aenykntqpi mdtdgsyfvy sklnvqksnw e
isysgstyyn lvtvsaaktt avlqsdlytl ssvfifppkp stfrsvselp makdkvsltc eagntftcsv
[0179] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Lambda
Chain Variable Region and Constant Region (IGLCl )) of 18H09 (SEQ ID NO: 106)

1 caggctgttg tgactcagga at caagtgccgg
61 acttgtcgct cact attatcac t
121 aaaccagatc attact
181 cctgccagat tctcaggctc atctgcactc accacatcac c ggctgttaca actagtaact t tggtctaata ggtgatacca acatccgagc cctgattgga gacaaggctg ccctcaccat cacaggggca

|  | gaggtgcagc |  |
| :---: | :---: | :---: |
| 61 | 1 acctgttctg |  |
| 21 | ccaggg |  |
| 181 | ccatctctca | at |
| 241 | cagttgattt | ctgtgactgc |
| 301 | gactatgcta | tggactactg |
| 361 | acacccccat | ctgtctatcc |
| 21 | accctgggat | gcctggtcaa |
| 481 | ggatccctgt | cagcggtgt |
| 541 | ctgagcagct | cagtgactgt |
| 601 | gttgcccacc | cggccagcag |
| 661 | tgtaagcctt | tgtac |
| 721 | cccaaggatg | tgctcaccat |
| 781 | agcaaggatg | atcccgaggt |
| 841 | gctcagacgc | aaccccggga |
| 901 | cccatcatgc | aggactg |
| 1 | gctttccctg | cccccatcga |
| 1021 | caggtgtaca | tccacc |
| 1081 | tgcatgataa | cagacttctt |
| 1141 | ccagcggaga | actacaagaa |
| 1201 | tacagcaagc | caatgtgca |
| 1261 | gttacatg | agggcctgca |
| 31 |  |  |

aggacctagc ctccatcacc catggggtac ctccatcact tgaggacaca gggtcaagga actggcccct gggctatttc gcacaccttc cocctccagc caccaaggtg agtcccagaa tactctgact ccagttcagc ggagcagttc gctcaatggc gaaaaccatc tcccaaggag ccctgaagac cactcagccc gaagagcaac caaccaccat actgagaaga ctcgtgaaac
agtggttact
ataagctaca
cgagacacat
gccacatatt
acctcagtca
ggatctgctg
cctgagccag
ccagctgtcc
acctggccca
gacaagaaaa
gtatcatctg
cctaaggtca
tggtttgtag
aacagcactt
aaggagttca
tccaaaacca
cagatggcca
attactgtgg
atcatggaca
tgggaggcag
actgagaaga
ctctcagac tctgtccctc ggaactggat ccggaaattc gtggtaaaac ttactacaat ccaagaacca ttactacctg actgtgcaag gtctaagtac ccgtctcctc agccaaaacg cccaaactaa ctccatggtg tgacagtgac ctggaactct tgcagtctga cctctacact gcgagaccgt cacctgcaac ttgtgcccag ggattgtggt tcttcatctt ccccccaaag cgtgtgttgt ggtagacatc atgatgtgga ggtgcacaca tccgctcagt cagtgaactt aatgcagggt caacagtgca aaggcagacc gaaggctcca aggataaagt cagtctgacc agtggcagtg gaatgggcag cagatggctc ttacttcgtc gaaatacttt cacctgctct gcctetcccaa ctetcotggt
[0182] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgGl Constant Region) of 29B06 (SEQ ID NO: 109)

| 1 evqlqesgps | lvkpsqtlsl | tcsvtgdsit | sgywnwirkf | pgnkleymgy | isysgktyyn |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 61 pslksrisit | rdtsknhyyl | qlisvtaedt | atyycarsky | dyamdywgqg | tsvtvssakt |
| 121 tppsvyplap | gsaaqtnsmv | tlgclvkgyf | pepvtvtwns | gslssgvhtf | pavlqsdlyt |
| 181 lsssvtvpss | twpsetvtcn | vahpasstkv | dkkivprdcg | ckpcictvpe | vSsvfifppk |
| 241 pkdvltitlt | pkvtcvvvdi | skddpevqf s | w fvddvevht | aqtqpreeqf | nstfrsvsel |
| 301 pimhqdwlng | kefkcrvnsa | afpapiekti | sktkgrpkap | qvytipppke | qmakdkvslt |
| 361 cmitdffped | itvewqwngq | paenykntqp | imdtdgsyf v | ysklnvqksn | weagntftcs |
| 421 vlheglhnhh | tekslshspg | k |  |  |  |

[0183] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa
Chain Variable Region and Constant Region) of 29B06 (SEQ ID NO: 110)
[0184] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 29B06 (SEQ ID NO: 111)

```
    1 divltqspas lavslgqrat iscraseivd nfgisfmnwf qqkpgqppkl liyaasnqgs
    6 1 ~ g v p a r f s g s g ~ s g t d f s l n i h ~ p v e e d d t a m y ~ f c q q s k e v p p ~ t f g g g t k l e i ~ k r a d a a p t v s
121 ifppsseqlt sggasvvcfl nnfypkdinv kwkidgserq ngvlnswtdq dskdstysms
1 8 1 \text { stltltkdey erhnsytcea thktstspiv ksfnrnec}
```

[0185] Table 4 shows the correspondence between the full-length sequences of the antibodies discussed in this Example with those presented in the Sequence Listing.

Table 4

| SEO II NO. | Nucleic Acid or Protein |
| :---: | :---: |
| 92 | 07F01 Heavy Variable + IgG1 Constant-nucleic acid |
| 93 | 07F01 Heavy Variable + IgG1 Constant-protein |
| 94 | 07F01 Kappa Variable + Constant-nucleic acid |
| 95 | 07F01 Kappa Variable + Constant-protein |
| 96 | 12B11 Heavy Variable + IgG1 Constant-nucleic acid |
| 97 | 12B11 Heavy Variable + IgG1 Constant-protein |
| 98 | 12B11 Kappa Variable + Constant-nucleic acid |
| 99 | 12B11 Kappa Variable + Constant-protein |
| 100 | 17F06 Heavy Variable + IgG2A Constant-nucleic acid |
| 101 | 17F06 Heavy Variable + IgG2A Constant-protein |
| 102 | 17F06 Lambda Variable + Constant (IGLC2) - nucleic acid |
| 103 | 17F06 Lambda Variable + Constant (IGLC2)-protein |
| 104 | 18H09 Heavy Variable + IgG1 Constant-nucleic acid |
| 105 | 18H09 Heavy Variable + IgG1 Constant-protein |
| 106 | 18H09 Lambda Variable + Constant (IGLC1)-nucleic acid |
| 107 | 18H09 Lambda Variable + Constant (IGLC1)-protein |
| 108 | 29B06 Heavy Variable + IgG1 Constant-nucleic acid |
| 109 | 29B06 Heavy Variable + IgG1 Constant-protein |
| 110 | 29B06 Kappa Variable + Constant-nucleic acid |
| 111 | 29B06 Kappa Variable + Constant-protein |

## Example 5: Binding Affinities

[0186] The binding affinities and kinetics of binding of antibodies 07F01, 29B06, 17F06, 18 H 09 , and 12B11 to recombinant human RON-ECD/mFc fusion protein (rhRON ECD $/ \mathrm{mFc}$ ) and recombinant human RON SEMA and PSI domains (rhRON SEMA + PSI) (R\&D Systems, Inc., Minneapolis, MN) were measured by surface plasmon resonance, using a Biacore ${ }^{\circledR}$ T100 instrument (GE Healthcare, Piscataway, NJ).
[0187] Rabbit anti-mouse IgGs (GE Healthcare) were immobilized on carboxymethylated dextran CM4 sensor chips (GE Healthcare) by amine coupling, according to a standard protocol. Analyses were performed at $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$, using PBS containing $0.05 \%$ surfactant P20 as running buffer. The antibodies were captured in individual flow cells at a flow rate of $10 \mu i ̈ / \mathrm{min}$. Injection time was varied for each antibody to yield an Rmax between 30 and 60 RU. $250 \mu \mathrm{~g} / \mathrm{mL}$ mouse Fc were injected at $30 \mu \mathrm{i} / \mathrm{min}$ for 120 seconds to block non-specific binding of antibodies to Fc portion of the protein when needed. Buffer, rhRon ECD/mFc or rhRON SEMA + PSI diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 300 seconds at $60 \mu \bar{\mu} /$ minute. The dissociation phase was monitored for up to 3600 seconds. The surface was then regenerated with two 60 -second injections of 10 mM Glycine- $\mathrm{HCl}, \mathrm{pH} 1.7$, at a flow rate of $60 \mu \mathrm{i} / \mathrm{min}$. The rhRON ECD $/ \mathrm{mFc}$ or rhRON SEMA + PSI concentration range tested was 0.625 nM to 20 nM .
[0188] Kinetic parameters were determined using the kinetic function of the BIAevaluation software (GE Healthcare) with double reference subtraction. Kinetic parameters for each antibody, $\mathrm{k}_{\mathrm{a}}$ (association rate constant), $\mathrm{k}_{\mathrm{d}}$ (dissociation rate constant) and $\mathrm{K}_{\mathrm{D}}$ (equilibrium dissociation constant) were determined. Kinetic values of the monoclonal antibodies on rhRON ECD $/ \mathrm{mFc}$ at $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$ are summarized in Table 5 .

Table 5
Antibody Binding to rhRON ECD/mFc

| Mulioody |  | Measuementaral 25 Ie |  |  | \# |  |  |  | \% |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | ka, MMs) | kl1 $11 / \mathrm{s}$ ) | Kı, M1. |  | lar MMs) | ka, 1 W) | Kemm |  |
| 07F01 | AVG | $4.0 \mathrm{E}+05$ | $9.3 \mathrm{E}-05$ | $2.3 \mathrm{E}-10$ | 4 | $2.1 \mathrm{E}+06$ | 3.5E-04 | $2.1 \mathrm{E}-10$ | 3 |
|  | STDEV | $7.1 \mathrm{E}+04$ | $5.5 \mathrm{E}-06$ | $3.4 \mathrm{E}-11$ |  | $2.4 \mathrm{E}+06$ | 2.8E-04 | $7.1 \mathrm{E}-11$ |  |
| 29B06 | AVG | $2.0 \mathrm{E}+05$ | $1.3 \mathrm{E}-04$ | $6.5 \mathrm{E}-10$ | 3 | $2.3 \mathrm{E}+06$ | 7.0E-04 | $2.8 \mathrm{E}-10$ | 3 |
|  | STDEV | $3.5 \mathrm{E}+04$ | $1.0 \mathrm{E}-05$ | $1.2 \mathrm{E}-10$ |  | $1.3 \mathrm{E}+06$ | 4.8E-04 | 7.8E-11 |  |
| 17F06 | AVG | $1.7 \mathrm{E}+05$ | $\begin{gathered} \hline \text { 4.6E- } \\ 08^{*} \end{gathered}$ | $\begin{gathered} \hline 2.9 \mathrm{E}- \\ 13^{*} \\ \hline \end{gathered}$ | 3 | $1.4 \mathrm{E}+05$ | 2.4E-05 | 2.1E-10 | 3 |
|  | STDEV | $4.8 \mathrm{E}+04$ | 3.3E-08 | $1.7 \mathrm{E}-13$ |  | $3.1 \mathrm{E}+04$ | 2.2E-05 | $2.4 \mathrm{E}-10$ |  |
| 18H09 | AVG | $3.3 \mathrm{E}+05$ | $5.7 \mathrm{E}-05$ | $2.2 \mathrm{E}-10$ | 3 | $1.8 \mathrm{E}+06$ | 7.0E-04 | $4.0 \mathrm{E}-10$ | 1 |
|  | STDEV | $1.5 \mathrm{E}+05$ | $2.3 \mathrm{E}-05$ | $1.6 \mathrm{E}-10$ |  |  |  |  |  |
| 12B11 | AVG | $1.2 \mathrm{E}+05$ | $5.9 \mathrm{E}-05$ | $5.0 \mathrm{E}-10$ | 3 | $2.0 \mathrm{E}+05$ | 2.0E-04 | 1.1E-09 | 3 |
|  | STDEV | $2.8 \mathrm{E}+04$ | $1.7 \mathrm{E}-05$ | $4.6 \mathrm{E}-11$ |  | $1.1 \mathrm{E}+05$ | 3.8E-05 | 4.6E-10 |  |

* Outside instrument limit of detection
[0189] The data in Table 5 demonstrate that antibodies 07F01, 29B06, 17F06, 18H09, and

12B 11 bind rhRON ECD/ mFc with a $\mathrm{K}_{\mathrm{D}}$ of about 1 nM or less, 750 pM or less, 650 pM or less, 600 pM or less, 500 pM or less, 400 pM or less, 300 pM or less, 250 pM or less, 200 pM or less, 150 pM or less, 100 pM or less, or 50 pM or less.
[0190] Kinetic values of the monoclonal antibodies on rhRON SEMA + PSI at $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$ are summarized in Table 6.

Table 6
Antibody Binding to rhRON SEMA + PSI

| Amilion § |  | Measmenmental 2 s |  |  | ^. | Measirements at 3\% \% |  |  | \# |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | ka (1M) | killus) | $\mathrm{K}_{\mathrm{N}} \mathrm{M}$ ) |  | k (1AMs) | kd/1s) | Kume |  |
| 07F01 | AVG | $5.2 \mathrm{E}+06$ | 3.6E-04 | 8.8E-11 | 3 | $2.0 \mathrm{E}+06$ | 8.0E-04 | $4.0 \mathrm{E}-10$ | 3 |
|  | STDEV | $7.0 \mathrm{E}+06$ | 4.3E-04 | $3.3 \mathrm{E}-11$ |  | $2.1 \mathrm{E}+05$ | $7.5 \mathrm{E}-05$ | 8.3E-12 |  |
| 29B06 | AVG | $4.2 \mathrm{E}+05$ | $7.0 \mathrm{E}-05$ | $1.8 \mathrm{E}-10$ | 3 | $5.2 \mathrm{E}+05$ | $6.9 \mathrm{E}-04$ | 1.3E-09 | 3 |
|  | STDEV | $1.2 \mathrm{E}+05$ | 8.7E-06 | $6.1 \mathrm{E}-11$ |  | $4.7 \mathrm{E}+04$ | $4.9 \mathrm{E}-05$ | $9.9 \mathrm{E}-11$ |  |
| 17F06 | AVG | $1.9 \mathrm{E}+05$ | 1.4E-06 | $9.0 \mathrm{E}-12$ | 4 | $2.6 \mathrm{E}+05$ | $2.1 \mathrm{E}-05$ | 1.3E-10 | 3 |
|  | STDEV | $3.6 \mathrm{E}+04$ | 1.7E-06 | $1.1 \mathrm{E}-11$ |  | $1.2 \mathrm{E}+05$ | $2.9 \mathrm{E}-05$ | $1.9 \mathrm{E}-10$ |  |
| 18H09 | AVG | $4.4 \mathrm{E}+05$ | $3.8 \mathrm{E}-06$ | $8.6 \mathrm{E}-12$ | 3 | $5.8 \mathrm{E}+05$ | $1.2 \mathrm{E}-04$ | $2.2 \mathrm{E}-10$ | 2 |
|  | STDEV | $2.7 \mathrm{E}+04$ | 6.3E-06 | $1.4 \mathrm{E}-11$ |  | $7.6 \mathrm{E}+04$ | 5.3E-05 | 1.2E-10 |  |
| 12B11 | AVG | No binding |  |  | 2 | No binding |  |  |  |

[0191] The data in Table 6 demonstrate that antibodies 07F01, 29B06, 17F06 and 18H09 bind rhRON SEMA + PSI with a $\mathrm{K}_{\mathrm{D}}$ of about 1 nM or less, 750 pM or less, 650 pM or less, 600 pM or less, 500 pM or less, 400 pM or less, 300 pM or less, 250 pM or less, 200 pM or less, 150 pM or less, 100 pM or less, 75 pM or less, 50 pM or less, or 10 pM or less. Antibody 12B 11 did not bind to rhRON SEMA + PSI.
[0192] Binding to cell surface human wild-type RON and the delta 160 RON variant by antibodies 29B06 and 07F01was measured at $4^{\circ} \mathrm{C}$, using Fluorescence Activated Cell Sorting (FACS). PC3 cells expressing the human wild-type RON, and HT29 cells expressing the delta 160 variant, were harvested using cell dissociation buffer (Invitrogen), washed twice with FACS buffer (PBS with $0.5 \%$ BSA), and treated for 10 minutes with Cyto Q Antibody diluent and FC receptor block (Innovex Biosciences, Richmond, CA). Purified antibodies were diluted in FACS buffer over a concentration range from 0.02 nM to 40 nM . Cells were incubated with $100 \mu i ̈$ of antibody for one hour, washed with FACS buffer three times, and incubated for 45 minutes with goat anti-mouse PE-conjugated antibody (Jackson ImmunoResearch Laboratories, West Grove, PA). Cells were washed three times with FACS buffer, resuspended in $300 \mu i ̈$ of FACS buffer, and analyzed using a Beckman Coulter Cytomics FC 500 FACS instrument. Results are summarized in Table 7.

Table 7

|  | 29806 | 07F01 |
| :---: | :---: | :---: |
| Human RON - $\mathrm{K}_{\mathrm{D}}(\mathrm{nM})$ | 0.133 | 0.032 |
| Human RON - $\mathrm{K}_{\mathrm{D}}$ range ( nM ) | 0.089-0.177 | 0.025-0.039 |
| Delta $160 \mathrm{RON}-\mathrm{K}_{\mathrm{D}}$ (nM) | 0.146 | 0.024 |
| Delta $160 \mathrm{RON}-\mathrm{K}_{\mathrm{D}}$ range ( nM ) | 0.100-0.192 | 0.020-0.029 |

[0193] The results in Table 7 demonstrate that antibodies 29B06 and 07F01 bind both wildtype RON and the delta 160 RON variant on the cell surface with similar affinity.

## Example 6: Cell Surface Binding

[0194] Binding to cell surface wild-type RON and delta 160 RON at $4^{\circ} \mathrm{C}$ was determined for antibodies 07F01, 12B11, 17F06, 18H09, and 29B06, using FACS. Cells expressing wildtype RON (PC3), and cells expressing delta 160 RON (HT-29), were harvested using cell dissociation buffer (Invitrogen), washed twice with FACS buffer ( $0.5 \%$ BSA PBS) and treated with CytoQ Antibody diluent and FC receptor block (Innovex). Purified antibodies were diluted at a concentration of $10 \mu \mathrm{~g} / \mathrm{ml}$, in FACS buffer. Cells were incubated with $100 \mu \mathrm{ï}$ of antibody mix for one hour, washed with FACS buffer three times, and incubated for 45 minutes with goat anti-mouse PE conjugated antibody (Jackson Immunoresearch Laboratories). Cells were washed three times with FACS buffer, resuspended in $300 \mu$ ï of FACS buffer and
analyzed using a Beckman Coulter Cytomics FC 500 FACS instrument. Percent binding as compared to murine IgG control is shown in Table 8.

Table 8

| Anibody | 1\%\%\% cell sumface binding | 11 $29 \%$ cell surface binding |
| :---: | :---: | :---: |
| 07 F 01 | 99.29 | 99.08 |
| 17F06 | 99.08 | 99.00 |
| 29B06 | 99.06 | 99.04 |
| 18H09 | 99.03 | 98.33 |
| 12B11 | 94.52 | 88.64 |
| mIgG | 5.50 | 5.62 |

[0195] The results in Table 8 demonstrate that antibodies 07F01, 29B06, 17F06, 18H09, and 12B 11 bind both wild-type RON and the delta 160 RON variant expressed on the surface of cells.

## Example 7: Receptor Internalization

[0196] Antibody-stimulated receptor internalization was measured using FACS. PC3 cells were used to measure antibody-stimulated internalization of the wild-type RON receptor. HT29 cells were used for the delta 160 RON receptor variant. Antibodies were first conjugated with R-Phycocerthrin (Prozyme cat. No. PJ31K). All cells were washed with PBS and treated with CytoQ Antibody diluent and FC receptor block (Innovex). Cells were incubated with the antibodies ( $10 \mu \mathrm{~g} / \mathrm{ml}$ ) for 2 hours at $37^{\circ} \mathrm{C}$ or at $4^{\circ} \mathrm{C}$. The cells were transferred to $4^{\circ} \mathrm{C}$, washed with an acidic solution ( $0.5 \mathrm{M} \mathrm{NaCl}, 0.18 \mathrm{M}$ Acetic Acid, $0.5 \% \mathrm{Na}$ azide) to strip off the antibody remaining on the cell surface, and fixed using BD cytofix/cytoperm Plus kit (BD Biosciences, cat. No. 555028) to measure antibodies retained intracellularly due to internalization. At $37^{\circ} \mathrm{C}$, cells can undergo antibody-mediated receptor internalization, and the process is inhibited at low temperature of $4^{\circ} \mathrm{C}$, thus serving as a baseline (no internalization). The cells were analyzed using a Beckman Coulter Cytomics FC 500 FACS instrument. A lowered anti-RON median fluorescent intensity (MFI) and a left shift of the histograms at $4^{\circ} \mathrm{C}$ compared to that obtained at $37^{\circ} \mathrm{C}$ indicate antibody-induced receptor internalization. Receptor internalization was quantified by subtracting MFI at $4^{\circ} \mathrm{C}$ from that at $37^{\circ} \mathrm{C}$. Results are summarized in Table 9.

Table 9

| Mullorly |  |  4 (in 11129 ells |
| :---: | :---: | :---: |
| mIgG control | -0.15 | -0.07 |
| 29B06 | 0.49 | 0.00 |
| 07 F 01 | 0.21 | 0.22 |
| 12B11 | 0.48 | 0.81 |

[0197] These results demonstrate that antibodies, 29B06, 07F01 and 12B11 induce receptor internalization in PC-3 cells expressing wild-type RON. Only 07F01 and 12B11 induce receptor internalization in HT-29 cells expressing delta 160 RON variant.

## Example 8: Inhibition of MSP-RON Binding

[0198] Antibodies 07F01, 12B 11, 17F06, 18H09, and 29B06 were tested for inhibition of MSP binding to hRON SEMA + PSI, as measured by electrochemiluminescence (ECL) assay as described in Example 3. The antibodies (concentration range: $0.006-10 \mu \mathrm{~g} / \mathrm{mL}$ ) were incubated for 45 minutes at room temperature.
[0199] The MSP-hRON binding interaction was inhibited by antibodies 07F01, 18H06, and 29B06, but not by antibodies 17F06 and 12B 11 (FIG. 6). The IC50 and maximum percent inhibition values for the antibodies (IgGl) are shown in Table 10.

Table 10

|  | $1 \text { Mथ. 川M }$ |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Muluely | average | Stillet | Average | Stal ler. | II |
| 07F01 | 0.26 | 0.05 | 88.3 | 2.1 | 3 |
| 18H09 | 0.91 | 0.15 | 86.9 | 6.7 | 3 |
| 29B06 | 1.11 | 0.06 | 87.6 | 4.7 | 3 |
| 12B11 | N/A | N/A | 44.8 | 20 | 3 |
| 17 F 06 | N/A | N/A | 7.9 | 11.2 | 2 |

[0200] The results in Table 10 demonstrate that antibodies 07F01, 18H09 and 29B06 block MSP binding to hRON SEMA + PSI, while antibodies 12B11 and 17F06 do not.

## Example 9: Inhibition of downstream signaling by anti-RON antibodies

[0201] Antibodies 07F01, 12B 11, 17F06, 18H09, and 29B06 were tested for inhibition of MSP-dependent phosphorylation of ERK, a RON downstream signaling molecule using the cell-based assay described in Example 3. The antibodies (concentration range: 0.006-10 $\mu \mathrm{g} / \mathrm{mL}$ ) in RPMI were added to the cells and incubated for one hour at $37^{\circ} \mathrm{C}$.
[0202] Dose-dependent inhibition of ERK phosphorylation by antibodies 07F01, 12B 11, 17F06, 18H09, and 29B06 is shown in Table 11 and FIG. 7.

Table 11

| Antiboll | Mean I( 50 (nM) | Sth Der | M |
| :---: | :---: | :---: | :---: |
| 07F01 | 0.07 | 0.02 | 3 |
| 18H09 | 0.71 | 0.36 | 3 |
| 29B06 | 0.44 | 0.27 | 3 |
| 12B11 | 5.91 | 5.92 | 3 |
| 17F06 | 0.96 | 0.4 | 3 |

[0203] The results in Table 11 and FIG. 7 demonstrate that antibodies 07F01, 18H09, 29B06, 12B11 and 17F06 inhibit MSP-induced ERK phosphorylation in T47D breast cancer cell line, even though 12B 11 and 17F06 do not effectively block MSP binding to RON (see Examples 3 and 8).

## Example 10: Inhibition of MSP-Dependent Cell Migration

[0204] Antibodies 07F01, 18H09, 29B06, 12B 11 and 17F06 were tested for inhibition of MSP-dependent cell migration. HPAF-II pancreatic cancer cells (ATCC) were incubated overnight under low serum conditions ( $1 \%$ FBS, MEM). Cells were trypsinized, counted, and placed at a concentration of $50,000 /$ well in $45 \mu$ ï of $1 \%$ FBS/MEM in the upper chamber of a BD 96-well FluoroBlok ${ }^{\mathrm{TM}}$ plate (Becton Dickinson). Antibodies were added at a concentration of $2 \mu \mathrm{~g} / \mathrm{ml}$, and cells were incubated for 2 hours. The bottom chamber contained $1 \%$ FBS MEM (200 $\mu \mathrm{i})$ and 1 nM MSP, and cells were incubated for 24 hours. The number of migrated cells was determined by the addition of Calcien Dye at $4 \mu \mathrm{~g} / \mathrm{ml}$ final concentration to the bottom chamber, followed by a one-hour incubation. Fluorescence intensity was measured using a Wallace 1420 instrument (Perkin Elmer). Baseline fluorescent measurements were done in the absence of MSP. Percent inhibition was determined by comparing antibody-treated and antibody-untreated samples to the baseline using the following formula: 100-(anti-RON antibody treated-baseline)/(control hulgG treated-baseline)*100. Results on inhibition of MSPinduced HPAFII cell migration by antibodies 07F01, 18H09, 29B06, 12B11, and 17F06 are summarized in Table 12 and FIG. 8.

Table 12

| Minlood, (2 yemml) | Percenilinlibilion |
| :---: | :---: |
| 07 F 01 | 95.63 |
| 29B06 | 96.79 |
| 17F06 | 70.74 |
| 18H09 | 106.96 |
| 12B11 | 98.93 |

[0205] The results in Table 12 demonstrate that antibodies 07F01, 18H09, 29B06, 12B 11 and 17F06 inhibit MSP-dependent cell migration in HPAF-II pancreatic cancer cell lines, even though 12B 11 and 17F06 do not effectively block MSP binding to RON.

## Example 11: Inhibition of Growth of Wild-Type RON-Dependent Tumor Model

[0206] Inhibition of tumor growth was tested in a directed complementation model of wildtype RON-driven tumor growth. "Directed complementation" tumors were obtained as described in Robinson et al., U.S. Patent No. 7,556,796. A cDNA encoding wild-type human RON was introduced into BH3 tumor cells by retroviral transfer. Transfected tumor cells were then implanted subcutaneously into recipient mice. Growth of the BH3 tumors was dependent on expression of an inducible HER2 gene, which was not induced. Therefore, tumors would grow only if the RON gene functionally complemented the uninduced HER2 gene. Growth of the directed complementation tumors was observed. Primary tumors were propagated in vivo to generate sufficient tumor material for drug efficacy studies. Quality control for the directed complemented tumors included RT-PCR for RON expression and immunohistochemistry (IHC) for protein expression. The tumors were stored as frozen archival aliquots of approximately $1.5 \times 10^{5}$ cells/vial. These tumors were thawed, washed once, resuspended in HBS+matrigel and injected subcutaneously. Tumor measurements were taken twice weekly using vernier calipers. Tumor volume was calculated using the formula: width x width x length $/ 2$. When tumors reached approximately $150 \mathrm{~mm}^{3}$, the mice were randomized into five groups of ten mice each. Each group (ten mice each) received one of the following antibody treatments: $07 \mathrm{~F} 01,29 \mathrm{~B} 06,12 \mathrm{~B} 11$, or 18 H 09 , or murine IgG control, all at $20 \mathrm{mg} / \mathrm{kg}$. Treatment was administered by intra-peritoneal injection, twice weekly, for two weeks. Antibodies 29B06 and 07F01 resulted in tumor growth inhibition ("TGI") greater than 50\% ( $\mathrm{p}<0.001$ ), while antibodies 18 H 09 and 12B11 exhibited TGI of $25 \%$ and $29 \%$, respectively (FIG. 9). All treatments were well-tolerated with no significant loss in body weight.
[0207] Pharmacodynamic changes in RON receptor levels after 29B06 and 07F01 treatment were evaluated. Tumors were treated with $20 \mathrm{mg} / \mathrm{kg}$ of the following antibodies: mlgG (control), 29B06 or 07F01 and tumors were harvested at 24 or 48 hours. After harvest, the tumors were lysed in standard RIPA buffer (Boston Bioproducts, cat. No. BP-1 15) containing protease inhibitors (Roche, catalog No. 04693159001) and phosphatase inhibitors I and II (Sigma, cat. Nos. P2350 and P5726). Lysates were cleared and protein concentration was measured. A Western blot for total RON was done using a polyclonal anti-RON antibody (Santa Cruz, cat. No. sc-322). The Western blot analysis showed that antibody 29B06 induced receptor degradation in vivo in RON-DC xenograft at 24 hours, and to a greater extent at 48 hours.

## Example 12: Inhibition of Growth of Delta 160 RON-Driven Tumor Model

[0208] Inhibition of tumor growth by the antibodies was tested in a directed complementation model of delta 160 RON-driven tumor growth. The model was obtained as described in Example 11, except that the transfected cDNA encoded human delta 160 (oncogenic) form of RON. Growth of the directed complementation tumors was observed. Primary tumors were propagated in vivo to generate sufficient tumor material for drug efficacy studies. Quality control for the directed complimented tumors included RT-PCR for RON expression and IHC for protein expression. The tumors were stored as frozen archival aliquots of approximately $1.5 \times 10^{5}$ cells/vial. These tumors were thawed, washed once, resuspended in HBS plus matrigel, and injected subcutaneously. Tumor measurements were taken twice weekly. When tumors reached approximately $150 \mathrm{~mm}^{3}$, the mice were randomized into five groups of ten mice each. Each group (ten mice per group) received one of the following treatments: murine IgG control, $07 \mathrm{~F} 01,29 \mathrm{~B} 06,12 \mathrm{~B} 11,17 \mathrm{~F} 06$, and 18 H 09 , all at $20 \mathrm{mg} / \mathrm{kg}$. Treatment was administered by intra-peritoneal injection, twice weekly, for two weeks. Each treatment group showed similar tumor growth inhibition of greater than $60 \%$ ( $\mathrm{p}<0.001$ ) except for 18 H 09 (TGI 54\%) as shown in FIG. 10. All treatments were well-tolerated, with no significant loss in body weight.

## Example 13: Inhibition of Growth of NCI-H358 Lung Xenograft Tumor Model

[0209] Inhibition of tumor growth by the 29B06 antibody was tested in an NCI-H358 lung xenograft model. The NCI-H358 cells were grown in culture at $37^{\circ} \mathrm{C}$ in an atmosphere containing $5 \% \mathrm{C}_{2}$, using RMPI medium (Invitrogen) containing $10 \%$ FBS. Cells were inoculated subcutaneously into the flank of 8-week old female CB. 17 SCID mice with $5 \times 10^{6}$
cells per mouse in $50 \%$ matrigel. Tumor measurements were taken twice weekly. When tumors reached approximately $150 \mathrm{~mm}^{3}$, the mice were randomized into two groups of ten mice each. Each group received one of the following treatments: murine IgG control or 29B06 at $40 \mathrm{mg} / \mathrm{kg}$. Treatment was administered by intra-peritoneal injection three times per week, for three weeks. Antibody 29B06 treatment resulted in tumor growth inhibition of 70\% ( $\mathbf{p}<0.001$ ) (FIG. 11). Treatment was well-tolerated, with no significant loss in body weight.

## Example 14: Humanization of Anti-RON Antibodies

## A. Construction of Humanized and Chimeric Anti-RON Antibodies

[0210] This Example describes the humanization of two murine antibodies, designated 07F01 and 29B06, and the characterization of the resulting humanized antibodies. The humanized anti-RON antibodies were designed using the SUPERHUMANIZATION ${ }^{T M}$ method (Cephalon, Inc. (Arana Therapeutics Ltd.) and Hwang, W.Y. et al. (2005) METHODS 36:3542), the CDR grafting method with back mutations (some human framework residues were changed to murine residues) (See e.g., U.S. Patent Nos. 5,530,101; 5,693,761; 5,693,762; 5,585,089; 6,180,370; 7,022,500), or the HUMAN ENGINEERING ${ }^{\mathrm{TM}}$ method (Studnicka et al, Protein Eng. 1994 Jun;7(6):805-14; also see, e.g., PCT Publication No. WO 93/11794 and U.S. Patent Nos. $5,766,886 ; 5,770,196 ; 5,821,123$; and $5,869,619$ ). With the exception of heavy chain CDR1, the Kabat CDR definitions were used for CDR grafting onto human frameworks (SUPERHUMANIZATION ${ }^{\mathrm{TM}}$ and CDR grafting with back mutations). In some cases, a combination of Kabat and Chothia definitions were used for grafting heavy CDR1. In some cases, CDR residues (Kabat or Chothia definitions) were changed to human residues to increase humanness. Models of the murine antibodies were created using the SWISS-MODEL web server (swissmodel.expasy.org). Predicted residue contacts were determined using the Contact Map Analysis web server (ligin.weizmann.ac.il/cma/), and residue surface accessibility was determined using the Accessible Molecular Surface web server (swift.cmbi.ru.nl/servers/html/accessres.html). Residues were selected for back mutation based on predicted surface accessibility, contact with CDR residues, and involvement in the interface between heavy and light chains. Additionally, a cysteine residue present in the heavy chain CDR3 of 07F01 was changed to serine to prevent potential aggregation, and in some examples, a predicted N -linked glycosylation consensus site (N-X-S/T) in 07F01 heavy CDR2 (e.g., N58, Y59, T60) was mutated (e.g., T60A) to prevent any possible glycosylation. The designed amino acid sequences were converted to codon-optimized DNA sequences and synthesized by DNA2.0, Inc. to include (in the following order): 5' Hindlll restriction site, Kozak consensus
sequence, amino terminal signal sequence, humanized variable region, human $\operatorname{IgGl}$ or Kappa constant region, stop codon, and a 3' EcoRI restriction site.
[0211] The anti-RON antibody chains humanized according to the SUPERHUMANIZATION ${ }^{\mathrm{TM}}$ method, as described herein, are designated with the prefix "Sh" before the antibody chain name. The anti-RON antibody chains humanized by the CDR grafting method with back mutations, as described herein, are designated with the prefix "Hu" before the antibody chain name. The anti-RON antibody chains humanized by the HUMAN ENGINEERING ${ }^{\mathrm{TM}}$ method, as described herein, are designated with the prefix "HE" before the antibody chain name.
[0212] The anti-RON antibody heavy chain 07F01 was humanized according to the SUPERHUMANIZATION ${ }^{\text {TM }}$ method. Human germline sequence IGHV3-48*01 (also referred to herein as Hv3-48) was selected as the human heavy chain framework. In some embodiments, the human Hv3-48 heavy chain framework sequence was mutated at amino acid position 28 (e.g., D28T). Amino acid numbering is based on the Kabat numbering system.
[0213] The anti-RON antibody light chain 07F01 was humanized according to the HUMAN ENGINEERING ${ }^{\text {TM }}$ method. Human germline sequence IGKV 1-9*01 was selected as the human light chain framework.
[0214] The anti-RON antibody heavy chain 29B06 was humanized by the CDR grafting method with back mutations. Human germline sequence IGHV4-59 *01 (also referred to herein as Hv4-59) was selected as the human framework. The human framework was backmutated at amino acid positions $27,30,39,44,47,48,67,71$, and 78 to the murine sequence when the Kabat CDR definitions were used. The back-mutated human Hv4-59 framework sequence was further mutated to comprise at least one amino acid substitution at positions 27, 30, 48, 67, and 78. Amino acid substitutions in the back-mutated Hv4-59 framework sequence (e.g., amino acid substitution from a murine residue to a human residue, e.g., a human residue found in IGHV4-59) may be selected from the group consisting of D27G, T30S, M48I, I67V and Y 78 F . Amino acid numbering is based on the Kabat numbering system.
[0215] The anti-RON antibody light chain 29B06 was humanized according to the SUPERHUMANIZATION ${ }^{\text {TM }}$ method. Human germline sequence IGKV2-28*01 was selected as the human light chain framework.
[0216] Chimeric (murine variable region and human constant region) 07F01 and 29B06 heavy (human IgGl) and light (human Kappa) chains were also constructed. The cysteine residue present in the heavy chain CDR3 of 07F01 was changed to serine to prevent potential aggregation. To generate chimeric antibodies, the murine variable regions were fused to the human constant region using overlap extension PCR, including (in the following order): 5' Hindlll restriction site, Kozak consensus sequence, amino terminal signal sequence, mouse variable region, human IgGl or Kappa constant region, stop codon, and 3' EcoRI restriction site.
[0217] The humanized and chimeric heavy chains were subcloned into pEE6.4 (Lonza, Basel, Switzerland) via Hindlll and EcoRI sites using In-Fusion ${ }^{\text {TM }}$ PCR cloning (Clontech, Mountain View, CA). The humanized and chimeric Kappa light chains were subcloned into pEE14.4 (Lonza) via Hindlll and EcoRI sites using In-Fusion ${ }^{\mathrm{TM}}$ PCR cloning.
[0218] Humanized antibody chains or chimeric antibody chains were transiently transfected into 293T cells to produce antibody. Antibody was either purified or used in cell culture media supernatant for subsequent in vitro analysis. Binding of the chimeric and humanized antibodies to human RON was measured as described below. The results are summarized in Table 20.
[0219] Additionally, some humanized antibody heavy and light chain combinations were stably expressed in CHOK1SV cells using the GS System ${ }^{\mathrm{TM}}$ (Lonza) in order to produce large quantities of purified humanized antibody. A single expression vector was constructed by combining pEE6.4 and pEE14.4 based vectors. First, pEE6.4 containing full length humanized heavy chain cDNA was digested with NotI and Sail to isolate the hCMV-MIE promoter + full length humanized heavy chain cDNA + SV40 poly A fragment. This fragment was inserted into the pEE14.4 vector already containing full length humanized light chain cDNA via Notl/Sall sites, thus creating an expression vector that simultaneously expresses heavy and light chains. The combined heavy and light chain vector was linearized and transfected into CHOK1SV cells. Stable clones were selected in the presence of methionine sulfoximine.
[0220] Each of the possible combinations of the humanized 07F01 immunoglobulin heavy chain and immunoglobulin light chain variable regions are set forth below in Table 13.

## Table 13

| Ihght Chan Variale Region | Meav! Cham Manble Region |
| :---: | :---: |
| HE L 07F01 Kv1-9 Light Variable (SEQ ID NO: 139) | Sh07F01 Hv3-48 Heavy Variable (SEQ ID NO: 135) |
| HE L 07F01 Kv1-9 Light Variable (SEQ ID NO: 139) | Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Variable (SEQ ID NO: 137) |
| Sh07F01 Kv1-9 F1 Light Variable (SEQ ID NO: 141) | Sh07F01 Hv3-48 Heavy Variable (SEQ ID NO: 135) |
| Sh07F01 Kv1-9 F1 Light Variable (SEQ ID NO: 141) | Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Variable (SEQ ID NO: 137) |

[0221] Each of the possible combinations of the humanized 29B06 immunoglobulin heavy chain and immunoglobulin light chain variable regions are set forth below in Table 14.

| İghi Cham Manble Region | Heay Chan Yarable Region |
| :---: | :---: |
| Sh29B06 Kv2-28 Kappa Variable (SEQ ID NO: 149) | Sh29B06 Hv4-59 Heavy Variable (SEQ ID NO: 143) |
| Sh29B06_Kv2-28 Kappa Variable <br> (SEQ ID NO: 149) | Hu29B06 Hv4-59 Heavy Variable (SEQ ID NO: 145) |
| Sh29B06 Kv2-28 Kappa Variable (SEQ ID NO: 149) | Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Variable (SEQ ID NO: 147) |

[0222] The nucleic acid sequences encoding and the protein sequences defining variable regions of the humanized 07F01 and 29B06 antibodies are summarized below (amino terminal signal peptide sequences are not shown). Sequences of the modified chimeric 07F01 heavy variable region in which the cysteine in CDR3 is changed to serine are also summarized below. CDR sequences (Kabat definition) are shown in bold and are underlined in the amino acid sequences.
[0223] Nucleic Acid Sequence Encoding the Chimeric 07F01 C102S Heavy Chain Variable Region (SEQ ID NO: 132)

```
    1 ~ g a g g t g a a g c ~ t t c t c g a g t c ~ t g g a g g t g g c ~ c t g g t g c a g c ~ c g g g t g g a t c ~ c c t g a a a c t c
6 1 ~ t c c t g t g c a g ~ c c t c a g g a t t ~ c g a t t t t a g t ~ a g a c a c t g g a ~ t g a g t t g g g t ~ c c g g c t g g c t ~
121 ccagggaaag ggctagaatg gatcgcagaa attaatccag atagcagaac gataaactat
1 8 1 ~ a c g c c a t c t c ~ t a a a g g a g a a ~ a t t c a t c a t c ~ t c c a g a g a c a ~ a c g c c a a a a a ~ t t c g c t g t t t ~
241 ctgcaaatga acagagtgag atctgaggac acagcccttt attactgtgc aagacgggta
3 0 1 ~ a g a a t t c a t t ~ a c t a c g g c g c ~ t a t g g a c a g c ~ t g g g g t c a a g ~ g a a c c t c a g t ~ c a c c g t c t c c
361 tea
```

[0224] Protein Sequence Defining the Chimeric 07F01 C102S Heavy Chain Variable
Region (SEQ ID NO: 133)

```
    1 evkllesggg lvqpggslkl scaasgfdfs rhwmswvrla pgkglewiae inpdsrtiny
6 1 ~ t p s l k e k f i i i ~ s r d n a k n s l f ~ l q m n r v r s e d ~ t a l y y c a r r v ~ r i h y y g a m d s ~ w g q g t s v t v s
121 s
```

[0225] Nucleic Acid Sequence Encoding the Sh07F01 Hv3-48 Heavy Chain Variable
Region (SEQ ID NO: 134)
1 gaggttcagc tggtagaatc cggaggaggg ttggtccaac ctggtggatc actcagactt
61 tcatgcgccg ccagcggctt tgacttctca cgacattgga tgagctgggt ccggcaggct
121 ccaggcaagg gcctcgagtg ggttagcgag atcaatccag acagcagaac cattaactat
181 acacccagtc tgaaggagcg gttcaccata agccgtgata atgccaagaa ctccctgtac
241 ttgcagatga actccttgcg cgctgaagat acagctgtgt actattgtgc aaggcgcgtg
301 cgaatccact attacggggc aatggattct tggggccagg gtactaccgt gactgtgagt
361 tct
[0226] Protein Sequence Defining the Sh07F01 Hv3-48 Heavy Chain Variable Region
(SEQ ID NO: 135)
1 evqlvesggg lvqpggslrl scaasgfdfs rhwmswvrqa pgkglewvse inpdsrtiny
61 tpslkerfti srdnaknsly lqmnslraed tavyycarrv rihyygamds wgqgttvtvs
121 S
[0227] Nucleic Acid Sequence Encoding the Sh07F01 Hv3-48 D28T T60A L63V E65G
Heavy Chain Variable Region (SEQ ID NO: 136)
1 gaggttcagc tggtagaatc cggaggaggg ttggtccaac ctggtggatc actcagactt
61 tcatgcgccg ccagcggctt taccttctca cgacattgga tgagctgggt ccggcaggct
121 ccaggcaagg gcctcgagtg ggttagcgag atcaatccag acagcagaac cattaactat
181 gcccccagtg tgaagggccg gttcaccata agccgtgata atgccaagaa ctccctgtac
241 ttgcagatga actccttgcg cgctgaagat acagctgtgt actattgtgc aaggcgcgtg
301 cgaatccact attacggggc aatggattct tggggccagg gtactaccgt gactgtgagt
361 tct
[0228] Protein Sequence Defining the Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Chain Variable Region (SEQ ID NO: 137)

```
evqlvesggg lvqpggslrl scaasgftfs rhwmswvrqa pgkglewvse inpdsrtiny
6 1 ~ a p s v k g r f t i ~ s r d n a k n s l y ~ l q m n s l r a e d ~ t a v y y c a r r v ~ r i h y y g a m d s ~ w g q g t t v t v s
1 2 1 ~ s
```

[0229] Nucleic Acid Sequence Encoding the HE L 07F01 Kyl-9 Kappa Chain Variable
Region (SEQ ID NO: 138)

```
    1 ~ g a t a t c c a g t ~ t g a c t c a g t c ~ t c a g t c c t t t ~ g t g a g t a c a t ~ c a g t g g g c g a ~ c a g g g t c a c c
6 1 ~ g t g a c c t g c c ~ g a g c a t c a c a ~ g a a c g t t g g a ~ a g c t c t c t t g ~ t c t g g t a t c a ~ g c a a a a g c c t
1 2 1 ~ g g g a a g a g c c ~ c c a a a a c c c t ~ c a t c t a t t c t ~ g c t t c c t t t c ~ t g t a c t c c g g ~ c g t a c c a a g t ~
1 8 1 ~ a g a t t c t c t g ~ g t a g c g g a t c ~ c g g g a c a g a g ~ t t c a c t c t c a ~ c a a t t a g c a g ~ t g t g c a g c c t
```

```
    -57 -
2 4 1 \text { gaggatttcg ccgactactt ctgtcagcaa tacaataact atcccctgac ttttggtggc}
3 0 1 ~ g g c a c c a a a g ~ t g g a a a t c a a ~ g \
```

[0230] Protein Sequence Defining the HE L 07F01 Kyl-9 Kappa Chain Variable Region
(SEQ ID NO: 139)

```
1 diqltqsqsf vstsvgdrvt vtcrasqnvg sslvwyqqkp gkspktliys asflysgvps
6 1 ~ r f s g s g s g t e ~ f t l t i s s v q p ~ e d f a d y f c q c j ~ y n n y p l t ~ f g g ~ g t k v e i k ,
```

[0231] Nucleic Acid Sequence Encoding the sh07F01 Kyl-9 F1 Kappa Chain Variable
Region (SEQ ID NO: 140)

| 1 | gacattcagc | tgactcagtc | gccgtcgttt | ttgtcggcgt | ccgtgggtga | cagagtgact |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 61 | atcacatgtc | gcgcttcgca | aaacgtcgga | tcatcgcttg | tgtggtatca | gcagaaaccc |
| 121 | ggtaaagccc | ctaagaccot | catctattca | gcgtcatttc | tgtatagcgg | ggtcccctca |
| 181 | cggttcagcg | gatccggctc | cgggaccgag | ttcacactca | ctatttcgag | cttgcagccg |
| 241 | gaagattttg | caacgtacta | ctgccagcaa | tacaataact | acccactcac | gttcggaggg |
| 301 | ggaacgaagg | tagagatcaa | g |  |  |  |

[0232] Protein Sequence Defining the sh07F01 Kyl-9 F1 Kappa Chain Variable Region
(SEQ ID NO: 141)

```
1 diqltqspsf lsasvgdrvt itcrasqnvg sslvwyqqkp gkapktliys asflysgvps
61 rfsgsgsgte ftltisslqp edfatyycqcj ynnyplt fqg gtkveik
```

[0233] Nucleic Acid Sequence Encoding the Sh29B06 Hv4-59 Heavy Chain Variable
Region (SEQ ID NO: 142)
[0234] Protein Sequence Defining the Sh29B06 Hv4-59 Heavy Chain Variable Region
(SEQ ID NO: 143)

[0235] Nucleic Acid Sequence Encoding the Hu29B06 Hv4-59 Heavy Chain Variable
Region (SEQ ID NO: 144)
1 caagttcagc tgcaagaatc cggaccagga ttggtcaaac ccagcgaaac actctctctt
61 acatgcaccg tgagcggcga ctctatcacc tcagggtatt ggaattggat tcggaaaccc
121 ccaggcaaga agctcgagta catgggttac atcagttaca gcgggaaaac ctactataac
181 cccagtctga agagcagaat caccataagc cgtgatacct ctaagaacca gtactccctg
241 aagctgagtt ccgtaacagc agctgataca gctgtgtact attgtgcaag gagtaagtat
301 gactacgcaa tggactattg gggccagggt actcttgtga ctgtgagttc t
[0236] Protein Sequence Defining the Hu29B06 Hv4-59 Heavy Chain Variable Region (SEQ ID NO: 145)

1 qvqlqesgpg lvkpsetlsl tctvsgdsit sgywnwirkp pgkkleymgy_ isysgktyyn 61 pslksritis rdtsknqysl klssvtaadt avyycarsky dyamdywggg tlvtvss
[0237] Nucleic Acid Sequence Encoding the Hu29B06 D27G T30S M48I I67V Y78F
Heavy Chain Variable Region (SEQ ID NO: 146)

|  |  | cggaccagga | ttggtcaaac | c |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 61 | tgagcggtgg | cagcatatcc | tccggttatt | ggaactggat | ca |
| 121 | agctcgagta | cattggctac | atcagctata | gcgggaaaac |  |
| 181 | agagccgagt | gaccataagc | agggatacaa | gtaagaacca | gttctccotg |
|  | ccgtgaccgc | cgctgataca | gctgtgtact | attgtgcaag | gtcaaagtat |
| 301 | tggacta | gggccagggt | actctggtga | ctgtgagttc | t |

[0238] Protein Sequence Defining the Hu29B06 D27G T30S M48I I67V Y78F Heavy
Chain Variable Region (SEQ ID NO: 147)

> 1 qvqlqesgpg lvkpsetlsl tctvsggsis sgywnwirkp pgkkleyigy_ isysgktyyn
> 61 pslksrvtis rdtsknqfsl klssvtaadt avyycarsky dyamdywgqg tlvtvss
[0239] Nucleic Acid Sequence Encoding the Sh29B06 Kv2-28 Kappa Chain Variable Region (SEQ ID NO: 148)

| 1 | gatatcgtta | tgacccagag cccacttagt ttgcctgtta ctcctggcga gcctgccagt |  |  |  |  |
| ---: | :--- | :--- | :--- | :--- | :--- | :--- |
| 61 | atttcttgcc | gtgctagcga | aatcgtggat aactttggta tatcattcat gaattggtat |  |  |  |
| 121 | ctccaaaaac | ctggccaaag | cccccagctc cttatctacg ccgctagcaa ccaggggtcc |  |  |  |
| 181 | ggggtacctg | atagattttc | aggcagcggc tctggaaccg acttcacact gaagatttcc |  |  |  |
| 241 | cgggtggagg | ccgaggacgt | gggcgtgtac tattgtcaac agtccaagga | agtccctccc |  |  |
| 301 | actttcggcg | gtgggacaaa | ggttgagatt | aag |  |  |

[0240] Protein Sequence Defining the Sh29B06 Kv2-28 Kappa Chain Variable Region (SEQ ID NO: 149)

1 divmtqspls lpvtpgepas iscraseivd nfgisfmnwy lqkpgqspql liyaasnggs 61 gvpdrfsgsg sgtdftlkis rveaedvgvy ycqqskevpp tfgggtkvei k
[0241] The amino acid sequences defining the immunoglobulin heavy chain variable regions for the antibodies produced in Example 14 are aligned in FIGs. 12A and 12B. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. $\mathrm{CDR}_{1}$, $\mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ (Kabat definition) are identified by boxes. FIGs. 13A and 13B show an alignment of the separate $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each of the variable region sequences shown in FIGs. 12A and 12B, respectively.
[0242] The amino acid sequences defining the immunoglobulin light chain variable regions for the antibodies in Example 14 are aligned in FIG. 14A and 14B. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$ and $\mathrm{CDR}_{3}$ are identified by boxes. FIGs. 15A and 15B show an alignment of the separate $\mathrm{CDR}_{1}, \mathrm{CDR}_{2}$, and $\mathrm{CDR}_{3}$ sequences for each of the variable region sequences shown in FIGs. 14A and 14B, respectively.
[0243] Table 15 is a concordance chart showing the SEQ ID NO. of each sequence discussed in this Example.

Table 15

| SEO. II) NO. | Nucleic Acid or IVolein |
| :---: | :---: |
| 132 | Chime ric 07F01 C102S Heavy Chain Variable Region—nucleic acid |
| 133 | Chime ric 07F01 C102S Heavy Chain Variable Region-protein |
| 5 | Chime ric 07F01 C102S Heavy Chain CDR 1 |
| 6 | Chime ric 07F01 C102S Heavy Chain CDR 2 |
| 123 | Chime ric 07F01 C102S Heavy Chain CDR 3 |
| 134 | Sh07F0 1 Hv3-48 Heavy Chain Variable Region-nucleic acid |
| 135 | Sh07F0 1 Hv3-48 Heavy Chain Variable Region - protein |
| 5 | Sh07F0 1 Hv3-48 Heavy Chain CDR 1 |
| 6 | Sh07F0 1 Hv3-48 Heavy Chain CDR 2 |
| 123 | Sh07F0 1 Hv3-48 Heavy Chain CDR 3 |
| 136 | Sh07F0 1 Hv3-48 D28T T60A L63V E65G Heavy Chain Variable Region—nucleic acid |
| 137 | Sh07F0 1 Hv3-48 D28T T60A L63V E65G Heavy Chain Variable Region-protein |
| 5 | Sh07F0 1 Hv3-48 D28T T60A L63V E65G Heavy Chain CDR ${ }_{1}$ |
| 122 | Sh07F0 1 Hv3-48 D28T T60A L63V E65G Heavy Chain CDR ${ }_{2}$ |
| 123 | Sh07F0 1 Hv3-48 D28T T60A L63V E65G Heavy Chain CDR ${ }_{3}$ |
| 138 | HE L (37F01 Kvl-9 Light (kappa) Chain Variable Regionnucleic: acid |
| 139 | HE L (37F01 Kvl-9 Light (kappa) Chain Variable Regionproteir ${ }_{1}$ |
| 130 | HE L (37F01 Kvl-9 Light (kappa) Chain CDR ${ }_{1}$ |
| 131 | HE L (37F01 Kvl-9 Light (kappa) Chain CDR 2 |
| 10 | HE L (37F01 Kvl-9 Light (kappa) Chain CDR 3 |
| 140 | Sh07F0 1 Kvl-9 Fl Light (kappa) Chain Variable Regionnucleic: acid |
| 141 | Sh07F0 1 Kvl-9 Fl Light (kappa) Chain Variable Region- |
| 130 | Sh07F0 1 Kvl-9 F1 Light (kappa) Chain $\mathrm{CDR}_{1}$ |
| 131 | Sh07F0 1 Kvl-9 Fl Light (kappa) Chain CDR 2 |
| 10 | Sh07F0 1 Kvl-9 F1 Light (kappa) Chain $\mathrm{CDR}_{3}$ |


| SEO. II) NO. | Nucleic Acid or Prolein |
| :---: | :---: |
| 142 | Sh291306 Hv4-59 Heavy Chain Variable Region - nucleic acid |
| 143 | Sh291306 Hv4-59 Heavy Chain Variable Region - protein |
| 45 | Sh291306 Hv4-59 Heavy Chain CDRi |
| 46 | Sh291306 Hv4-59 Heavy Chain CDR 2 |
| 47 | Sh291306 Hv4-59 Heavy Chain CDR 3 |
| 144 | Hu29 B06 Hv4-59 Heavy Chain Variable Region - nucleic acid |
| 145 | Hu29 [B06 Hv4-59 Heavy Chain Variable Region - protein |
| 45 | Hu29 B06 Hv4-59 Heavy Chain CDRi |
| 46 | Hu29 B06 Hv4-59 Heavy Chain CDR 2 |
| 47 | Hu29 B06 Hv4-59 Heavy Chain CDR ${ }_{3}$ |
| 146 | Hu29 B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain Varia Ible Region - nucleic acid |
| 147 | Hu29 B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain Varia ble Region - protein |
| 45 | Hu29 B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain CDR] |
| 46 | Hu29 B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain $\mathrm{CDR}_{2}$ |
| 47 | Hu29 B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain CDR; |
| 148 | Sh291306 Kv2-28 Light (kappa) Chain Variable Region nucle tc acid |
| 149 | Sh291306 Kv2-28 Light (kappa) Chain Variable Region protei n |
| 48 | Sh291306 Kv2-28 Light (kappa) Chain CDRi |
| 49 | Sh291306 Kv2-28 Light (kappa) Chain CDR 2 |
| 50 | Sh291306 Kv2-28 Light (kappa) Chain CDR 3 |

[0244] Humanized monoclonal antibody heavy chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 16.

Table 16

| kibat |  |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { RHWMS } \\ & \text { (SEQ ID NO: 5) } \end{aligned}$ | $\begin{aligned} & \text { EINPDSRTINYTPSLKE } \\ & \text { (SEQ ID NO: 6) } \end{aligned}$ | $\begin{aligned} & \text { RVRIHYYGAMDC } \\ & \text { (SEQ ID NO: 7) } \\ & \hline \end{aligned}$ |
| $\begin{aligned} & \text { Chimeric } 07 \mathrm{~F} 01 \\ & \text { C102S } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { RHWMS } \\ & \text { (SEQ ID NO: 5) } \end{aligned}$ | EINPDSRTINYTPSLKE (SEQ ID NO: 6) | RVRIHYYGAMDS (SEQ ID NO: 123) |
| $\begin{aligned} & \text { Sh07F01 Hv3- } \\ & 48 \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { RHWMS } \\ & \text { (SEQ ID NO: 5) } \end{aligned}$ | $\begin{aligned} & \hline \text { EINPDSRTINYTPSLKE } \\ & \text { (SEQ ID NO: 6) } \\ & \hline \end{aligned}$ | RVRIHYYGAMDS (SEQ ID NO: 123) |
| Sh07F01 Hv348 D28T T60A L63V E65G | RHWMS <br> (SEQ ID NO: 5) | EINPDSRTINYAPSVKG (SEQ ID NO: 122) | RVRIHYYGAMDS (SEQ ID NO: 123) |
| 29B06 | SGYWN (SEQ ID NO: 45) | YISYSGKTYYNPSLKS (SEQ ID NO: 46) | SKYDYAMDY (SEQ ID NO: 47) |
| $\begin{aligned} & \text { Sh29B06 Hv4- } \\ & 59 \end{aligned}$ | $\begin{aligned} & \text { SGYWN } \\ & \text { (SEQ ID NO: 45) } \end{aligned}$ | YISYSGKTYYNPSLKS (SEQ ID NO: 46) | $\begin{aligned} & \text { SKYDYAMDY (SEQ } \\ & \text { ID NO: 47) } \end{aligned}$ |
| $\begin{aligned} & \text { Hu29B06 Hv4- } \\ & 59 \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { SGYWN } \\ & \text { (SEQ ID NO: 45) } \end{aligned}$ | YISYSGKTYYNPSLKS (SEQ ID NO: 46) | $\begin{aligned} & \text { SKYDYAMDY (SEQ } \\ & \text { ID NO: 47) } \end{aligned}$ |
| $\begin{aligned} & \hline \text { Hu29B06 Hv4-59 } \\ & \text { D27G T30S } \\ & \text { M48I I67V Y78F } \end{aligned}$ | SGYWN <br> (SEQ ID NO: 45) | YISYSGKTYYNPSLKS <br> (SEQ ID NO: 46) | SKYDYAMDY (SEQ <br> ID NO: 47) |
| Cholla |  |  |  |
|  | CDRI | CDR2 | SDR3 |
| 07F01 | $\begin{aligned} & \text { GFDFSRH } \\ & \text { (SEQ ID NO: 51) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { NPDSRT } \\ & \text { (SEQ ID NO: 52) } \end{aligned}$ | $\begin{aligned} & \text { RVRIHYYGAMDC } \\ & \text { (SEQ ID NO: 7) } \\ & \hline \end{aligned}$ |
| $\begin{aligned} & \text { Chimeric } 07 \mathrm{~F} 01 \\ & \text { C102S } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { GFDFSRH } \\ & \text { (SEQ ID NO: 51) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { NPDSRT } \\ & \text { (SEQ ID NO: 52) } \\ & \hline \end{aligned}$ | RVRIHYYGAMDS (SEQ ID NO: 125) |
| Sh07F01 Hv3- $48$ | $\begin{aligned} & \hline \text { GFDFSRH } \\ & \text { (SEQ ID NO: 51) } \\ & \hline \end{aligned}$ | $\begin{array}{\|l} \hline \text { NPDSRT } \\ \text { (SEQ ID NO: 52) } \\ \hline \end{array}$ | RVRIHYYGAMDS <br> (SEQ ID NO: 125) |
| Sh07F01 Hv348 D28T T60A L63V E65G | $\begin{aligned} & \hline \text { GFTFSRH } \\ & \text { (SEQ ID NO: 124) } \end{aligned}$ | $\begin{aligned} & \hline \text { NPDSRT } \\ & \text { (SEQ ID NO: 52) } \end{aligned}$ | RVRIHYYGAMDS (SEQ ID NO: 125) |
| 29B06 | $\begin{aligned} & \hline \text { GDSITSG } \\ & \text { (SEQ ID NO: 59) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \begin{array}{l} \text { SYSGK } \\ \text { (SEQ ID NO: 60) } \end{array} \\ & \hline \end{aligned}$ | SKYDYAMDY (SEQ ID NO: 47) |
| Sh29B06 Hv4- 59 | $\begin{aligned} & \hline \text { GGSISSG } \\ & \text { (SEQ ID NO: 126) } \end{aligned}$ | $\begin{aligned} & \text { SYSGK } \\ & \text { (SEQ ID NO: 60) } \end{aligned}$ | SKYDYAMDY (SEQ ID NO: 47) |
| $\begin{aligned} & \text { Hu29B06 Hv4- } \\ & 59 \end{aligned}$ | $\begin{aligned} & \hline \text { GDSITSG } \\ & \text { (SEQ ID NO: 59) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \begin{array}{l} \text { SYSGK } \\ \text { (SEQ ID NO: 60) } \end{array} \end{aligned}$ | $\begin{aligned} & \hline \text { SKYDYAMDY } \\ & \text { (SEQ ID NO: 47) } \end{aligned}$ |
| $\begin{aligned} & \text { Hu29B06 Hv4- } \\ & 59 \text { D27G T30S } \\ & \text { M48I I67V } \\ & \text { Y78F } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { GGSISSG } \\ & \text { (SEQ ID NO: 126) } \end{aligned}$ | $\begin{aligned} & \text { SYSGK } \\ & \text { (SEQ ID NO: 60) } \end{aligned}$ | SKYDYAMDY (SEQ ID NO: 47) |

Table 16 Con't

| MM11 |  |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \hline \text { GFDFSRHW } \\ & \text { (SEQ ID NO: 61) } \\ & \hline \end{aligned}$ | $\begin{array}{\|l\|} \hline \text { INPDSRTI } \\ \text { (SEQ ID NO: 62) } \\ \hline \end{array}$ | $\begin{aligned} & \text { ARRVRIHYYGAMDC } \\ & \text { (SEQ ID NO: 63) } \\ & \hline \end{aligned}$ |
| $\begin{aligned} & \text { Chimeric } 07 \mathrm{~F} 01 \\ & \mathrm{C} 102 \mathrm{~S} \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { GFDFSRHW } \\ & \text { (SEQ ID NO: 61) } \end{aligned}$ | $\begin{array}{\|l\|} \hline \text { INPDSRTI } \\ \text { (SEQ ID NO: 62) } \\ \hline \end{array}$ | ARRVRIHYYGAMDS (SEQ ID NO: 128) |
| $\begin{aligned} & \text { Sh07F01 Hv3- } \\ & 48 \end{aligned}$ | $\begin{aligned} & \text { GFDFSRHW } \\ & \text { (SEQ ID NO: 61) } \end{aligned}$ | $\begin{aligned} & \text { INPDSRTI } \\ & \text { (SEQ ID NO: 62) } \end{aligned}$ | ARRVRIHYYGAMDS (SEQ ID NO: 128) |
| Sh07F01 Hv348 D28T T60A L63V E65G | $\begin{aligned} & \hline \text { GFTFSRHW } \\ & \text { (SEQ ID NO: 127) } \end{aligned}$ | INPDSRTI (SEQ ID NO: 62) | ARRVRIHYYGAMDS (SEQ ID NO: 128) |
| 29B06 | $\begin{aligned} & \hline \text { GDSITSGY } \\ & \text { (SEQ ID NO: 73) } \\ & \hline \end{aligned}$ | $\begin{array}{\|l\|} \hline \text { ISYSGKT } \\ \text { (SEQ ID NO: 74) } \\ \hline \end{array}$ | $\begin{aligned} & \text { ARSKYDYAMDY } \\ & \text { (SEQ ID NO: 75) } \\ & \hline \end{aligned}$ |
| $\begin{aligned} & \text { Sh29B06 Hv4- } \\ & 59 \end{aligned}$ | $\begin{aligned} & \text { GGSISSGY } \\ & \text { (SEQ ID NO: 129) } \end{aligned}$ | $\begin{array}{\|l} \hline \text { ISYSGKT } \\ \text { (SEQ ID NO: 74) } \end{array}$ | $\begin{aligned} & \text { ARSKYDYAMDY } \\ & \text { (SEQ ID NO: } 75 \text { ) } \end{aligned}$ |
| $\begin{aligned} & \text { Hu29B06 Hv4- } \\ & 59 \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline \text { GDSITSGY } \\ & \text { (SEQ ID NO: 73) } \end{aligned}$ | $\begin{array}{\|l\|} \hline \text { ISYSGKT } \\ \text { (SEQ ID NO: 74) } \\ \hline \end{array}$ | ARSKYDYAMDY (SEQ ID NO: 75) |
| $\begin{aligned} & \hline \text { Hu29B06 Hv4- } \\ & 59 \text { D27G T30S } \\ & \text { M48I I67V } \\ & \text { Y78F } \end{aligned}$ | $\begin{aligned} & \hline \text { GGSISSGY } \\ & \text { (SEQ ID NO: 129) } \end{aligned}$ | $\begin{aligned} & \hline \text { ISYSGKT } \\ & \text { (SEQ ID NO: 74) } \end{aligned}$ | ARSKYDYAMDY (SEQ ID NO: 75) |

[0245] Humanized monoclonal antibody Kappa light chain CDR sequences (Kabat,
Chothia, and IMGT definitions) are shown in Table 17.
Table 17

|  | Kabav/ homba |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | KASQNVGSSLV (SEQ ID NO 8 ) (SEQ ID NO: 8) | $\begin{aligned} & \text { SASFRYS } \\ & \text { (SEQ ID NO: 9) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { QQYNNYPLT } \\ & \text { (SEQ ID NO: } 10 \text { ) } \end{aligned}$ |
| HE L 07F01 Kv1-9 | RASQNVGSSLV (SEQ ID NO: 130) | SASFLYS <br> (SEQ ID NO: 131) | QQYNNYPLT <br> (SEQ ID NO: 10) |
| Sh07F01 Kv1-9 F1 | RASQNVGSSLV (SEQ ID NO: 130) | $\begin{array}{\|l} \hline \text { SASFLYS } \\ \text { (SEQ ID NO: 131) } \\ \hline \end{array}$ | $\begin{aligned} & \text { QQYNNYPLT } \\ & \text { (SEQ ID NO: } 10 \text { ) } \end{aligned}$ |
| 29B06 | RASEIVDNFGISFMN (SEQ ID NO: 48) | $\begin{array}{\|l} \hline \text { AASNQGS } \\ \text { (SEQ ID NO: 49) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { QQSKEVPPT } \\ & \text { (SEQ ID NO: } 50 \text { ) } \end{aligned}$ |
| Sh29B06 Kv2-28 | $\begin{aligned} & \hline \text { RASEIVDNFGISFMN } \\ & \text { (SEQ ID NO: 48) } \\ & \hline \end{aligned}$ | $\begin{array}{\|l} \hline \text { AASNQGS } \\ \text { (SEQ ID NO: 49) } \\ \hline \end{array}$ | $\begin{aligned} & \hline \text { QQSKEVPPT } \\ & \text { (SEQ ID NO: 50) } \end{aligned}$ |

Table 17 Con't

|  | MMOT |  |  |
| :---: | :---: | :---: | :---: |
|  | CDR1 | CDR2 | CDR3 |
| 07F01 | $\begin{aligned} & \text { QNVGSS } \\ & \text { (SEQ ID NO: 76) } \end{aligned}$ | SAS | QQYNNYPLT <br> (SEQ ID NO: 10) |
| HE L 07F01 Kv1-9 | $\begin{aligned} & \text { QNVGSS } \\ & \text { (SEQ ID NO: 76) } \end{aligned}$ | SAS | $\begin{aligned} & \text { QQYNNYPLT } \\ & \text { (SEQ ID NO: } 10 \text { ) } \\ & \hline \end{aligned}$ |
| Sh07F01 Kv1-9 F1 | $\begin{aligned} & \hline \text { QNVGSS } \\ & \text { (SEQ ID NO: 76) } \end{aligned}$ | SAS | $\begin{aligned} & \hline \text { QQYNNYPLT } \\ & \text { (SEQ ID NO: } 10 \text { ) } \\ & \hline \end{aligned}$ |
| 29B06 | EIVDNFGISF (SEQ ID NO: 81) | AAS | $\begin{aligned} & \hline \text { QQSKEVPPT } \\ & \text { (SEQ ID NO: 50) } \\ & \hline \end{aligned}$ |
| Sh29B06 Kv2-28 | EIVDNFGISF (SEQ ID NO: 81) | AAS | QQSKEVPPT (SEQ ID NO: 50) |

[0246] To create the complete chimeric and humanized heavy or kappa chain antibody sequences, each variable sequence above is combined with its respective human constant region. For example, a complete heavy chain comprises a heavy variable sequence followed by a human IgGl heavy chain constant sequence. A complete kappa chain comprises a kappa variable sequence followed by the human kappa light chain constant sequence.
[0247] Nucleic Acid Sequence Encoding the Human IgGl Heavy Chain Constant Region (SEQ ID NO: 150)

|  | gcctcaacaa | aaggaccaag | tgtgttccca | ctcgccecta |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 61 | ggcactgcag | cactcggctg | cctcgtcaag | gattattttc | cagagccagt |  |
| 121 | tggaacagtg | gagcactcac | ttctggtgtc | catacttttc | ctgctgtcct |  |
| 181 | ggcetgtact | cactcagctc | cgtcgtgacc | gtgccatct | catctctggg |  |
| 241 | tacatctgta | atgtaaacca | caagcctagc | aatactaag | tcgataagcg | ggtgga |
| 301 | aagagctgc | acaa | cacttgtcco | ccatgccot | cccctgaact | tctgggcggt |
| 361 | cccagcgtc | ttttgttcco | accaaagcc | aaagatac | tgatgataa | tag |
| 421 | gaggtgacat | gtgttgttgt | gacgtttc | cacgaggac | cagaggtta | gttcaact |
| 481 | tacgttgatg | gagtcgaagt | acataatgct | aagaccaag | ctagagagga | gcag |
| 541 | agtacatacc | gtgtagtcag | tgttctcaca | gtgctgcacc | aagactggct | ac |
| 601 | gaatacaaat | gcaaagtgtc | caacaaagca | ctcccagccc | ctatcgagaa | gactattagt |
| 661 | aaggcaaagg | ggcagcctcg | tgaaccacag | gtgtacactc | tgccacccag | agaggaa |
| 721 | atgacaaaga | accaagtctc | attgacctgc | ctggtgaaag | gcttc | 析 |
| 781 | gccgttgagt | gggagagtaa | cggtcagcct | gagaacaat | caagacaa | ccccagtg |
| 841 | ctggatagtg | acgggtcttt | ctttctgtac | agtaagctga | ctgtggacaa | tccogctg |
| 901 | cagcagggta | acgtcttcag | ctgttccgtg | atgcacgagg | ttgcaca | ccactacacc |
|  | cagaagtcac | tgagcctgag | cccagggaag |  |  |  |

[0248] Protein Sequence Defining the Human IgGl Heavy Chain Constant Region (SEQ
ID NO: 151)

```
astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
121 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
1 8 1 ~ s t y r v v s v l t ~ v l h q d w l n g k ~ e y k c k v s n k a ~ l p a p i e k t i s ~ k a k g q p r e p q ~ v y t l p p s r e e ~
2 4 1 ~ m t k n q v s l t c ~ l v k g f y p s d i ~ a v e w e s n g q p ~ e n n y k t t p p v ~ l d s d g s f f l y ~ s k l t v d k s r w ,
301 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0249] Nucleic Acid Sequence Encoding the Human Kappa Light Chain Constant Region (used for chimeric antibodies) (SEQ ID NO: 152)

```
cgcacagtcg ccgctccctc cgtgttcatc tttccaccaa gtgatgagca actgaagtct
ggtactgctt cagtcgtgtg tctgctgaac aatttctacc ctcgagaagc caaagtccaa
tggaaggtag acaacgcact gcagtccggc aatagccaag aatcagttac cgaacaggat
tcaaaggaca gtacatattc cctgagcagc actctgaccc tgtcaaaggc cgattacgag
aaacacaagg tctatgcttg cgaagtgaca catcagggac tgtccagccc agtgacaaaa
tcttttaacc gtggggagtg t
```

[0250] Nucleic Acid Sequence Encoding the Human Kappa Light Chain Constant Region
(used for humanized antibodies) (SEQ ID NO: 153)

```
cgcacagttg ctgcccccag cgtgttcatt ttcccaccta gcgatgagca gctgaaaagc
ggtactgcct ctgtcgtatg cttgctcaac aacttttacc cacgtgaggc taaggtgcag
1 2 1 ~ t g g a a a g t g g ~ a t a a t g c a c t ~ t c a a t c t g g a ~ a a c a g t c a a g ~ a g t c c g t g a c ~ a g a a c a g g a c
1 8 1 ~ a g c a a a g a c t ~ c a a c t t a t t c ~ a c t c t c t t c c ~ a c c c t g a c t c ~ t g t c c a a g g c ~ a g a c t a t g a a ,
2 4 1 ~ a a a c a c a a g g ~ t a t a c g c c t g ~ c g a g g t t a c a ~ c a c c a g g g t t ~ t g t c t a g t c c ~ t g t c a c c a a g
3 0 1 ~ t c c t t c a a t a ~ g g g g c g a a t g ~ t ~
```

[0251] Protein Sequence Defining the Human Kappa Light Chain Constant Region (used for chimeric and humanized antibodies) (SEQ ID NO: 154)

```
1 rtvaapsvfi fppsdeqlks gtasvvclln nfypreakvq wkvdnalqsg nsqesvteqd
6 1 ~ s k d s t y s l s s ~ t l t l s k a d y e ~ k h k v y a c e v t ~ h q g l s s p v t k ~ s f n r g e c
```

[0252] The following sequences represent the actual or contemplated full length heavy and light chain sequence (i.e., containing both the variable and constant regions sequences) for each antibody described in this Example. Signal sequences for proper secretion of the antibodies (e.g., signal sequences at the 5 ' end of the DNA sequences or the amino terminal end of the protein sequences) are not shown in the full length heavy and light chain sequences disclosed herein and are not included in the final secreted protein. Also not shown are stop codons for termination of translation required at the 3 ' end of the DNA sequences. It is within ordinary skill in the art to select a signal sequence and/or a stop codon for expression of the disclosed full length IgG heavy chain and light chain sequences. It is also contemplated that the variable
region sequences can be ligated to other constant region sequences to produce active full length IgG heavy and light chains.
[0253] Nucleic Acid Sequence Encoding the Full Length Chimeric 07F01 C102S Heavy
Chain (Mouse Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO:
155)

[0254] Protein Sequence Defining the Full Length Chimeric 07F01 C102S Heavy Chain
(Mouse Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO: 156)

$$
\begin{aligned}
& \text { evkllesggg lvqpggslkl scaasgfdfs rhwmswvrla pgkglewiae inpdsrtiny } \\
& 61 \text { tpslkekfii srdnaknslf l } \\
& \begin{array}{l}
121 \text { sastkgpsvf plapssksts } \\
181 \text { sglyslssvv tvpssslgtq }
\end{array} \\
& 241 \text { gpsvflfppk } \\
& 301 \text { nstyrvvsvl tvlhqdwlng } \\
& 361 \text { emtknqvslt clvkgfypsd } \\
& 421 \text { wqqgnvfscs } \\
& \text { qmnrvrsed talyycarrv r } \\
& \text { kdyfpepvtv } \\
& \text { sntkvdkrve p } \\
& \text { shedpevkfn wyvdgvevhn } \\
& \text { alpapiekti skakgqprep } \\
& \text { k }
\end{aligned}
$$

[0255] Nucleic Acid Sequence Encoding the Full Length Chimeric 07F01 Light Chain
(Mouse Kappa Chain Variable Region and Human Kappa Constant Region) (SEQ ID NO: 157)

| 1 | gacattgtgt |
| ---: | :--- |
| 61 | gtcacctgca |
| 121 | ggtcaatctc |
| ctaaaacact | gatttactcg |
| 181 | cgcttcacag |
| 241 | gaagacttgg |
| 301 | gggaccaagc |
| 3 | tggagctgatc |

361 agtgatgagc aactgaagtc tggtactgct tcagtcgtgt gtctgctgaa caatttctac 421 cctcgagaag ccaaagtcca atggaaggta gacaacgcac tgcagtccgg caatagccaa 481 gaatcagtta ccgaacagga ttcaaaggac agtacatatt ccctgagcag cactctgacc 541 ctgtcaaagg ccgattacga gaaacacaag g 601 ctgtccagcc cagtgacaaa a atcttttaac cgtggggagt gt
[0256] Protein Sequence Defining the Full Length Chimeric 07F01 Light Chain (Mouse
Kappa Chain Variable Region and Human Kappa Constant Region) (SEQ ID NO: 158)
(Mouse Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO: 159)
lvkpsqtlsl rdtsknhyyl sskstsggta sslgtqtyic lmisrtpevt qdwlngkeyk gfypsdiave alhnhytqks

sgywnwirkf atyycarsky pepvtvswns vdkrvepksc pevkfnwyvd piektiskak ykttppvlds
pgnkleymgy isysgktyyn dyamdywgqg tsvtvssast galtsgvhtf pavlqssgly dkthtcppcp apellggpsv gvevhnaktk preeqynsty gqprepqvyt Ippsreemtk dgsfflyskl tvdksrwqqg

$$
\begin{aligned}
1 & \text { evqlqesgps } \\
61 & \text { pslksrisit } \\
121 & \text { kgpsvfplap } \\
181 & \text { slssvvtvps } \\
241 & \text { flfppkpkdt } \\
301 & \text { rvvsvltvlh } \\
361 & \text { nqvsltclvk } \\
421 & \text { nvfscsvmhe }
\end{aligned}
$$

 121 sdeqlksgta svvcllnnfy preakvqwkv dnalqs
181 lskadyekhk vyacevthqg lsspvtksfn rgec
vtckasqnvg
edladyfcqq preakvqwkv 121 sdeqlksgta svvcllnnfy preakvqwkv dnalqs
181 lskadyekhk vyacevthqg lsspvtksfn rgec
sslvwyqqkp gqspktliys asfrysgvpd ynnypltfga gtklelkrtv aapsvfifpp dnalqsgnsq esvteqdskd styslsstlt

[0258] Protein Sequence Defining the Full Length Chimeric 29B06 Heavy Chain (Mouse
Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO: 160)
[0259] Nucleic Acid Sequence Encoding the Full Length Chimeric 29B06 Light Chain (Mouse Kappa Chain Variable Region and Human Kappa Constant Region) (SEQ ID NO: 161)

1 gaggttcagc tggtagaatc

61 tcatgcgccg
121 ccaggcaagg 181 acacccagtc 241 ttgcagatga 301 cgaatccact 361 tctgcctcaa 421 gggggcactg 481 agctggaaca 541 tctggcctgt 601 acctacatct 661 cccaagagct 721 ggtcccagcg 781 cccgaggtga 841 tggtacgttg 901 aatagtacat 961 aaagaataca 1021 agtaaggcaa 1081 gaaatgacaa 1141 atcgccgttg 1201 gtgctggata 1261 tggcagcagg 1321 acccagaagt
ccagcggctt gcctcgagtg tgaaggagcg actccttgcg attacggggc caaaaggacc cagcactcgg gtggagcact actcactcag gtaatgtaaa gcgacaagac tctttttgtt catgtgttgt atggagtcga accgtgtagt aatgcaaagt aggggcagcc agaaccaagt agtgggagag gtgacgggtc gtaacgtctt cactgagcct
cggaggaggg tgacttctca ggttagcgag gttcaccata cgctgaagat aatggattct aagtgtgttc ctgcctcgtc cacttctggt ctccgtcgtg ccacaagcct tcacacttgt cccaccaaag tgtagacgtt agtacataat cagtgttctc gtccaacaaa tcgtgaacca ctcattgacc taacggtcag tttctttctg cagctgttcc gagcccaggg
ttggtccaac ctggtggatc actcagactt cgacattgga tgagctgggt ccggcaggct atcaatccag acagcagaac cattaactat agccgtgata atgccaagaa ctccctgtac acagctgtgt actattgtgc aaggcgcgtg tggggccagg gtactaccgt gactgtgagt ccactcgccc ctagcagcaa gagtacatcc aaggattatt ttccagagcc agtaaccgtg gtccatactt ttcctgctgt cctgcaaagc accgtgccat cttcatctct gggcactcag agcaatacta aggtcgataa gcgggtggaa cccccatgcc ctgcccctga acttctgggc cctaaagata ctctgatgat aagtagaaca tcccacgagg acccagaggt taagttcaac gctaagacca agcctagaga ggagcagtat acagtgctgc accaagactg gctcaacggc gcactcccag cccctatcga gaagactatt caggtgtaca ctctgccacc cagtagagag tgcctggtga aaggcttcta ccccagcgac cctgagaaca attacaagac aaccccccca tacagtaagc tgactgtgga caagtcccgc gtgatgcacg aggcattgca caaccactac
[0262] Protein Sequence Defining the Full Length Humanized Sh07F01 Hv3-48 Heavy
Chain (Humanized Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID
NO: 164)

## [0264] Protein Sequence Defining the Full Length Humanized Sh07F01 Hv3-48 D28T

T60A L63V E65G Heavy Chain (Humanized Heavy Chain Variable Region and Human IgGl
Constant Region) (SEQ ID NO: 166)


421 wqqgnvfscs vmhealhnhy tqkslslspg $k$
[0265] Nucleic Acid Sequence Encoding the Full Length Humanized HE L 07F01 Kyl-9
Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID
1 gatatccagt tgactcagtc tcagtccttt gtgagtacat cagtgggcga cagggtcacc
61 gtgacctgcc
121
gggaagcatcaca
181
agattctctg
ccaaaaccct
catcttgga
[0266] Protein Sequence Defining the Full Length Humanized HE L 07F01 Kyl-9 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO:
168)

$$
\begin{aligned}
1 & \text { diqltqsqsf vstsvgdrvt vtcrasqnvg sslvwyqqkp gkspktliys asflysgvps } \\
61 & \text { rfsgsgsgte ftltissvqp edfadyfcqq ynnypltfgg gtkveikrtv aapsvfifpp } \\
121 & \text { sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt } \\
181 & \text { lskadyekhk vyacevthqg lsspvtksfn rgec }
\end{aligned}
$$

[0267] Nucleic Acid Sequence Encoding the Full Length Humanized sh07F01 Kyl-9 F1
Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 169)

| 1 | gacattcagc tgactcagtc gccgtcgttt ttgtcggcgt ccgtgggtga cagagtgact |
| ---: | :--- |
| 61 | atcacatgtc |
| 121 | ggtaaagccc ctacgca |
| 181 | cggttcagcg gatccggctc cgggaccgag ttcacactca ctatttcgag cttgcagccg |
| 241 | gaagattttg caacgtacta ctgccagcaa tacaataact acccactcac gttcggaggg |
| 301 | ggaacgaagg tagagatcaa gcgcacagtt gctgccccca gcgtgttcat tttcccacct |
| 361 | agcgatgagc agctgaaaag cggtactgcc tctgtcgtat gcttgctcaa caacttttac |
| 421 | ccacgtgagg ctaaggtgca gtggaaagtg gataatgcac ttcaatctgg aaacagtcaa |
| 481 | gagtccgtga cagaacagga cagcaaagac tcaacttatt cactctcttc caccctgact |
| 541 | ctgtccaagg cagactatga aaaacacaag gtatacgcct gcgaggttac acaccagggt |
| 601 | ttgtctagtc ctgtcaccaa gtccttcaat aggggcgaat gt |

[0268] Protein Sequence Defining the Full Length Humanized sh07F01 Kyl-9 Fl Light
Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 170)
1 diqltqspsf lsasvgdrvt itcrasqnvg sslvwyqqkp gkapktliys asflysgvps
61 rfsgsgsgte ftltisslqp edfatyycqq ynnypltfgg gtkveikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

\author{

- 70 - <br> 181 lskadyekhk vyacevthqg lsspvtksfn rgec
}
[0269] Nucleic Acid Sequence Encoding the Full Length Humanized Sh29B06 Hv4-59
Heavy Chain (Humanized Heavy Chain Variable Region and Human IgGl Constant Region) NO: 172)
tgcaagaatc
tgagcggtgg gcctcgagtg agagccgagt ccgtgaccgc tggactattg gtgtgttccc gcctcgtcaa cttctggtgt ccgtcgtgac acaagcctag acacttgtcc caccaaagcc tagacgtttc tacataatgc gtgttctcac ccaacaaagc gtgaaccaca cattgacctg acggtcagcc tctttctgta gctgttccgt gcccagggaa
cggaccagga
cagcatatcc gattggctac gaccataagc cgctgataca gggccagggt actcgcccct ggattatttt ccatactttt cgtgccatct caatactaag cccatgccct taaagatact ccacgaggac taagaccaag agtgctgcac actcccagcc ggtgtacact cctggtgaaa tgagaacaat cagtaagctg gatgcacgag g

| ttggtcaaac | cttcagagac | actcagcctg |
| :--- | :--- | :--- |
| tccggttatt | ggaactggat | ccggcagcca |
| atcagctata | gcgggaaaac | ctattacaac |
| gtcgatacaa | gtaagaacca | gttctccctg |
| gctgtgtact | attgtgcaag | gtcaaagtat |
| actctggtga | ctgtgagttc | tgcctcaaca |
| agcagcaaga | gtacatccgg | gggcactgca |
| ccagagccag | taaccgtgag | ctggaacagt |
| cctgctgtcc | tgcaaagctc | tggcctgtac |
| tcatctctgg | gcactcagac | ctacatctgt |
| gtcgataagc | gggtggaacc | caagagctgc |
| gcccctgaac | ttctgggcgg | tcccagcgtc |
| ctgatgataa | gtagaacacc | cgaggtgaca |
| ccagaggtta | agttcaactg | gtacgttgat |
| cctagagagg | agcagtataa | tagtacatac |
| caagactggc | tcaacggcaa | agaatacaaa |
| cctatcgaga | agactattag | taaggcaaag |
| ctgccaccca | gtagagagga | aatgacaaag |
| ggcttctacc | ccagcgacat | cgccgttgag |
| tacaagacaa | cccccccagt | gctggatagt |
| actgtggaca | agtcccgctg | gcagcagggt |
| gcattgcaca | accactacac | ccagaagtca |

ttggtcaaac cttcagagac actcagcctg ccggttatt ggaactggat ccggcagcca ctattacaac gttctccctg gtcaaagtat gggcactgca ctggaacagt ggcctgtac caagagctgc tcccagcgtc cgaggtgaca gtacgttgat tagtacatac agaatacaaa aatgacaaag cgccgttgag tggatagt ccagaagtca
[0270] Protein Sequence Defining the Full Length Humanized Sh29B06 Hv4-59 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID

> qvqlqesgpg lvkpsetlsl tctvsggsis sgywnwirqp pgkglewigy isysgktyyn 61 pslksrvtis vdtsknqfsl klssvtaadt avyycarsky 121 kgpsvfplap sskstsggta 181 slssvvtvps sslgtqtyic 241 flfppkpkdt 301 rvvsvltvlh lmisrtpevt qdwlngkeyk gfypsdiave wesngqpenn alhnhytqks lslspgk

## [0271] Nucleic Acid Sequence Encoding the Full Length Humanized Hu29B06 Hv4-59

Heavy Chain (Humanized Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO: 173)
1 caagttcagc tgcaagaatc cggaccagga ttggtcaaac ccagcgaaac actctctctt
61 acatgcaccg tgagcggcga ctctatcacc tcagggtatt ggaattggat tcggaaaccc
121 ccaggcaaga agctcgagta catgggttac atcagttaca gcgggaaaac ctactataac
181 cccagtctga agagcagaat caccataagc cgtgatacct ctaagaacca gtactccctg
241 aagctgagtt ccgtaacagc agctgataca gctgtgtact attgtgcaag gagtaagtat
tggactattg gtgtgttccc gcctcgtcaa cttctggtgt ccgtcgtgac acaagcctag acacttgtcc caccaaagcc tagacgtttc tacataatgc gtgttctcac ccaacaaagc gtgaaccaca cattgacctg acggtcagcc tctttctgta gctgttccgt gcccagggaa
gggccagggt actcgcccct ggattatttt ccatactttt cgtgccatct caatactaag cccatgccct taaagatact ccacgaggac taagaccaag agtgctgcac actcccagcc ggtgtacact cctggtgaaa tgagaacaat cagtaagctg gatgcacgag g
actcttgtga ctgtgagttc t agcagcaaga gtacatccgg ccagagccag taaccgtgag cctgctgtcc tgcaaagctc tcatctctgg gcactcagac gtcgataagc gggtggaacc gcccctgaac ttctgggcgg ctgatgataa gtagaacacc ccagaggtta agttcaactg cctagagagg caagactggc cctatcgaga ctgccaccca ggcttctacc tacaagacaa actgtggaca gcattgcaca accactacac ccagaagtca agcagtataa tagtacatac tcaacggcaa agaatacaaa agactattag taaggcaaag gtagagagga aatgacaaag ccagcgacat cgccgttgag cccccccagt gctggatagt agtcccgctg gcagcagggt accactacac ccagaagtca
tgcctcaaca gggcactgca ctggaacagt tggcctgtac ctacatctgt caagagctgc tcccagcgtc cgaggtgaca gtacgttgat taaggcaaag aatgacaaag

20 [0272] Protein Sequence Defining the Full Length Humanized Hu29B06 Hv4-59 Heavy
Chain (Humanized Heavy Chain Variable Region and Human IgGl Constant Region) (SEQ ID NO: 174)
1
61 pvqlqesgpg
lvkpsetlsl tctvsgdsit rdtsknqysl klssvtaadt sskstsggta sslgtqtyic lmisrtpevt qdwlngkeyk gfypsdiave alhnhytqks
algclvkdyf nvnhkpsntk cvvvdvshed ckvsnkalpa wesngqpenn lslspgk
sgywnwirkp avyycarsky pepvtvswns vdkrvepksc pevkfnwyvd piektiskak ykttppvlds pgkkleymgy isysgktyyn dyamdywgqg tlvtvssast galtsgvhtf pavlqssgly dkthtcppcp apellggpsv gvevhnaktk preeqynsty gqprepqvyt lppsreemtk dgsfflyskl tvdksrwqqg
[0273] Nucleic Acid Sequence Encoding the Full Length Humanized Hu29B06 Hv4-59
D27G T30S M48I I67V Y78F Heavy Chain (Humanized Heavy Chain Variable Region and
Human IgGl Constant Region) (SEQ ID NO: 175)

1 caagttcagc tgcaagaatc 61 acttgcaccg 121 ccaggcaaga 181 cccagtctga 241 aagctctcat 301 gactacgcaa 361 aaaggaccaa 421 gcactcggct 481 ggagcactca 541 tcactcagct 601 aatgtaaacc 661 gacaagactc 721 tttttgttcc 781 tgtgttgttg 841 ggagtcgaag 901 cgtgtagtca 961 tgcaaagtgt 1021 gggcagcctc 1081 aaccaagtct
tgcaagaatc
tgagcggtgg agctcgagta agagccgagt ccgtgaccgc tggactattg gtgtgttccc gcctcgtcaa cttctggtgt ccgtcgtgac acaagcctag acacttgtcc caccaaagcc tagacgtttc tacataatgc gtgttctcac ccaacaaagc gtgaaccaca cattgacctg
cggaccagga cagcatatcc cattggctac gaccataagc cgctgataca gggccagggt actcgcccct ggattatttt ccatactttt cgtgccatct caatactaag cccatgccct taaagatact ccacgaggac taagaccaag agtgctgcac actcccagcc ggtgtacact cctggtgaaa
tggtcaaac tccggttatt atcagctata agggatacaa gctgtgtact actctggtga agcagcaaga ccagagccag cctgctgtcc tcatctctgg gtcgataagc gcccctgaac ctgatgataa ccagaggtta cctagagagg caagactggc cctatcgaga ctgccaccca ggcttctacc
cttcagagac ggaactggat gcgggaaaac gtaagaacca attgtgcaag ctgtgagttc gtacatccgg taaccgtgag tgcaaagctc gcactcagac gggtggaacc ttctgggcgg gtagaacacc agttcaactg agcagtataa tcaacggcaa agactattag gtagagagga ccagcgacat
actcagcctg ccggaagcca ctattacaac gttctccctg gtcaaagtat tgcctcaaca gggcactgca ctggaacagt tggcctgtac ctacatctgt caagagctgc tcccagcgtc cgaggtgaca gtacgttgat tagtacatac agaatacaaa taaggcaaag aatgacaaag cgccgttgag

```
1 1 4 1 ~ t g g g a g a g t a ~ a c g g t c a g c c ~ t g a g a a c a a t ~ t a c a a g a c a a ~ c c c c c c c a g t ~ g c t g g a t a g t ~
1 2 0 1 ~ g a c g g g t c t t ~ t c t t t c t g t a ~ c a g t a a g c t g ~ a c t g t g g a c a ~ a g t c c c g c t g ~ g c a g c a g g g t ~
1 2 6 1 ~ a a c g t c t t c a ~ g c t g t t c c g t ~ g a t g c a c g a g ~ g c a t t g c a c a ~ a c c a c t a c a c ~ c c a g a a g t c a ,
1 3 2 1 ~ c t g a g c c t g a ~ g c c c a g g g a a ~ g
```

| 1 |  | lvkpsetlsl | tctvsggsïs | sgywnwirkp | y | lsysgktyyn |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 61 | pslksrvtis | knqfsl | ssvtaadt | avyycarsky | dyamdywgqg | tvssast |
| 121 | kgpsvfplap | sskstsggta | algclvkdyf | pepvtvswns | galtsgvhtf | pavlqssgly |
| 81 | slssvvtvps | sslgtqtyic | nvnhkpsntk | vdkrvepksc | dkthtcppcp | apellggpsv |
| 41 | flfppkpkdt | lmisrtpevt | cvvvdvshed | pevkfnwyvd | gvevhnaktk | preeqynsty |
| 01 | rvvsvltvlh | qdwlngkeyk | ckvsnkalpa | piektiskak | gqprepqvyt | lppsreemtk |
| 361 | nqvsltclvk | gfypsdi | wesngqpenn | ykttppvlds | dgsfflyskl | tvdksrwqqg |
| 21 | nvfscsvmhe | alhnhytqks | lslspgk |  |  |  |

## [0275] Nucleic Acid Sequence Encoding the Full Length Humanized Sh29B06 Kv2-28

Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID

NO: 177)


## [0276] Protein Sequence Defining the Full Length Humanized Sh29B06 Kv2-28 Light

Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO:
178)

| 1 | divmtqspls | lpvtpgepas | iscraseivd | nfgisfmnwy | lqkpgqspql | liyaasnggs |
| ---: | :--- | :--- | :--- | :--- | :--- | :--- |
| 61 | gvpdrfsgsg | sgtdftlkis rveaedvgvy | ycqqskevpp | tfgggtkvei | krtvaapsvf |  |
| 121 | ifppsdeqlk | sgtasvvcll nnfypreakv | qwkvdnalqs | gnsqesvteq | dskdstysls |  |
| 181 | stltlskady | ekhkvyacev thqglsspvt ksfnrgec |  |  |  |  |

[0277] For convenience, Table 18 provides a concordance chart showing the SEQ ID NO.
of each sequence discussed in this Example.

Table 18

| $\begin{aligned} & \text { SEQ } \\ & \text { PE NO. } \end{aligned}$ | Nucleic Acid or Protein |
| :---: | :---: |
| 150 | Human IgG1 constant-nucleic acid |
| 151 | Human IgG1 constant-protein |
| 152 | Human Kappa constant (used for chimeric antibodies)-nucleic acid |
| 153 | Human Kappa constant (used for humanized antibodies)-nucleic acid |
| 154 | Human Kappa constant (used for chimeric and humanized antibodies)-p protein |
| 155 | Chimeric 07F01 C102S Mouse Heavy Chain Variable + Human IgG1 constantnucleic acid |
| 156 | Chimeric 07F01 C102S Mouse Heavy Chain Variable + Human IgG1 constantprotein |
| 157 | Chimeric 07F01 Mouse Light Chain Variable + Human Kappa constant-nucleic acid |
| 158 | Chimeric 07F01 Mouse Light Chain Variable + Human Kappa constant-protein |
| 159 | Chimeric 29B06 Mouse Heavy Chain Variable + Human IgG1 constant-nucleic acid |
| 160 | Chimeric 29B06 Mouse Heavy Chain Variable + Human IgG1 constant-protein |
| 161 | Chimeric 29B06 Mouse Light Chain Variable + Human Kappa constant-nucleic acid |
| 162 | Chimeric 29B06 Mouse Light Chain Variable + Human Kappa constant-protein |
| 163 | Humanized Sh07F01 Hv3-48 Heavy Human Variable + Human IgG1 constantnucleic acid |
| 164 | Humanized Sh07F01 Hv3-48 Heavy Human Variable + Human IgG1 constantprotein |
| 165 | Humanized Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Human Variable + Human IgG1 constant-nucleic acid |
| 166 | Humanized Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Human Variable + Human IgG1 constant-protein |
| 167 | Humanized HE L 07F01 Kv1-9 Human Variable + Human Kappa constant—nucleic acid |
| 168 | Humanized HE L 07F01 Kv1-9 Human Variable + Human Kappa constant-protein |
| 169 | Humanized sh07F01 Kv1-9 F1 Human Variable + Human Kappa constant—nucleic acid |
| 170 | Humanized sh07F01 Kv1-9 F1 Human Variable + Human Kappa constant-protein |
| 171 | Humanized Sh29B06 Hv4-59 Heavy Human Variable + Human IgG1 constantnucleic acid |
| 172 | Humanized Sh29B06 Hv4-59 Heavy Human Variable + Human IgG1 constantprotein |
| 173 | Humanized Hu29B06 Hv4-59 Heavy Human Variable + Human IgG1 constantnucleic acid |
| 174 | Humanized Hu29B06 Hv4-59 Heavy Human Variable + Human IgG1 constantprotein |
| 175 | Humanized Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Human Variable <br> + Human IgG1 constant-nucleic acid |
| 176 | Humanized Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Human Variable <br> + Human IgG1 constant-protein |
| 177 | Humanized Sh29B06 Kv2-28 Human Variable + Human Kappa constant—nucleic acid |
| 178 | Humanizecl Sh29B06 Kv2-28 Human Variable + Human Kappa constant-protein |

[0278] Table 19 below shows antibodies containing chimeric immunoglobulin heavy and light chains and each of the possible combinations of the full-length chimeric or humanized immunoglobulin heavy and light chains.

Table 19

| Anmbody Name | Mgh Mam | ПеаM! (hair |
| :---: | :---: | :---: |
| Sh07F01-2 | Chimeric 07F01 Kappa (SEQ ID NO: 158) | $\begin{aligned} & \text { Chimeric 07F01 C102S Heavy IgG1 } \\ & \text { (SEQ ID NO: 156) } \end{aligned}$ |
| Sh07F01-43 | HE L 07F01 Kv1-9 Kappa (SEQ ID NO: 168) | $\begin{aligned} & \text { Sh07F01 Hv3-48 IgG1 } \\ & \text { (SEQ ID NO: 164) } \end{aligned}$ |
| Sh07F01-62 | HE L 07F01 Kv1-9 Kappa (SEQ ID NO: 168) | $\begin{aligned} & \text { Sh07F01 Hv3-48 D28T T60A L63V } \\ & \text { E65G IgG1 } \\ & \text { (SEQ ID NO: 166) } \end{aligned}$ |
| Sh07F01-69 | $\begin{aligned} & \text { Sh07F01 Kv1-9 F1 Kappa } \\ & \text { (SEQ ID NO: 170) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { Sh07F01 Hv3-48 IgG1 } \\ & \text { (SEQ ID NO: 164) } \\ & \hline \end{aligned}$ |
| Sh07F01-83 | Sh07F01 Kv1-9 F1 Kappa (SEQ ID NO: 170) | $\begin{aligned} & \text { Sh07F01 Hv3-48 D28T T60A L63V } \\ & \text { E65G IgG1 } \\ & \text { (SEQ ID NO: 166) } \end{aligned}$ |
| Sh07F01-99 | Chimeric 07F01 Kappa (SEQ ID NO: 158) | $\begin{aligned} & \text { Sh07F01 Hv3-48 IgG1 } \\ & \text { (SEQ ID NO: 164) } \\ & \hline \end{aligned}$ |
| Sh07F01-100 | Chimeric 07F01 Kappa (SEQ ID NO: 158) | $\begin{aligned} & \text { Sh07F01 Hv3-48 D28T T60A L63V } \\ & \text { E65G IgG1 } \\ & \text { (SEQ ID NO: 166) } \\ & \hline \end{aligned}$ |
| Sh07F01-101 | HE L 07F01 Kv1-9 Kappa (SEQ ID NO: 168) | Chimeric 07F01 C102S Heavy IgG1 (SEQ ID NO: 156) |
| Sh07F01-102 | $\begin{aligned} & \text { Sh07F01 Kv1-9 F1 Kappa } \\ & \text { (SEQ ID NO: 170) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { Chimeric 07F01 C102S Heavy IgG1 } \\ & \text { (SEQ ID NO: 156) } \end{aligned}$ |
| Sh29B06-1 | Chimeric 29B06 Kappa (SEQ ID NO: 162) | Chimeric 29B06 Heavy IgG1 (SEQ ID NO: 160) |
| Sh29B06-2 | Chimeric 29B06 Kappa (SEQ ID NO: 162) | $\begin{aligned} & \text { Hu29B06 Hv4-59 IgG1 } \\ & \text { (SEQ ID NO: 174) } \\ & \hline \end{aligned}$ |
| Sh29B06-4 | Chimeric 29B06 Kappa (SEQ ID NO: 162) | $\begin{aligned} & \hline \text { Sh29B06 Hv4-59 IgG1 } \\ & \text { (SEQ ID NO: 172) } \\ & \hline \end{aligned}$ |
| Sh29B06-9 | Sh29B06 Kv2-28 Kappa <br> (SEQ ID NO: 178) | $\begin{aligned} & \text { Chimeric 29B06 Heavy IgG1 } \\ & \text { (SEQ ID NO: 160) } \\ & \hline \end{aligned}$ |
| Sh29B06-23 | $\begin{aligned} & \text { Sh29B06 Kv2-28 Kappa } \\ & \text { (SEQ ID NO: 178) } \\ & \hline \end{aligned}$ | $\begin{aligned} & \text { Hu29B06 Hv4-59 IgG1 } \\ & \text { (SEQ ID NO: 174) } \\ & \hline \end{aligned}$ |
| Sh29B06-25 | Sh29B06 Kv2-28 Kappa (SEQ ID NO: 178) | $\begin{aligned} & \text { Sh29B06 Hv4-59 IgG1 } \\ & \text { (SEQ ID NO: 172) } \\ & \hline \end{aligned}$ |
| Sh29B06-78 | $\begin{aligned} & \text { Sh29B06 Kv2-28 Kappa } \\ & \text { (SEQ ID NO: 178) } \end{aligned}$ | ```Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgG1 (SEQ ID NO: 176)``` |
| Sh29B06-84 | Chimeric 29B06 Kappa (SEQ ID NO: 162) | $\begin{aligned} & \text { Hu29B06 Hv4-59 D27G T30S M48I } \\ & \text { I67V Y78F IgG1 } \\ & \text { (SEQ ID NO: } 176 \text { ) } \end{aligned}$ |

The antibody constructs containing the full length chimeric heavy and light chains are designated below:

Chimeric 07F01 C102S = Full Length Chimeric 07F01 C102S Heavy Chain (Mouse Variable Region with C102S mutation and Human IgGl Constant Region) (SEQ ID NO: 156) plus Full Length Chimeric 07F01 Light Chain (Mouse Variable Region and Human Kappa Constant Region) (SEQ ID NO: 158)

Chimeric 29B06= Full Length Chimeric 29B06 Heavy Chain (Mouse Variable Region and Human IgGl Constant Region) (SEQ ID NO: 160) plus Full Length Chimeric 29B06 Light Chain (Mouse Variable Region and Human Kappa Constant Region) (SEQ ID NO: 162)
[0280] Two of the possible antibody constructs containing the full length immunoglobulin heavy and light chains containing humanized variable regions are designated below:

Sh07F01-62 = Humanized Sh07F01 Hv3-48 D28T T60A L63V E65G Heavy Chain Variable Region and Human IgGl Constant Region (SEQ ID NO: 166) plus HE L 07F01 Kvl-9 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 168)

Sh29B06-78 = Humanized Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F Heavy Chain Variable Region and Human IgGl Constant Region (SEQ ID NO: 176) plus Sh29B06 Kv2-28 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 178)
B. Binding Affinities of Humanized and Chimeric Anti-RON Monoclonal Antibodies
[0281] The binding affinities and kinetics of interaction of monoclonal antibodies produced in Example 14 against recombinant human RON SEMA and PSI domains (rhRON SEMA + PSI) (R\&D Systems, Inc., Minneapolis, MN) were measured by surface plasmon resonance using a Biacore T100 (Biacore (GE Healthcare), Piscataway, NJ) instrument.
[0282] Goat anti-human IgG Fc (Jackson ImmunoResearch, Catalog No. 109-005-098) was immobilized on carboxymethylated dextran CM4 sensor chips (Biacore) by amine coupling (Biacore) using a standard coupling protocol according to the vendor's instructions. The analyses were performed at $37^{\circ} \mathrm{C}$ using PBS (Invitrogen) containing $0.05 \%$ surfactant P20 (Biacore) as running buffer.
[0283] The antibodies were captured in individual flow cells at a flow rate of $60 \mu \mathrm{i} /$ minute. Injection time was varied for each antibody to yield an $R_{\max }$ between 30 and 60 RU . Buffer or rhRON SEMA + PSI diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 300 seconds at $60 \mu \mathrm{i} /$ minute. The dissociation phase was monitored for up to 1200 seconds. The surface was then regenerated with two 60 second injections of Glycine pH 2.25 (made from Glycine pH 2.0 (Biacore) and pH 2.5 (Biacore)) at $60 \mu \mathrm{i} /$ minute. For the initial screening, only one or two concentrations of rhRON SEMA + PSI were tested, typically 10.0 and 2.5 nM (results are summarized in Table 20).
[0284] Kinetic parameters were determined using the kinetic function of the BIAevaluation software (Biacore) with double reference subtraction. Kinetic parameters for each antibody, $\mathrm{k}_{\mathrm{a}}$ (association rate constant), $\mathrm{k}_{\mathrm{d}}$ (dissociation rate constant) and $\mathrm{K}_{\mathrm{D}}$ (equilibrium dissociation constant) were determined. Certain monoclonal antibodies were screened using cell culture media supernatant containing secreted antibody, and kinetic values of the monoclonal antibodies on rhRON SEMA + PSI at $37^{\circ} \mathrm{C}$ are summarized in Table 20.

Table 20

| Amiloody | kaylys. | \#, | W以 M | \# |
| :---: | :---: | :---: | :---: | :---: |
| $51107 \mathrm{FGl} \geqslant 2$ | 2.0E4-06 | $7.3 \mathrm{E}-04$ | $3.8 \mathrm{E}-10$ | 3 |
| 1 MOMOM11 | 3.9E+-06 | $1.4 \mathrm{E}-03$ | $3.6 \mathrm{E}-10$ | 2 |
| ShO7F01-69 | 2.3E4-06 | $1.2 \mathrm{E}-03$ | $5.6 \mathrm{E}-10$ | 2 |
| ShO7F0i-76 | 2.3E4-06 | $1.3 \mathrm{E}-03$ | $5.7 \mathrm{E}-10$ | 2 |
| Sh07FOU 83 | $2.6 \mathrm{E}+-06$ | $1.4 \mathrm{E}-03$ | $5.4 \mathrm{E}-10$ | 2 |
| Sh29B00.1 | 6.7E4-05 | 7.6E-04 | $1.1 \mathrm{E}-09$ | 3 |
| Sl\%)SO39 | $8.7 \mathrm{E} 4-05$ | $2.2 \mathrm{E}-04$ | $2.6 \mathrm{E}-10$ | 1 |
| SH1\% | 7.8E+-05 | 4.8E-04 | $6.4 \mathrm{E}-10$ | 4 |
| 11 U29111 \% | No Binding |  |  |  |

[0285] The results in Table 20 demonstrate that the chimeric and each of the humanized antibodies, except Sh29B06-25, have fast association rates ( $\mathrm{k}_{\mathrm{a}}$ ), very slow disassociation rates $\left(\mathrm{k}_{\mathrm{d}}\right)$ and very high affinities $\left(\mathrm{K}_{\mathrm{D}}\right)$. In particular, the antibodies have affinities ranging from about 260 pM to about 1.1 nM . No binding was observed for Sh29B06-25. Because Sh29B0625 does not bind rhRON SEMA + PSI and Sh29B06-23 does, one or more of the back mutations present in the heavy chain of Sh29B06-23 appear to be required for binding with high affinity.
[0286]
The binding affinities and kinetics of certain purified monoclonal antibodies were also determined. To further characterize certain antibodies, the surface plasmon resonance experiments described above were conducted using concentrations of rhRON SEMA + PSI between 0.3125 nM and 10.0 nM (a 2-fold serial dilution).
[0287] The kinetic values of certain purified monoclonal antibodies (i.e., Sh07F01-62 and Sh29B06-78) on rhRON SEMA + PSI at $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$ are summarized in Table 21.

Table 21
Antibody Binding to rhRON SEMA + PSI

|  | Measurements at $25 . \mathrm{C}$ |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| A11inoty | सa (M) | \4 Ms) | K1 M | $\stackrel{8}{ }$ | Ma (1M\%) | Ma M. | K1 M | $\square$ |
| Shu7 012 | $1.2 \mathrm{E}+06$ | $9.8 \mathrm{E}-05$ | 8.2E-11 | 9 | $1.7 \mathrm{E}+06$ | 5.3E-04 | $3.1 \mathrm{E}-10$ | 9 |
| Sholivili | $1.2 \mathrm{E}+06$ | 1.1E-04 | $9.0 \mathrm{E}-11$ | 3 | $1.8 \mathrm{E}+06$ | 5.6E-04 | $3.0 \mathrm{E}-10$ | 3 |
| Shollul 62 | $1.8 \mathrm{E}+06$ | 1.6E-04 | 8.5E-11 | 4 | $2.8 \mathrm{E}+06$ | 6.9E-04 | 2.5E-10 | 4 |
| S107M1.\% | $1.1 \mathrm{E}+06$ | 1.4E-04 | 1.2E-10 | 2 | $2.5 \mathrm{E}+06$ | 7.8E-04 | 3.0E-10 | 2 |
| S1071017\% | $9.8 \mathrm{E}+05$ | 1.3E-04 | 1.3E-10 | 2 | $2.4 \mathrm{E}+06$ | 7.9E-04 | 3.3E-10 | 2 |
| Shol101-83 | $1.6 \mathrm{E}+06$ | 1.8E-04 | 1.1E-10 | 2 | $3.2 \mathrm{E}+06$ | 7.9E-04 | 2.4E-10 | 2 |
| Sh29106m | $5.3 \mathrm{E}+05$ | 2.0E-04 | 3.6E-10 | 6 | 8.2E+05 | 7.0E-04 | 8.6E-10 | 5 |
| Sh29106-23 | $6.7 \mathrm{E}+05$ | 9.5E-05 | 1.4E-10 | 4 | $7.3 \mathrm{E}+05$ | 3.3E-04 | 4.6E-10 | 5 |
| S129130678 | $7.5 \mathrm{E}+05$ | 3.9E-05 | 5.2E-11 | 7 | $1.0 \mathrm{E}+06$ | $1.1 \mathrm{E}-04$ | $1.1 \mathrm{E}-10$ | 9 |

[0288] The results in Table 21 demonstrate the purified antibodies have affinities ranging from about 52 pM to 360 pM when tested at $25^{\circ} \mathrm{C}$ or about 110 pM to about 860 pM when tested at $37^{\circ} \mathrm{C}$.
[0289] Binding to cell surface human wild-type RON and the delta 160 RON variant by antibodies 07F01, Sh07F01-62, 29B06, and Sh29B06-78 was measured at $4^{\circ} \mathrm{C}$, using Fluorescence Activated Cell Sorting (FACS). PC3 cells expressing the human wild-type RON, and HT29 cells expressing the delta 160 variant, were harvested using cell dissociation buffer (Invitrogen), washed twice with FACS buffer (PBS with 0.5\% BSA), and treated 10 minutes with Cyto Q Antibody diluent and FC receptor block (Innovex Biosciences, Richmond, CA). Purified antibodies were diluted in FACS buffer over a concentration range from 0.01 nM to 25 nM . Cells were incubated with $100 \mu \mathrm{ï}$ of antibody for one hour, washed with FACS buffer three times, and incubated for 45 minutes with goat anti-mouse PE-conjugated antibody (Jackson ImmunoResearch Laboratories, West Grove, PA) or donkey anti-human PEconjugated antibody (Jackson ImmunoResearch Laboratories, West Grove, PA). Cells were
washed three times with FACS buffer, resuspended in $300 \mu$ ï of FACS buffer, and analyzed using a Beckman Coulter Cytomics FC 500 FACS instrument. All four antibodies were compared in the same experiment. Results are summarized in Table 22.

Table 22

|  | 07F01 | Sh07101-62 | $29 \mathrm{B06}$ | Sl129B06-78 |
| :---: | :---: | :---: | :---: | :---: |
| $\begin{aligned} & \text { Human RON }-\mathrm{K}_{\mathrm{D}} \\ & (\mathrm{nM}) \end{aligned}$ | 0.053 | 0.043 | 0.136 | 0.090 |
| $\begin{aligned} & \text { Human RON }-\mathrm{K}_{\mathrm{D}} \\ & \text { range }(\mathrm{nM}) \\ & \hline \end{aligned}$ | $\begin{gathered} \hline 0.036 \text { to } \\ 0.069 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.026 \text { to } \\ 0.060 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.083 \text { to } \\ 0.190 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.063 \text { to } \\ 0.117 \\ \hline \end{gathered}$ |
| $\begin{aligned} & \text { Delta } 160 \text { RON }-\mathrm{K}_{\mathrm{D}} \\ & (\mathrm{nM}) \end{aligned}$ | 0.100 | 0.118 | 0.167 | 0.239 |
| Delta 160 RON - K range ( nM ) | $\begin{gathered} \hline 0.071 \text { to } \\ 0.129 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.045 \text { to } \\ 0.191 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.066 \text { to } \\ 0.267 \\ \hline \end{gathered}$ | $\begin{gathered} \hline 0.202 \text { to } \\ 0.277 \\ \hline \end{gathered}$ |

[0290] The results in Table 22 demonstrate that the humanized antibodies Sh07F01-62 and Sh29B06-78 retain their ability to bind both wild-type RON and the delta 160 RON variant on the cell surface with affinities equivalent to their murine antibody counterparts (i.e., 07 F 01 and 29B06, respectively).

## C. Comparison of Other Anti-RON Antibodies

[0291] Three antibodies that inhibit the function of human RON were constructed and expressed using published information. One antibody, referred to as 1P3B2-BIIB Ab, was constructed based on the disclosure of Huet et al., U.S. Patent Publication No. 2009/0226442 (Biogen Idee, Inc.). Two additional antibodies, referred to as RON6 and RON8, were constructed based on the disclosure of Pereira et al., U.S. Patent Publication No. 2009/0136510 (Imclone Systems, Inc.).
[0292] Kinetic parameters for the 1P3B2-BIIB Ab, RON6, and RON8 antibodies on rhRON SEMA + PSI at $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$ were determined by Biacore as described above (See Section B. Binding Affinities of Humanized and Chimeric Anti-RON Monoclonal Antibodies). The kinetic values for each antibody are summarized in Table 23.

Table 23

## Antibody Binding to rhRON SEMA + PSI

|  | Measurements at 25 C |  |  |  | Mearuenents a 37. |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Amibuty | ка (M1) | kd Ms) | КリM1 | 1 | अ/1/Ms) | kil/s. | M1 M | \% |
| Sh29100678 | $6.8 \mathrm{E}+05$ | 3.1E-05 | 4.8E-11 | 6 | $9.6 \mathrm{E}+05$ | $1.0 \mathrm{E}-04$ | $1.1 \mathrm{E}-10$ | 8 |
| Shollul 62 | $1.8 \mathrm{E}+06$ | 1.6E-04 | 8.5E-11 | 4 | $2.8 \mathrm{E}+06$ | $6.9 \mathrm{E}-04$ | $2.5 \mathrm{E}-10$ | 4 |
| IP3B2-BIIB | $1.5 \mathrm{E}+06$ | 1.2E-03 | 8.0E-10 | 1 | $2.2 \mathrm{E}+07$ | $2.6 \mathrm{E}-02$ | 1.2E-09 | 1 |
| ROMO | $2.3 \mathrm{E}+06$ | 2.6E-03 | 1.1E-09 | 1 | $1.9 \mathrm{E}+10$ | $1.9 \mathrm{E}-01$ | $1.0 \mathrm{E}-09$ | 1 |
| RON8 | $1.2 \mathrm{E}+06$ | 6.8E-04 | 6.7E-10 | 3 | $7.0 \mathrm{E}+06$ | $2.5 \mathrm{E}-03$ | $9.2 \mathrm{E}-10$ | 3 |

[0293] The results in Table 23 demonstrate that the overall equilibrium dissociation constant $\left(\mathrm{K}_{\mathrm{D}}\right)$ for Sh29B06-78 and Sh07F01-62 were smaller (i.e., higher affinity) than the $\mathrm{K}_{\mathrm{D}}$ for 1P3B2-BIIB, RON6, and RON8 at both $25^{\circ} \mathrm{C}$ and $37^{\circ} \mathrm{C}$. The $\mathrm{K}_{\mathrm{D}}$ of 1P3B2-BIIB, RON6, and RON8 antibodies can also be compared with other humanized 29B06 or 07F01 variants by comparing Tables 21 and 23.
[0294] Therefore, the binding affinities of Sh29B06-78 and Sh07F01-62 are significantly higher than the affinities of 1P3B2-BIIB, RON6, and RON8 antibodies as disclosed herein.

## Example 15: Inhibition of MSP-RON Binding

[0295] The chimeric and humanized antibodies produced in Example 14 were tested for inhibition of MSP binding to hRON SEMA +PSI, as measured by electrochemiluminescence (ECL) assay as described in Example 3. The antibodies (concentration range: $0.006-10 \mu \mathrm{~g} / \mathrm{mL}$ ) were incubated for 45 minutes at room temperature.
[0296] The MSP-hRON binding interaction was inhibited by the chimeric and humanized antibodies listed in Table 24, which were tested in this assay. The $\mathrm{IC}_{50}$ for the antibodies (IgGl) are shown in Table 24.

Table 24

| Antibody | Mean IC $\mathbf{s 0}_{0}$ | Std Dev of IC $\mathbf{5 0}_{0}$ | N |
| :---: | :---: | :---: | :---: |
| Sh29B06-1 | 1.73 | 1.24 | 8 |
| Sh29B06-23 | 1.24 | 1.57 | 9 |
| Sh29B06-78 | 0.41 | 0.24 | 8 |
| Sh07F01-2 | 0.91 | 1.42 | 8 |
| Sh07F01-43 | 0.22 | 0.09 | 2 |
| Sh07F01-62 | 0.32 | 0.12 | 6 |
| Sh07F01-69 | 0.28 | 0.18 | 2 |
| Sh07F01-76 | 0.38 | 0.33 | 2 |
| Sh07F01-83 | 0.33 | 0.24 | 2 |

[0297] The results in Table 24 demonstrate that the chimeric and humanized anti- RON antibodies listed in Table 24 (i.e., Sh29B06-1, Sh29B06-23, Sh29B06-78, Sh07F01-2, Sh07F01-43, Sh07F01-62, Sh07F01-69, Sh07F01-76, and Sh07F01-83) retain the ability to block MSP binding to hRON SEMA +PSI with high potency.

## Example 16: Inhibition of downstream signaling by anti-RON antibodies

[0298] The chimeric and humanized anti-RON antibodies produced in Example 14 were tested for their ability to inhibit MSP-induced phosphorylation of ERK, a RON downstream signaling molecule, using the cell-based assay described in Example 3. The antibodies (concentration range: $0.006-10 \mu \mathrm{~g} / \mathrm{mL}$ ) in RPMI were added to the cells and incubated for one hour at $37^{\circ} \mathrm{C}$. The IC50s of ERK phosphorylation inhibition by the chimeric and humanized anti-RON antibodies tested in this assay are shown in Table 25.

Table 25

| Antibody | Mean IC50 | Std Dev of IC ${ }^{\text {c }}$ | N |
| :---: | :---: | :---: | :---: |
| Sh29B06-1 | 0.10 | 0.10 | 6 |
| Sh29B06-23 | 0.11 | 0.08 | 10 |
| Sh29B06-78 | 0.13 | 0.08 | 5 |
| Sh07F01-2 | 0.06 | 0.06 | 7 |
| Sh07F01-43 | 0.02 | 0.00 | 3 |
| Sh07F01-62 | 0.03 | 0.03 | 2 |
| Sh07F01-69 | 0.05 | 0.02 | 2 |
| Sh07F01-76 | 0.10 | 0.03 | 2 |
| Sh07F01-83 | 0.03 | 0.02 | 2 |

[0299] The results in Table 25 demonstrate that the chimeric and humanized anti-RON antibodies listed in Table 25 (i.e., Sh29B06-1, Sh29B06-23, Sh29B06-78, Sh07F01-2, Sh07F01-43, Sh07F01-62, Sh07F01-69, Sh07F01-76, and Sh07F01-83) inhibit MSP-induced ERK phosphorylation in T47D breast cancer cell line with high potency. following formula: 100-(anti-RON antibody treated-baseline)/(control hulgG treatedbaseline)*100. Results on inhibition of MSP-induced HPAF-II cell migration by anti-RON antibodies, sh29B06-78 and sh07F01-62, are summarized in Table 26 and FIG. 16.

Table 26

|  | Sh29B06.78 |  | sh071001-62 |  |
| :---: | :---: | :---: | :---: | :---: |
| AB concentration $\mathrm{no} / \mathrm{ml}$ | AVG | Std DEV | AVG | Std DEV |
| 1000.00 | 94.82 | 3.34 | 98.96 | 3.79 |
| 200.00 | 90.67 | 2.37 | 97.80 | 1.12 |
| 40.00 | 59.85 | 12.50 | 67.18 | 7.67 |
| 8.00 | 59.71 | 2.87 | 37.22 | 4.16 |
| 1.60 | 63.95 | 20.15 | 38.91 | 13.79 |
| 0.32 | 42.03 | 39.88 | 43.27 | 5.76 |
| 0.06 | 60.37 | 11.92 | 34.40 | 2.31 |

[0301] The results in Table 26 demonstrate that humanized anti-RON antibodies, sh29B0678 and sh07F01-62, potently inhibit MSP-induced cell migration in HPAF-II pancreatic cancer cell lines.

## Example 18: Inhibition of MSP-induced Cell Invasion

[0302] Humanized antibodies sh29B06-78 and sh07F01-62 as produced in Example 14 were tested for their ability to inhibit MSP-induced cell invasion. HPAF-II pancreatic cancer cells were trypsinized, counted, and placed at a concentration of $50,000 /$ well in $45 \mu \mathrm{i}$ of $10 \%$ FBS/MEM in the upper chamber of a BD 96-well BD BioCoat Matrigel invasion FluoroBlok ${ }^{\text {TM }}$
plate (Becton Dickinson). Antibodies were added at a concentration of $30 \mu \mathrm{~g} / \mathrm{ml}$ and cells were incubated for 2 hours. The bottom chamber contained $10 \%$ FBS MEM ( $200 \mu_{1}$ ) and 1 nM MSP, and cells were incubated for 24 hours. The number of cells that underwent invasion through the membrane was determined by the addition of Calcien Dye at $4 \mu \mathrm{~g} / \mathrm{ml}$ final concentration to the bottom chamber, followed by a one-hour incubation. Fluorescence intensity was measured using a Wallace 1420 instrument. Results on inhibition of MSP-induced HPAFII cell invasion by anti-RON antibodies are summarized in FIG. 17.
[0303] The results in Figure 17 demonstrate that humanized anti-RON antibodies sh29B0678 and sh07F01-6 potently inhibit MSP-dependent cell invasion in HPAF-II pancreatic cancer cell line.

## Example 19: Inhibition of Growth of NCI-H358 Lung Xenograft Tumor Model

[0304] Inhibition of tumor growth by the humanized anti-RON antibodies was tested in an NCI-H358 lung xenograft model. The NCI-H358 cells (ATCC) were grown in culture at $37^{\circ} \mathrm{C}$ in an atmosphere containing $5 \% \mathrm{C}_{2}$, using RMPI medium (Invitrogen) containing $10 \%$ FBS. Cells were inoculated subcutaneously into the flank of 8 -week old female CB. 17 SCID mice (Taconic Labs) with $5 \times 10^{6}$ cells per mouse in $50 \%$ matrigel (Becton Dickinson). Tumor measurements were taken twice weekly using vernier calipers. When tumors reached approximately $150 \mathrm{~mm}^{3}$, the mice were randomized into six groups of ten mice each. Each group received one of the following treatments: human $\operatorname{IgG}$ (hulgG) control, mu29B06, sh29B06-78, mu07F01, sh07F01-62 and RON8. Treatment was administered by intraperitoneal injection two times per week at $10 \mathrm{mg} / \mathrm{kg}$ for seven weeks. Treatment was welltolerated, with no significant loss in body weight. Tumor growth inhibition is expressed as percent inhibition (baseline subtracted) to the hulgG control and statistical analysis was conducted using ANOVA. Results for tumor growth inhibition on day 41 in the NCI-H358 model are shown in Fig. 18 and Table 27.

Table 27

| Træatmen! |  | ANOVA rempared lo hulg() |
| :---: | :---: | :---: |
| mu29B06 | 88.93 | $\mathrm{P}<0.01$ |
| sh29B06-78 | 89.02 | $\mathrm{P}<0.01$ |
| mu07F01 | 34.15 | $\mathrm{P}>0.05$ |
| sh07F01-62 | 39.05 | $\mathrm{P}>0.05$ |
| RON8 | 37.99 | $\mathrm{P}>0.05$ |

[0305] Anti-RON antibody treatments resulted in tumor growth inhibition compared to hulgG control. Specifically, mu29B06 antibody treatment resulted in tumor growth inhibition of $89 \%$ ( $\mathrm{P}<0.01$ ); sh29B06-78 antibody treatment resulted in tumor growth inhibition of $89 \%$ ( $\mathrm{P}<0.01$ ); mu07F01 antibody treatment resulted in tumor growth inhibition of $34 \%$ ( $\mathrm{P}>0.05$ ); sh07F01-62 antibody treatment resulted in tumor growth inhibition of $39 \%$ ( $\mathrm{P}>0.05$ ); and RON8 antibody treatment resulted in tumor growth inhibition of $38 \%$ ( $\mathrm{P}>0.05$ ). These results demonstrate that sh29B06-78 and mu29B06 inhibit tumor growth in a NCI-H358 xenograft model ( $\mathrm{P}<0.01$ ), whereas the mu07F01, sh07F01-62, and RON8 antibodies did not inhibit tumor growth in this model ( $\mathrm{P}>0.05$, which is not statically significant).

## [0306] Example 20: RON Receptor Degradation

[0307] Western blots were performed to determine total levels of RON receptor at the end of treatment. Four tumor samples from each of the treatment groups were weighed, lysed in RIPA buffer (Boston Bioproducts), ImM EDTA(Boston Bioproducts), 1 mM Sodium OrthoVandadate (Sigma), IX protease inhibitor (Sigma) and IX Phosphatase Inhibitor I and II (Sigma). The samples were homogenized using a hand-held electric homogenizer and incubated for 10 minutes on ice. Samples are spun down at 11,000 RPM for 30 minutes at $4^{\circ} \mathrm{C}$. Supernatants were collected and protein concentrations were determined using Pierce BCA assay kit according to the manufacturers protocol. The C-20 (Santa Cruz) antibody was used to detect total RON protein. $\beta$-tubulin (Cell Signaling Technologies) was blotted as loading control. The Western blots were blocked for one hour in 5\% Milk in IX TBST (TBS- $0.1 \%$ TWEEN) (Sigma), followed by primary antibody incubation over night at $4^{\circ} \mathrm{C}$ in $5 \%$ BSA IX TBST at 1:1000 for both antibodies. Western blots were washed three times with IX TBST, incubated with anti-rabbit HRP conjugated secondary antibody (Cell Signaling Technologies),
for one hour at room temperature. Western blots were washed three times with IX TBST and then developed using Dura Signal (Pierce).
[0308] The results in Fig. 19 demonstrate RON receptor degradation in the mu29B06 and sh29B06-78 treated samples and to a lesser extent in the mu07F01 and sh07F01-62 treated samples. RON receptor degradation was not observed in the RON8 treated samples.

## INCORPORATION BY REFERENCE

[0309] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

## EQUIVALENTS

[0310] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and the range of equivalency of the claims are intended to be embraced therein.
[0311] WHAT IS CLAIMED IS:

1. An isolated antibody that binds human RON, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region selected from the group consisting of:
(a) (i) an immunoglobulin heavy chain variable region comprising a $\mathbf{C D R}_{\mathbf{H}} \mathbf{i}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 45 (29B06), SEQ ID NO: 59 (29B06), and SEQ ID NO: 126 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), $\mathrm{a} \mathrm{CDR}_{\mathbf{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 46 (29B06), and a CDR $_{\mathbf{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 47 (29B06);
(ii) an immunoglobulin light chain variable region comprising a $\mathbf{C D R}_{\mathbf{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 48 (29B06), a $_{\mathbf{C D R}}^{\mathbf{L} 2}$ comprising the amino acid sequence of SEQ ID NO: 49 (29B06), and a $\mathbf{C D R}_{\mathbf{L 3}}$ comprising the amino acid sequence of SEQ ID NO: 50 (29B06);
(b) (i) an immunoglobulin heavy chain variable region comprising a $\mathbf{C D R} \mathbf{H}_{\mathbf{H}} \mathbf{i}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 5 (07F01), SEQ ID NO: 51 (07F01) and SEQ ID NO: 124 (Sh07F01 Hv3-48 D28T T60A L63V E65G), a CDR $\mathbf{H}_{2}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6 (07F01) and SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and a CDR ${ }_{\text {H3 }}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO:7 (07F01) and SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G); and
(ii) an immunoglobulin light chain variable region comprising a $\mathbf{C D R}_{\mathbf{L} 1}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 8 ( $\mathbf{0 7 F 0 1}$ ) and SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 FI), a CDR L 2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 9 (07F01) and SEQ ID NO: 131 (HEL 07F01 Kvl-9, Sh07F01 Kvl-9 Fl), and a CDR ${ }_{\text {L3 }}$ comprising the amino acid sequence of SEQ ID NO: 10 (07F01);
(c) (i) an immunoglobulin heavy chain variable region comprising a $\mathbf{C D R}_{\mathbf{H}} \mathbf{I}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 15 (12B11) and
 (12B11), and a CDR ${ }_{\mathbf{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 17 (12B11); and
(ii) an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 18 (12B11), a CDR $_{\text {L2 }}$ comprising the amino acid sequence of SEQ ID NO: 19 (12B11), and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 20 (12B11);
(d) (i) an immunoglobulin heavy chain variable region comprising a $\mathrm{CDR}_{\mathrm{H}} \mathrm{i}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 25 (17F06) and SEQ ID NO: 55 (17F06), a CDR ${ }_{\text {H2 }}$ comprising the amino acid sequence of SEQ ID NO: 26 (17F06), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 27 (17F06); and
(ii) an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 28 ( $\mathbf{1 7 F 0 6 )}$, a $\mathrm{CDR}_{\mathrm{L} 2}$ comprising the amino acid sequence of SEQ ID NO: 29 (17F06), and a $\mathrm{CDR}_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO:30 (17F06); and
(e) (i) an immunoglobulin heavy chain variable region comprising a $\mathrm{CDR}_{\mathrm{H}} \mathrm{I}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 35 (18H09) and SEQ ID NO: 57 ( $\mathbf{1 8 H 0 9 ) , ~ a ~ C D R ~}{ }_{\text {H2 }}$ comprising the amino acid sequence of SEQ ID NO: 36 (18H09), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 37 (18H09); and
(ii) an immunoglobulin light chain variable region comprising a $\mathrm{CDR}_{\mathrm{L}} \mathrm{I}$ comprising the amino acid sequence of SEQ ID NO: 38 ( $\mathbf{1 8 H 0 9 )}$, a $\mathrm{CDR}_{\mathrm{L} 2}$ comprising the amino acid sequence of SEQ ID NO: 39 ( $\mathbf{1 8 H 0 9 )}$, and a $\mathrm{CDR}_{\text {L3 }}$ comprising the amino acid sequence of SEQ ID NO: 40 ( $\mathbf{1 8 H 0 9 ) .}$
2. The antibody of claim 1 , wherein the immunoglobulin heavy chain variable region comprises a CDR ${ }_{H} \mathrm{i}$ comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 45 (29B06) and SEQ ID NO: 126 (Sh29B06 Hv4-59, Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), a CDR ${ }_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 46 (29B06), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 47 (29B06); and the immunoglobulin light chain variable region comprises a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 48 (29B06), a CDR L2 $_{2}$ comprising the amino acid sequence of SEQ ID NO: 49 (29B06), and a CDR ${ }_{\text {L3 }}$ comprising the amino acid sequence of SEQ ID NO: 50 (29B06).
3. The antibody of claim 1 , wherein the immunoglobulin heavy chain variable region comprises a $\mathrm{CDR}_{\mathrm{H}} \mathrm{i}^{\mathrm{i}}$ comprising an amino acid sequence selected from the group consisting of

SEQ ID NO: 5 (07F01) and SEQ ID NO: 124 (Sh07F01 Hv3-48 D28T T60A L63V E65G), a $\mathrm{CDR}_{\mathrm{H} 2}$ comprising the amino acid sequence of SEQ ID NO: 122 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and a CDR ${ }_{\mathrm{H} 3}$ comprising the amino acid sequence of SEQ ID NO: 123 (Chimeric 07F01 C102S, Sh07F01 Hv3-48, Sh07F01 Hv3-48 D28T T60A L63V E65G); and the immunoglobulin light chain variable region comprises a $\mathrm{CDR}_{\mathrm{L} 1}$ comprising the amino acid sequence of SEQ ID NO: 130 (HE L 07F01 Kvl-9, Sh07F01 Kvl-9 Fl), a CDR ${ }_{\text {L2 }}$ comprising the amino acid sequence of SEQ ID NO: 131 (HE L 07F01 Kvl-9, Sh07F01 Kvl$\mathbf{9} \mathbf{F l}$ ), and a CDR $_{\mathrm{L} 3}$ comprising the amino acid sequence of SEQ ID NO: 10 ( $\mathbf{0 7 F 0 1 )}$.
4. The antibody of anyone of claims 1-3, wherein the CDR sequences are interposed between human and humanized framework sequences.
5. The antibody of claim 2 , further comprising a human germline framework sequence.
6. The antibody of claim 5 , wherein the human germline framework sequence is IGHV4$59 * 01$.
7. The antibody of claim 6, wherein the framework sequence comprises at least one substitution at amino acid position $27,30,48,67$ or 78 , where in the amino acid numbering is based on Kabat.
8. The antibody of claim 7, wherein the at least one substitution is selected from the group consisting of D27G, T30S, M48I, I67V, and Y78F.
9. The antibody of anyone of claims 1-8, wherein the antibody is an antigen-binding fragment.
10. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain variable region of any one of claims 1-3.
11. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain variable region of any one of claims 1-3.
12. An expression vector comprising the nucleic acid of claim 10.
13. An expression vector comprising the nucleic acid of claim 11.
14. The expression vector of claim 13 , further comprising the nucleic acid of claim 10 .
15. A host cell comprising the expression vector of claim 12.
16. A host cell comprising the expression vector of claim 13.
17. A host cell comprising the expression vector of claim 14.
18. The host cell comprising of claim 16 , further comprising the expression vector of claim 12.
19. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:
(a) growing the host cell of claim 15 or 16 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and
(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.
20. A method of producing an antibody that binds human RON or an antigen binding fragment of the antibody, the method comprising:
(a) growing the host cell of claim 17 or 18 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and the immunoglobulin light chain variable region, thereby producing the antibody or the antigenbinding fragment of the antibody; and
(b) purifying the antibody or the antigen-binding fragment of the antibody.
21. An isolated antibody that binds human RON, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region selected from the group consisting of:
(a) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 42 (29B06), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 44 (29B06);
(b) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 147 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 149 (Sh29B06 Kv2-28)
(c) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 ( $\mathbf{0 7 F 0 1}$ ), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 (07F01);
(d) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 139 (HE L 07F01 Kvl-9);
(e) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 12 (12B11), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (12B11);
(f) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22 ( $\mathbf{1 7 F 0 6 ) , ~ a n d ~ a n ~ i m m u n o g l o b u l i n ~ l i g h t ~ c h a i n ~ v a r i a b l e ~ r e g i o n ~ c o m p r i s i n g ~ t h e ~}$ amino acid sequence of SEQ ID NO: 24 (17F06); and
(g) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 32 ( $\mathbf{1 8 H 0 9 )}$, and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 34 (18H09).
22. The antibody of claim 21, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 42 (29B06), and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 44 (29B06).
23. The antibody of claim 21, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 147 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F), and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 149 (Sh29B06 Kv2-28).
24. The antibody of claim 21, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 2 ( $\mathbf{0 7 F 0 1}$ ), and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 4 (07F01).
25. The antibody of claim 21, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 137 (Sh07F01 Hv3-48 D28T T60A L63V E65G), and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 139 (HE L 07F01 Kvl-9).
26. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain variable region of claim 21.
27. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain variable region of claim 21.
28. An expression vector comprising the nucleic acid of claim 36.
29. An expression vector comprising the nucleic acid of claim 37.
30. The expression vector of claim 29, further comprising the nucleic acid of claim 36 .
31. A host cell comprising the expression vector of claim 28.
32. A host cell comprising the expression vector of claim 29.
33. A host cell comprising the expression vector of claim 30.
34. The host cell of claim 32, further comprising the expression vector of claim 28.
35. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:
(a) growing the host cell of claim 31 or 32 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and
(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.
36. A method of producing an antibody that binds human RON or an antigen binding fragment of the antibody, the method comprising:
(a) growing the host cell of claim 33 or 34 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and the immunoglobulin light chain variable region, thereby producing the antibody or the antigenbinding fragment of the antibody; and
(b) purifying the antibody or the antigen-binding fragment of the antibody.
37. An isolated antibody that binds human RON comprising an immunoglobulin heavy chain and an immunoglobulin light chain selected from the group consisting of:
(a) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 109 (29B06), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 111 (29B06);
(b) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 176 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgGI), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 178 ( $\mathbf{S h} 29 B 06$ Kv2-28

## Kappa);

(c) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 93 ( $\mathbf{0 7 F 0 1}$ ), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 95 (07F01);
(d) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 166 (Sh07F01 Hv3-48 D28T T60A L63V E65G IgGI), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 168 (HE L 07F01 Kvl-9 Kappa);
(e) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 97 (12B11), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 99 (12B11);
(f) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 101 (17F06), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 103 (17F06); and
(g) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 105 ( $\mathbf{1 8 H 0 9}$ ), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 107 ( $\mathbf{1 8 H 0 9 ) .}$
38. The antibody of claim 37, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 109 (29B06), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 111 (29B06).
39. The antibody of claim 37, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 93 (07F01), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 95 (07F01).
40. The antibody of claim 37, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 176 (Hu29B06 Hv4-59 D27G T30S M48I I67V Y78F IgGI), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 178 (Sh29B06 Kv2-28 Kappa).
41. The antibody of claim 37, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 166 (Sh07F01 Hv3-48 D28T T60A L63V E65G IgGl), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 168 (HE L 07F01 Kvl-9 Kappa).
42. The antibody of any one of claims 21 or 37 , wherein the antibody is an antigen-binding fragment.
43. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain of claim 37.
44. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain of claim 37.
45. An expression vector comprising the nucleic acid of claim 43.
46. An expression vector comprising the nucleic acid of claim 44.
47. The expression vector of claim 46, further comprising the nucleic acid of claim 43.
48. A host cell comprising the expression vector of claim 45.
49. A host cell comprising the expression vector of claim 46.
50. A host cell comprising the expression vector of claim 47.
51. The host cell of claim 49, further comprising the expression vector of claim 45.
52. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:
(a) growing the host cell of claim 48 or 49 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and
(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.
53. A method of producing an antibody that binds human RON or an antigen binding fragment of the antibody, the method comprising:
(a) growing the host cell of claim 50 or 51 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and the
immunoglobulin light chain variable region, thereby producing the antibody or the antigenbinding fragment of the antibody; and
(b) purifying the antibody or the antigen-binding fragment of the antibody.
54. The antibody of any one of claims 1-9, 21-25, or 37-42, wherein the antibody binds human RON with a $K_{D}$ of 900 pM or lower as measured by surface plasmon resonance.
55. The antibody of claim 54 , wherein the antibody binds human RON with a $\mathrm{K}_{\mathrm{D}}$ of 500 pM or lower as measured by surface plasmon resonance.
56. The antibody of claim 55 , wherein the antibody binds human RON with a $K_{D}$ of 250 pM or lower as measured by surface plasmon resonance.
57. An isolated antibody that inhibits the biological activity of human RON without inhibiting binding of MSP to human RON.
58. A method of inhibiting or reducing proliferation of a tumor cell comprising exposing the cell to an effective amount of the antibody of any one of claims 1-9, 21-25, 37-42 or 54-57 to inhibit or reduce proliferation of the tumor cell.
59. A method of inhibiting or reducing tumor growth in a mammal, the method comprising exposing the mammal to an effective amount of the antibody of any one of claims 1-9, 21-25, $37-42$ or 54-57 to inhibit or reduce proliferation of the tumor.
60. A method of treating cancer in a human patient, the method comprising administering an effective amount of the antibody of any one of claims 1-9, 21-25, 37-42 or 54-57 to a mammal in need thereof.
61. The method of claim 60 , wherein the cancer is selected from the group consisting of breast, ovarian, prostate, cervical, colorectal, lung, pancreatic, gastric, and head and neck cancers.
62. The antibody of any one of claims 1-9, 21-25, 37-42 or 54-57 for use in therapy.
63. The antibody of any one of claims 1-9, 21-25, 37-42 or 54-57 for use in inhibiting or reducing proliferation of a tumor cell.
64. The antibody of any one of claims 1-9, 21-25, 37-42 or 54-57 for use inhibiting or reducing tumor growth in a mammal.

FIG. 1
Complete Heavy Chain Variable Region Amino Acid Alignments
CDR1
(1) EVKLLESGGGLVQPGGSLKLSCAASGEDFS RHWMSWVRLAFGKGLEWIA EINEDSRTINYTPSLKEREII
(1) EVQLVESGGGLVKPGGSLKLSCAASGFTES YYAMSWIRQTPEKRLEWVAGITNGGSFTYYPDTVKGRETI
(1) EVKLVESGGGLVKPGASLKLSCAASGFIFS SYGMSWVRQTSDKRLEWVA SISSGGGTTYYLDTVKGRFTI
(1) EVQLQESGFSLVKPSQTESLICYVIGDSIT SDYWNWIRKFPGNKLEYMGYIS-YSGSTYYNPSLKSRISI
(I) EVQLQESGPSLVKPSQTLSLICSVTGDSITSGYWNWIRKFPGNKLEYMGYIS-YSGKTYYNPSLKSRISI
(71) SRDNAKNSLFLQMNRVRSEDTALYYCAR RVRIHYYGAMDCWGQGTSVTVSS (SEQ ID NO: 2)
(71) SRDNARNILYLQMSGLRSEDTAMYYCAR QGYYGVNF--DYWGQGTLTVSS (SEQ ID NO: 12)
(71) SRENAKDTLYLQMSGLKSEDTALYYCTR GQWLLKE---AYWGQGILVTVSA (SEQ ID NO: 22)
(70) TRDTSKNQFYLRLNSVTTEDTATYYCARTHILTI----AYWGQGTLVTVSA (SEQ ID NO: 32)
(70) TRDTSKNHYYLQLISVTAEDTATYYCAFSKYDYAM---DYWGQGTSVTVSS (SEQ ID NO: 42)
Fig. 2

| Antibody | CDR1 |  |  |  | CDR2 |  |  |  |  | CDR3 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 07F01 | RHWMS | (SEQ | ID NO: | 5) | EINPDSRTINYTPSLKE | (SEQ | ID | NO: | 6) | RVRIHYYGAMDC | (SEQ | ID | NO: 7) |
| $12 \mathrm{B11}$ | TYAMS | (SEQ | ID NO: | 15) | GITNGGSETYYPDTVKG | (SEQ | ID | NO: | 16) | QGYYGVNF--DY | (SEQ | ID | NO: 17) |
| 17506 | SYGMS | (SEQ | ID NO: | 25) | SISSGGGTTYYLDTVKG | (SEQ | ID | NO: | 26) | GQWLLKF---AY | (SEQ | ID | NO: 27) |
| 18 HO 9 | SDYWN | (SEQ ID | ID NO: | 35) | YIS-YSGSTYYNPSLES | (SEQ | ID | NO: | 36) | THILTI---AY | (SEQ | ID | NO: 37) |
| 29806 | SGYWN | (SEQ ID | ID NO: | 45) | YIS-YSGKTYYNPSLES | (SEQ | ID | NO: | 46) | SKYDYAM---DY | (SEQ | ID | NO: 47) |

Complete Light (Kappa or Lambda) Chain Variable Region Amino Acid Alignments

|  | CDR1 | CDR2 |
| :---: | :---: | :---: |
|  | DIVLTQSQKIVSTSVGARVSVTCKASQ----NVGSSLTWY | YSASFR---YSGVPDR |
| (1) | DAVMTQTPLSLPVSLGDQASISCRSSQSLENSNGNTYLRWYLQRPGQSP | YRVSNR----FSGVPDR |
| (1) | QLVLTQSSS-ASFSLGASAKLTCTLSSQ----HITYTIEWYQQLPLKPPK | ME ERKDGSHSTGYGIPDR |
| (1) | QAVVTQESA-LTTSPGETVILTCRSSAGAV--ITSNFARNVQEKPDHLF | IGDTNIR---APGVEAR |
|  | DIVLTQSPASLAVSLGQRATISCRASEIVDN-FGISFMNWFQQKPGQPE | YASNQ---GSGVPAR |
| DR3 |  |  |
| (62) | FTGSGSGTDFILTISNVQSEDLADYFCQQYNNYP----ITEGAGTKLELK | (SEQ ID NO: 4) |
|  | FSGSGSGTDFTLKIIRVEAEDLGLYFCLQVTHVP----HTFGGGTKLELK | (SEQ ID NO: 14) |
|  | FSGSSSGADRYITISNIQPEDEAIYICGVGETIEDQFVYVEGGGTKVIVL | (SEQ ID NO: 24) |
|  | ESGSLIGDKAALTITGAQTEDEATYFCALWYSNHY---WVFGGGTKLTVL | (SEQ ID NO: 34) |
|  | ESGSGSGTDFSLNIHPVEEDDTAMYEQQSKEVP----PTFGGGTKLEIK | (SEQ ID NO: 44) |

Fig. 4
Light（Kappa or Lambda）Chain CDR Amino Acid Alignments
음아영
＂̈̆8 $\ddot{z} \ddot{8} \ddot{z}$
虽只昌品品



$\ddot{g} \ddot{g} \ddot{g} \ddot{g} \ddot{z} \ddot{z}$
日昌日品


Fig． 5

FIG. 6


FIG. 7


FIG. 8


FIG. 9


FIG. 10


FIG. 11

Complete Heavy Chain Variable Region Amino Acid Alignments


## Fig. 12A

Fig. 12B
Heavy Chain CDR Amino Acid Alignments


## Fig．13A

的宛教
部美家
明早品


＂̈̈色关总
日早昌
惫曷置思
等思
DR2
Fig．13B
Fig. 14A

[^1]Fig. 14B
Light (Kappa) Chain CDR Amino Acid Alignments

Fig. 15B


Fig. 16


Fig. 17


Fig. 18


Fig. 19


[^0]:    1 davmtqtpls lpvslgdqas iscrssqsle nsngntylnw ylqkpgqspq lliyrvsnrf
    61 sgvpdrfsgs gsgtdftlki irveaedlgl yfclqvthvp htfgggtkle lkradaaptv 121 sifppsseql tsggasvvcf lnnfypkdin vkwkidgser qngvlnswtd qdskdstysm 181 sstltltkde yerhnsytce athktstspi vksfnrnec

[^1]:    CDR2
    AASNQGSGVPARFSGSG
    
    (SEQ ID NO: 44)
    (SEQ ID NO: 149)

