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(54) Title: TISSUE-SPECIFIC WNT SIGNAL ENHANCING MOLECULES AND USES

(57) Abstract: The present disclosure provides tissue-specific Wnt signal enhancing molecules, and related methods of using these molecules to increase Wnt signaling in liver tissues.

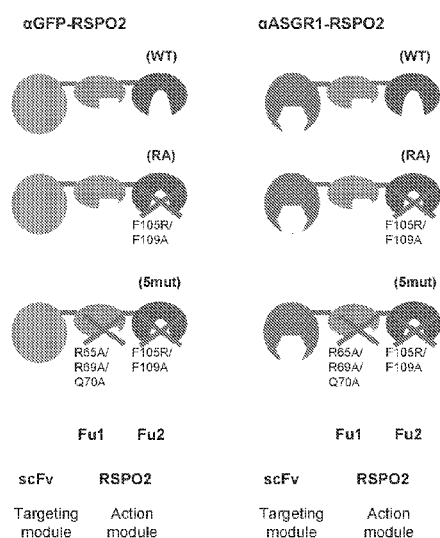


FIG. 1B

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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TISSUE-SPECIFIC WNT SIGNAL ENHANCING MOLECULES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/695,509, filed on July 9, 2018, U.S. Provisional Application No. 62/770,026, filed on November 20, 2018, and U.S. Provisional Application No. 62/822,731, filed on March 22, 2019, each of which is incorporated by reference herein in its entirety.

STATEMENT REGARDING SEQUENCE LISTING

[0002] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is SRZN_010_03WO_ST25.txt. The text file is 661 KB, was created on July 9, 2019, and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

[0003] The present disclosure relates to tissue-specific Wnt signal enhancing molecules, e.g., fusion proteins, comprising a domain that binds an E3 ubiquitin ligase, ZNRF3 or RNF43, and a tissue-specific cell surface receptor binding domain, as well as related methods of using the tissue-specific Wnt signal enhancing molecules to mediate tissue-specific internalization or sequestration of the E3 ligases, ZNRF3/RNF43, thus stabilizing Wnt receptors and enhancing Wnt signaling in a tissue-specific manner, and to treat and prevent a variety of diseases and disorders.

BACKGROUND OF THE INVENTION

[0004] Wnt (“Wingless-related integration site” or “Wingless and Int-1” or “Wingless-Int”) ligands and their signals play key roles in the control of development, homeostasis and regeneration of many essential organs and tissues, including bone, liver, skin, stomach, intestine, kidney, central nervous system, mammary gland, oral mucosa, taste bud, ovary, cochlea and many other tissues (reviewed, e.g., by Clevers, Loh, and Nusse, 2014; 346:1248012). Modulation of Wnt signaling pathways has potential for treatment of degenerative diseases and tissue injuries. To achieve this goal, it is desirous to develop

strategies to modulate Wnt signaling activity in a tissue-specific or cell type-specific manner to avoid unwanted effects. One of the challenges for modulating Wnt signaling as a therapeutic is the existence of multiple Wnt ligands and Wnt receptors, Frizzled 1-10 (Fzd1-10), with many tissues expressing multiple and overlapping Fzds. Canonical Wnt signals also involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors, which are broadly expressed in various tissues, in addition to Fzds.

[0005] R-spondins 1-4 are a family of ligands that amplify Wnt signals. Each of the R-spondins work through a receptor complex that contains Zinc and Ring Finger 3 (ZNRF3) or Ring Finger Protein 43 (RNF43) on one end and a Leucine-rich repeat-containing G-protein coupled receptor 4-6 (LGR4-6) on the other (reviewed, e.g., by Knight and Hankenson 2014, *Matrix Biology*; 37: 157-161). R-spondins might also work through additional mechanisms of action. ZNRF3 and RNF43 are two membrane-bound E3 ligases specifically targeting Wnt receptors (Fzd1-10 and LRP5 or LRP6) for degradation. Binding of an R-spondin to ZNRF3/RNF43 and LGR4-6 causes clearance or sequestration of the ternary complex, which removes E3 ligases from Wnt receptors and stabilizes Wnt receptors, resulting in enhanced Wnt signals. Each R-spondin contains two Furin domains (1 and 2), with Furin domain 1 binding to ZNRF3/RNF43, and Furin domain 2 binding to LGR4-6. Fragments of R-spondins containing Furin domains 1 and 2 are sufficient for amplifying Wnt signaling. While R-spondin effects depend on Wnt signals, since both LGR4-6 and ZNRF3/RNF43 are widely expressed in various tissues, the effects of R-spondins are not tissue-specific.

[0006] There is clearly a need in the art for tissue-specific Wnt signal enhancing molecules for the treatment and prevention of specific diseases and disorders. The present invention addresses this need by providing compositions and methods useful for enhancing Wnt activity in a tissue-specific manner.

SUMMARY OF THE INVENTION

[0007] The present invention relates to tissue-specific Wnt signal enhancing molecules and uses thereof, e.g., in increasing Wnt signaling in a target tissue and treating disease and conditions that would benefit from increased Wnt signaling. In particular embodiments, the tissue is liver.

[0008] In one embodiment, the present invention provides a tissue-specific Wnt signal enhancing molecule, or a pharmaceutically acceptable salt thereof, comprising a first domain

that specifically binds one or more transmembrane E3 ubiquitin ligases selected from ZNRF3 and RNF43, and a second domain that specifically binds a tissue-specific cell surface molecule, wherein the molecule increases Wnt signaling in the tissue. In certain embodiments, the Wnt signal enhancing molecule is liver-specific, and the second domain specifically binds a liver-specific cell surface molecule and increases Wnt signaling in the liver or liver cells. In various embodiments, either or both of the first domain and the second domain are polypeptides, antibodies, small molecules, natural ligands, non-natural ligands, or variants thereof.

[0009] In particular embodiments of Wnt signal enhancing molecules, the first domain comprises a first polypeptide sequence and/or the second domain comprises a second polypeptide sequence. In particular embodiments, the molecule is a fusion protein comprising the first polypeptide sequence and the second polypeptide sequence. In certain embodiments, the first polypeptide sequence comprises an R-Spondin sequence or a fragment or variant thereof. In particular embodiments, the R-spondin is an R-spondin-1, an R-spondin-2, an R-spondin-3, or an R-spondin-4, e.g., a human R-spondin-1-4. In certain embodiments, the first polypeptide sequence comprises an R-spondin Furin domain 1 or a fragment or variant thereof. In particular embodiments, the first polypeptide sequence is a wild-type R-spondin-derived sequence or a modified sequence. In addition, the first polypeptide sequence could have increased, similar, or reduced binding to LGR4-6 as compared to the corresponding native full length R-spondin. In some embodiments, the R-spondin or the R-spondin Furin domain 1 has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% identity to any of the R-spondins or R-spondin Furin 1 domains present in SEQ ID NOs:1-4. In certain embodiments, the first polypeptide is an antibody or antigen-binding fragment thereof that specifically binds ZNRF3 and/or RNF43. In particular embodiments, the first polypeptide is an antibody or an antigen-binding fragment thereof, comprising: a) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or b) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the first polypeptide is an antibody or an antigen-binding fragment thereof, comprising a nanobody, VH or VL sequence set forth in Table 2B or SEQ ID NOs:78-150 or 165-170, or a fragment or variant thereof.

[0010] In certain embodiments, the second polypeptide sequence is polypeptide, an antibody or fragment or variant thereof, or a ligand or fragment or variant thereof. In certain

embodiments, the second polypeptide is an antibody or antigen-binding fragment thereof that specifically binds ASGR1 and/or ASGR2. In particular embodiments, the second polypeptide is an antibody or an antigen-binding fragment thereof, comprising: a) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or b) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the first polypeptide is an antibody or an antigen-binding fragment thereof, comprising a nanobody, VH or VL sequence set forth in Table 3B or SEQ ID NOs:47-77, 151-154, 171-179, or 274-305, or a fragment or variant thereof.

[0011] In certain illustrative embodiments of the tissue-specific Wnt signal enhancing molecules disclosed herein: the tissue is bone tissue, and the cell surface receptor is parathyroid hormone receptor 1 (PTH1R); the tissue is liver tissue, and the cell surface receptor is asialoglycoprotein receptor 1 (ASGR1), asialoglycoprotein receptor 2 (ASGR2), transferrin receptor 2 (TFR2) or solute carrier family 10 member 1 (SLC10A1); or the tissue is oral mucous tissue, and the cell surface receptor is LY6/PLAUR Domain Containing 3 (LYPD3) or Desmoglein 3 (DSG3). In particular embodiments, the second polypeptide is an antibody or an antigen-binding fragment thereof, comprising a nanobody, VH or VL sequence set forth in Table 3C or SEQ ID NOs:180-186, or a fragment or variant thereof.

[0012] In certain illustrative embodiments of the tissue-specific Wnt signal enhancing molecules disclosed herein: the cell surface molecule is a PTH1, and the second polypeptide sequence specifically binds PTH1R; the cell surface molecule is ASGR1, and the second polypeptide sequence specifically binds ASGR1; the cell surface molecule is ASGR2, and the second polypeptide sequence specifically binds ASGR2; the cell surface molecule is SLC10A1, and the second polypeptide sequence specifically binds SLC10A1; the cell surface molecule is TFR2, and the second polypeptide sequence specifically binds TFR2; the cell surface molecule is LYPD3, and the second polypeptide sequence specifically binds LYPD3; or the cell surface molecule is DSG3, and the second polypeptide sequence specifically binds DSG3, wherein the second polypeptide is an antibody or fragment thereof, a small molecule, or a ligand, or fragment or variant thereof, of the cell surface molecule.

[0013] In particular embodiments of the tissue-specific Wnt signal enhancing molecules described herein, the first domain and the second domain are joined by a linker moiety. In certain embodiments, the linker moiety is a peptidyl linker sequence. In particular

embodiments, the peptidyl linker sequence comprises one or more amino acids selected from the group consisting of: Glycine, Asparagine, Serine, Threonine and Alanine

[0014] In particular embodiments, the tissue-specific Wnt signal enhancing molecules described herein consist of a single polypeptide, e.g., a fusion protein comprising the first domain and the second domain. In certain embodiments, the tissue-specific Wnt signal enhancing molecules described herein comprise two or more polypeptides, such as dimers or multimers comprising two or more fusion proteins, each comprising the first domain and the second domain, wherein the two or more polypeptides are linked, e.g., through a linker moiety or via a bond between amino acid residues in each of the two or more polypeptides, e.g., an intermolecular disulfide bond between cysteine residues. In particular embodiments, the tissue-specific Wnt signal enhancing molecules described herein comprise two or more polypeptide sequences. For example, a tissue-specific Wnt signal enhancing molecule may comprise antibody heavy and light chains (or antigen-binding fragments thereof) that constitute either the first domain or the second domain, wherein the other domain (i.e., the second domain or first domain) is linked to the antibody heavy chain or light chain, either as a fusion protein or via a linker moiety. In particular embodiments, the other domain is linked to the N-terminus of the heavy chain, the C-terminus of the heavy chain, the N-terminus of the light chain, or the C-terminus of the light chain. Such structures may be referred to herein as appended IgG scaffolds or formats.

[0015] In a related embodiment, the present invention includes a nucleic acid sequence encoding for a tissue-specific Wnt signal enhancing fusion protein disclosed herein or a subunit thereof, e.g., an antibody heavy chain or light chain having an appended or fused first domain or second domain. In a further related embodiment, the present invention includes a vector comprising the nucleic acid sequence. In some embodiments, the vector is an expression vector comprising a promoter sequence operatively linked to the nucleic acid sequence, e.g., in a manner suitable for expression in bacterial or eukaryotic cells. In another embodiment, the vector is engineered for in vitro translation and modification of functional mRNA. In a further related embodiment, the present invention includes a host cell comprising the vector. In yet another further related embodiment, the present invention includes a process for producing a tissue-specific Wnt signal enhancing fusion protein described herein, comprising culturing the host cell under conditions wherein the fusion polypeptide is expressed by the expression vector. In some embodiments, the process further comprises the step of isolating the fusion polypeptide that is produced.

[0016] In another embodiment, the present invention provides a pharmaceutical composition comprising a tissue-specific Wnt signal enhancing molecule described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, adjuvant or carrier.

[0017] In another embodiment, the present invention provides a pharmaceutical composition comprising a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, adjuvant or carrier. In particular embodiments, the nucleic acid sequence comprises DNA or mRNA, optionally a modified mRNA.

[0018] In another embodiment, the present invention provides a pharmaceutical composition comprising a vector comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, adjuvant or carrier. In particular embodiments, the vector comprises a promoter operatively linked to the nucleic acid sequence, which drives expression of the tissue-specific Wnt signal enhancing molecule. In certain embodiments, the vector is an expression vector or a viral vector.

[0019] In another embodiment, the present invention provides a pharmaceutical composition comprising: a tissue-specific Wnt signal enhancing molecule described herein, or a pharmaceutically acceptable salt thereof; a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable diluent, adjuvant or carrier.

[0020] In another embodiment, the present invention provides a pharmaceutical composition comprising: a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule described herein, or a pharmaceutically acceptable salt thereof; a polynucleotide comprising a nucleic acid sequence encoding a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable diluent, adjuvant or carrier. In particular embodiments, the nucleic acid sequence comprises DNA or mRNA, optionally a modified mRNA.

[0021] In another embodiment, the present invention provides a pharmaceutical composition comprising: a vector comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule, or a pharmaceutically acceptable salt thereof; a vector comprising a nucleic acid sequence encoding a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable

diluent, adjuvant or carrier. In particular embodiments, the vector comprises a promoter operatively linked to the nucleic acid sequence, which drives expression of the tissue-specific Wnt signal enhancing molecule. In certain embodiments, the vector is an expression vector or a viral vector.

[0022] In a further embodiment, the present invention includes a method for increasing Wnt signaling in a target tissue, comprising contacting the target tissue with a tissue-specific Wnt signal enhancing molecule described herein, wherein the second domain specifically binds a cell-specific surface molecule on the target tissue, and wherein the tissue-specific Wnt signal enhancing molecule binds the target tissue and sequesters or increases endocytosis of one or more transmembrane E3 ubiquitin ligase selected from ZNRF3 and RNF43 in the target tissue.

[0023] In certain embodiments of any of the methods described herein: the tissue is bone tissue, and the cell surface molecule is PTH1R; the tissue is liver tissue, and the cell surface molecule is ASGR1, ASGR2, TFR2, or SLC10A1; or the tissue is oral mucous tissue and the cell surface receptor is LYPD3 or DSG3. In particular embodiments, the target tissue or cell is contacted with a polynucleotide comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule, or a vector comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule, e.g., an expression vector or viral vector.

[0024] In a further embodiment, the present invention includes a method for increasing Wnt signaling in a target tissue, comprising contacting the target tissue with: a tissue-specific Wnt signal enhancing molecule described herein, wherein the second domain specifically binds a cell-specific surface molecule on the target tissue, and wherein the tissue-specific Wnt signal enhancing molecule binds the target tissue and sequesters or increases endocytosis of one or more transmembrane E3 ubiquitin ligase selected from ZNRF3 and RNF43 in the target tissue, and a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist, or a pharmaceutically acceptable salt thereof. In particular embodiments, the target tissue or cell is contacted with a polynucleotide comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and a nucleic acid encoding the Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist. In other embodiments, the target tissue or cell is contacted with a vector comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and a vector encoding the Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist.

[0025] In yet another related embodiment, the present invention includes a method for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is associated with reduced Wnt signaling or would benefit from increased Wnt signaling, comprising providing to the subject an effective amount of a pharmaceutical composition comprising the tissue-specific Wnt signal enhancing molecule, or a pharmaceutically acceptable salt thereof, either alone or in combination with a Wnt, Norrin, or a Wnt activating/mimetic molecule. In particular embodiments, the method is performed using a pharmaceutical composition comprising a polynucleotide comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule (e.g., a DNA or mRNA), or a vector comprising a nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule (e.g., an expression vector or viral vector), alone or in combination with a pharmaceutical composition comprising a polynucleotide comprising a nucleic acid sequence encoding the Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule (e.g., a DNA or mRNA), or a vector comprising a nucleic acid sequence encoding the Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule (e.g., an expression vector or viral vector).

[0026] In particular embodiments of any of the methods of treatment described herein, the disease or disorder is a liver disease or disorder of a tissue selected from the group consisting of: acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, end stage liver disease (ESLD), nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, liver surgery, liver injury, liver transplantation, “small for size” syndrome in liver surgery and transplantation, congenital liver disease and disorders, any other liver disorder or defect resulting from genetic diseases, degeneration, aging, drugs, or injuries. In particular embodiments of any of the methods of treatment or prevention described herein, the pharmaceutical composition is provided systemically, parenterally, orally, intramuscularly, locally, or topically. In particular embodiments, the subject is a mammal, optionally a human.

[0027] In another embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds to a RNF43 or a ZNRF3 polypeptide, comprising a

sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 2B or SEQ ID NOs:78-150 or 165-170, or a heavy chain variable region comprising an amino acid sequence set forth in Table 2B or SEQ ID NOs:78-150 or 165-170. In particular embodiments, the antibody, or antigen-binding fragment thereof comprises a light chain variable region comprising an amino acid sequence having at least 90% identity to the amino acid sequence set forth in Table 2B or SEQ ID NOs:78-150 or 165-170, or a light chain variable region comprising the amino acid sequence set forth in Table 2B or SEQ ID NOs:78-150 or 165-170.

[0028] In another embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds to an ASGR1 or ASGR2 polypeptide, comprising a sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 3B or SEQ ID NOs 47-77, 151-154, 171-179 or 274-305, or a heavy chain variable region comprising an amino acid sequence set forth in Table 3B or SEQ ID NOs 47-77, 151-154, 171-179 or 274-305. In certain embodiments, the antibody, or antigen-binding fragment thereof comprises a light chain variable region comprising an amino acid sequence having at least 90% identity to the amino acid sequence set forth in Table 3B or SEQ ID NOs:47-77, 151-154, 171-179 or 274-305, or a light chain variable region comprising the amino acid sequence set forth in Table 3B or SEQ ID NOs:47-77, 151-154, 171-179 or 274-305.

[0029] In particular embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region or light chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 3C or SEQ ID NOs:180-185, or a fragment or variant thereof.

[0030] The present disclosure also provides antibodies and antigen-binding fragments thereof that compete for binding with any of the antibodies or antigen binding fragments thereof disclosed herein.

[0031] In a related embodiment, the disclosure provides a pharmaceutical composition comprising any of the antibodies or antigen-binding fragments thereof disclosed herein.

[0032] In a further embodiment, the disclosure provides a method for increasing liver to body weight ratio, promoting liver regeneration, increasing liver cell proliferation or mitosis, decreasing liver fibrosis, optionally following a chronic liver injury, increasing hepatocyte function, or decreasing coagulation time in liver, comprising providing to a subject in need thereof an effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof disclosed herein that binds to an ASGR1 or ASGR2 polypeptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0034] Features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings.

[0035] **FIGS. 1A-1D. Design of tissue-specific Wnt signaling enhancer molecules.** (FIG. 1A) Alignment of all four human R-spondin proteins (Rspo1 (SEQ ID NO:1); Rspo2 (SEQ ID NO:2); Rspo3 (SEQ ID NO:3); and Rspo4 (SEQ ID NO:4), with the Furin domain 1 (Fu1) and 2 (Fu2) shaded in light and dark shading, respectively. The Fu1 domain generally corresponds to: about amino acid residues 38-94 of SEQ ID NO:1; about amino acid residues 37-93 of SEQ ID NO:2; about amino acid residues 39-95 of SEQ ID NO:3; and about amino acid residues 32-88 of SEQ ID NO:4. The Fu2 domain generally corresponds to: about amino acid residues 97-144 of SEQ ID NO:1; about amino acid residues 96-143 of SEQ ID NO:2; about amino acid residues 98-144 of SEQ ID NO:3; and about amino acid residues 91-137 of SEQ ID NO:4. (FIG. 1B) Scheme of illustrative designed molecules. Fragments of RSPO2 spanning the Fu1 and Fu2 domains (action module) were fused to the C-terminus of scFv antibodies (targeting module) to generate the constructs shown in FIG. 1B, which correspond to the polynucleotide

and polypeptide sequences set forth in SEQ ID NO:5-16. Specific mutations in the Fu1 and Fu2 domains are indicated. (FIG. 1C) Bio-layer interferometry analysis of LGR5 binding to the anti-GFP series and anti-ASGR1 series of fusion proteins, as indicated. Entire steps of the binding assay with 111 nM of RSPO2-derived fusion proteins are shown on top. The binding response composed of association and dissociation phases are separately shown in the inserted boxes. The average responses between 140 to 145 seconds of association phase from 7 different concentrations were analyzed by steady-state analysis to determine K_D values (bottom). (FIG. 1D) Analysis of binding of the indicated constructs to RNF43 and ZNRF3, as indicated (SEQ ID NOs: 43-46).

[0036] FIGS. 2A-2C. In vitro activity of hepatocyte-specific Wnt signaling enhancer molecules. (FIG. 2A) Semi-quantitative PCR analysis of *ASGR1*, and *ASGR2* (top) and *TFRC* (bottom) gene expression level in HEK293, Huh-7 and A431 cells (shown left to right for each gene). The signals were normalized to *ACTB*. (FIG. 2B) SuperTop Flash (STF) reporter activity of specified proteins (SEQ ID NO:5-16) in HEK293 (upper graphs) or Huh-7 (lower graphs), in the presence (left graphs) or absence (right graphs) of exogenous Wnt sources (30% Wnt3a conditioned media). (FIG. 2C) Western Blot analysis on LRP6 receptor and DVL2 phosphorylation in Huh-7 cells. Asterisk indicates a nonspecific band that is detected in Huh-7 by the antibody used. The lower bands indicated by the arrow correspond to DVL2 with and without phosphorylation. Tubulin (TUB) is used as the loading control.

[0037] FIGS. 3A-3C. Dependence of the specific Wnt signal enhancer activity on the targeted receptor. (FIG. 3A) STF activity in HEK293 cells transiently transfected with *TFRC* (encoding transferrin receptor *TFR1* as the control, top), *ASGR1* (middle), and *ASGR1* together with *ASGR2* (bottom), either in the presence (left) or absence (right) of exogenous Wnt source (30% Wnt3a conditioned media). (FIG. 3B) STF activity in A431 cells with *TFRC* or *ASGR1* over expression as specified. (FIG. 3C) Flow cytometry analysis of cell surface level of Fzd proteins. HEK293 cells were transiently transfected with either *ZNRF3* alone (top) or *ASGR1* and *ZNRF3* (bottom), treated with fusion proteins as specified at 10 nM, then stained by the pan-Fzd antibody 18R5.

[0038] FIGS. 4A-4E. Validation of the mechanism with another molecule targeting a different receptor, TFR1. (FIG. 4A) LGR5 binding of the anti-TFR1 series of fusion constructs (SEQ ID NOs:17-22) by Bio-layer interferometry analysis. Entire steps of the binding assay with 111 nM of RSPO2-derived fusion proteins are shown on top. The binding response composed of association and dissociation phases are separately shown in the inserted

box. The average responses between 140 to 145 seconds of association phase from 7 different concentrations were analyzed by steady-state analysis to determine K_D values (bottom). (FIG. 4B) Analysis of binding of the anti-TFR1 series of fusion constructs to RNF43 (left) and ZNRF3 (right), with steady state-fitting analyses for α TFR-RSPO2, α TFR-RSPO2-RA and α TFR-RPOS-5mut from left to right in the lower graphs. (FIG. 4C) STF activity of specified proteins on HEK293 (top) or Huh-7 (bottom) in the presence (left) or absence (right) exogenous Wnt source (30% Wnt3a conditioned media). (FIG. 4D) Western Blot analysis on LRP6 receptor and DVL2 phosphorylation in HEK293 cells. Tubulin (TUB) is used as the loading control. (FIG. 4E) Flow cytometry analysis of cell surface level of Fzd proteins following treatment with fusion proteins or controls. HEK293 cells were transiently transfected with *ZNRF3*, treated with fusion proteins as specified at 10 nM, and then stained by the pan-Fzd antibody 18R5.

[0039] **FIGS. 5A-5D. Wnt-response gene, *Axin2*, induction by the hepatocyte-specific Wnt signal enhancing molecule.** (FIG. 5A) STF activity of the targeted Wnt signal enhancing molecule in the IgG format (SEQ ID NOs: 23-34), in HEK293 (top) or Huh-7 (bottom), in the presence (left) or absence (right) of exogenous Wnt sources (30% Wnt3a conditioned media). (FIG. 5B) Study design. (FIG. 5C) Liver and (FIG. 5D) small intestine expression of *Axin2*, 8 hours after i.p. injection of α -GFP-IgG (SEQ ID NOs: 25-26 and 33-34), Fc-RSPO2-WT (SEQ ID NOs: 23-24), α GFP-RSPO2-RA-IgG (SEQ ID NOs: 25-28) or α ASGR1-RSPO2-RA-IgG (SEQ ID NOs: 29-31) (n=8 mice per group). Statistical analysis was performed using 1-way ANOVA: (ns) not significant, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

[0040] **FIGS. 6A-6E. Liver specific induction of proliferation marker, Ki-67 by the hepatocyte-specific Wnt signal enhancing molecules** (SEQ ID NOs: 25-34). (FIG. 6A) Study design. (FIG. 6B) Semi-quantitative PCR analysis of Liver expression of *Mki67*, 48 hours after treatment as specified (n=10 mice per group). (FIG. 6C) Average number of Ki-67+ parenchymal cell nuclei in livers per field of view under 10x objective after treatment. Statistical analysis was performed using 1-way ANOVA: (**) $p < 0.01$, (****) $p < 0.0001$. (FIG. 6D) Representative images of liver sections stained for Ki67 protein. (FIG. 6E) Semi-quantitative PCR analysis of *Mki67* expression in small intestine.

[0041] **FIGS. 7A-7C. Examples of characterization of binders against hASGR1/2.** (FIG. 7A) Bio-layer interferometry analysis of hASGR1 binding of three Fab antibodies (024S-D03, -E03, and -A04; SEQ ID NOs: 47-52), identified by phage display. On top are sensorgrams, and on the bottom are steady-state fitting analyses to determine the K_D . (FIG. 7B) Binding of

two Fabs against hASGR2 from hybridoma development (ABV-3D11 and -10B8; SEQ ID NOs:151-154). (FIG. 7C) Binding of two Fabs against hASGR1 from hybridoma development (LP1-2I13 and LP1-8M24; SEQ ID NOs:284-285 and 298-299).

[0042] FIG. 8. Scheme of illustrative liver-specific Wnt signaling enhancers. In certain embodiments, the targeting module may be an IgG antibody against hASGR1 or hASGR2, and/or the action module can be RSPO derivatives with wild type or mutated activities. RSPO derivatives can be appended to different positions of the IgG (N- or C- termini of light or heavy chain). In certain configurations, the activation domain can be antibodies or antigen-binding fragments thereof that bind to human ZNRF3/RNF43, e.g., in the form of nanobodies (nAbs), single chain variable regions (scFvs), Fab fragments, or full IgGs. Unlike nAbs and scFv, Fabs contains two polypeptide chains, both of which may be attached to the targeting module, e.g., covalently. Hybrid IgGs are another optional configuration, which contain one Fab as the targeting module and another Fab as the action module. Additionally, in certain configurations, the targeting module can be in the form of nAb/scFv/Fab, while the action module is in the form of IgGs (not shown).

[0043] FIGS. 9A-9D. Dose titration of a liver-specific Wnt signaling enhancer in naïve healthy mice. (FIG. 9A) Biolayer interferometry analysis of cross-species reactivity of the ASGR1 antibody used to construct α ASGR1-RSPO2-RA-IgG (expressed as a Fab, SEQ ID NOs: 29-30 and 161-162). Human and mouse ASGR1 ECDs (SEQ ID NOs: 35-36 and 163-164) were used. Kd determined by curve model fitting was indicated. (FIG. 9B) *Axin2* and (FIG. 9C) *Ki67* expression in liver (upper panel) and small intestine (lower panel) were analyzed by semi-quantitative PCR, 48 hours after i.p. injection of proteins as specified (n=8 mice per group). Statistical analysis was performed using 1-way ANOVA: (ns) not significant, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$. (FIG. 9D) Immunohistochemistry staining of liver samples from 10 mg/kg treatment groups. Anti- β -galactosidase (α - β -Gal-IgG, SEQ ID NOs: 155-158) was a neutral antibody used as a control. SEQ ID NOs of other tested proteins are as described in FIG. 5 legends.

[0044] FIGS 10A-10D. Efficacy of targeted RSPO mimetic in a TAA mouse model of chronic liver disease. (FIG. 10A) Semi-quantitative PCR analysis of Wnt ligands, and *Rspo* genes in normal and TAA treated mice. (FIG. 10B) Study design. (FIG. 10C) Semi-quantitative PCR analysis of *Axin2* (left) and *Ki67* (right) gene expression in liver (upper) and small intestine (bottom). (n=10 mice per group). (FIG. 10D) International Normalized Ratio (INR) of prothrombin time during treatment. Statistical analysis was performed using 1-way

ANOVA: (**) $p < 0.01$, (****) $p < 0.0001$ ($n=10$ mice per group). Anti- β -galactosidase (α - β -Gal-IgG, SEQ ID NOs: 155-156 and 159-160) was a neutral antibody used as a control. SEQ ID NOs of other tested proteins are as described in FIG. 5 legends.

[0045] **FIGS 11A-11BR.** Sequences of Wnt signal enhancers components.

[0046] **FIG. 12.** Scheme of illustrative CCl₄-induced liver fibrosis mouse model and treatment protocol. 8-9 week-old C57BL/6 males (Jackson Laboratories) were intermittently treated with CCl₄ (0.5 mL/kg at day 1, 4, 7, 10, blue arrows) plus allyl alcohol (0.0125 mL/kg at day 2, 5, 8 yellow arrows) for first 10 days, followed by twice/week of 8 weeks CCl₄ treatment (0.5 mL/kg, blue arrows). Following CCl₄ treatment, mice were dosed with protein for 2 weeks. Treatment groups are as follows: no protein control, $n=8$; 10 mpk anti- β Gal, $n=8$ (twice/week dosing); 4.6 mpk RSPO2, $n=7$ (twice/week dosing); 10 mpk anti-eGFP-mutRspo2, $n=8$ (daily dosing); 10 mpk α ASGR1-RSPO2-RA-IgG2, $n=8$ (daily dosing). Additional control groups included no CCl₄ treatment (olive oil carrier, 0.5 mL/kg), $n=8$; naïve control, $n=7$. Blood was drawn from mice on day 69, 72, 76 for INR (international normalized ratio) testing. All mice were terminated on day 83.

[0047] **FIG. 13 Percent Sirius red staining of various treatment groups of CCl₄-induced fibrosis model.** FIG. 13 is a graph showing Sirius red staining of collagen in mouse livers following two weeks of protein treatment as indicated. * represents the statistical significance ($p < 0.05$) of α ASGR-1-RSPO2-RA-IgG vs. α eGFP-mutRSPO2; ** represents the statistical significance of Fc-RSPO2-WT vs. α eGFP-mutRSPO2; *** represents the statistical significance of α ASGR-1-RSPO2-RA-IgG vs. $\alpha\beta$ gal; **** represents the statistical significance of Fc-RSPO2-WT vs. $\alpha\beta$ gal.

[0048] **FIGS. 14A-14D. In vitro hepatocyte-specific activity of RSPO mimetic molecules constructed with internally hybridoma-derived ASGR1 binders.** Fusion proteins (SEQ ID NO:190-271) were constructed by joining mutant RSPO2 to the C-terminus of IgG2 heavy chain (FIG. 14A and FIG. 14 B), or the N-terminus of IgG1 (N297G) heavy chain (FIG. 14C and FIG. 14D) of the ASGR1 binders. Purified proteins were tested for their SuperTop Flash (STF) reporter activity in HEK293 (upper graphs) or Huh-7 (lower graphs), in the presence of exogenous Wnt surrogate molecules (100 pM R2M3-26, described in WO2019126398). Controls used are: Fc-RSPO2-WT (SEQ ID NOs: 23-24), α GFP-RSPO2-RA-IgG (RSPO2 appended to the N-terminus of heavy chain, SEQ ID NOs: 25-28; or RSPO2 appended to the C-terminus of heavy chain, SEQ ID NOs: 25-26 and 188-189) or α - β -Gal-RSPO2-RA-IgG (RSPO2 appended to the C-terminus of heavy chain, SEQ ID NOs: 155-156 and 186-187). In

each panel a table was provided summarizing the EC50 and Emax comparing with the Fc-RSPO positive control.

[0049] FIG. 15. Wnt-response gene, liver *Axin2*, induction by RSPO mimetic molecules derived from invernal hybridoma binders. Mice were injected with 1×10^{11} genomic particles of AAV-TBG-hASGR1 and AAV-TBG-hASGR2 respectively, five days prior to protein dosing. Liver samples were collected 24 hours after protein dosing and processed for semi-quantitative PCR analysis. (A) Sequence ID numbers, name, dose and number of mice used in the study. (B) Liver expression of *Axin2*, after i.p. injection. Statistical analysis was performed using 1-way ANOVA: (**) $p < 0.01$, (***) $p < 0.001$

DETAILED DESCRIPTION OF THE INVENTION

[0050] The present disclosure provides tissue-specific Wnt signal enhancing molecules, where in certain embodiments, the molecules: 1) selectively bind to a tissue- or cell-specific cell surface receptor; 2) mediate internalization or sequestration of ZNRF3/RNF43 in the targeted tissue or cell type; and/or 3) enhance Wnt signaling in a tissue-specific manner. In certain embodiments, the molecules are fusion proteins. In certain embodiments, the molecules are antibodies having an additional appended binding domain. Also provided are pharmaceutical compositions and methods for the use of any of the compositions disclosed herein for enhancing, i.e., increasing, Wnt signaling in a targeted tissue or cell type, e.g., for the treatment or prophylaxis of a disease or disorder. In particular embodiments, the molecules bind liver tissue and may be used to increase Wnt signaling in liver tissue or liver cells. These and other objects, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the compositions and methods as more fully described below.

Definitions

[0051] A "vector" as used herein refers to a macromolecule or association of macromolecules that comprises or associates with a polynucleotide and which can be used to mediate delivery of the polynucleotide to a cell. Illustrative vectors include, for example, plasmids, viral vectors, liposomes, and other gene delivery vehicles.

[0052] The term "polynucleotide" refers to a polymeric form of nucleotides of any length, including deoxyribonucleotides or ribonucleotides, or analogs thereof. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs, and may be interrupted by non-nucleotide components. If present, modifications to the nucleotide

structure may be imparted before or after assembly of the polymer. The term polynucleotide, as used herein, refers interchangeably to double- and single-stranded molecules. Unless otherwise specified or required, any embodiment of the invention described herein that is a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form.

[0053] A polynucleotide or polypeptide has a certain percent "sequence identity" to another polynucleotide or polypeptide, meaning that, when aligned, that percentage of bases or amino acids are the same when comparing the two sequences. Sequence similarity can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the worldwide web at ncbi.nlm.nih.gov/BLAST/. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wis., USA, a wholly owned subsidiary of Oxford Molecular Group, Inc. Other techniques for alignment are described in *Methods in Enzymology*, vol. 266: *Computer Methods for Macromolecular Sequence Analysis* (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. Of particular interest are alignment programs that permit gaps in the sequence. The Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. See *Meth. Mol. Biol.* 70: 173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. See *J. Mol. Biol.* 48: 443-453 (1970)

[0054] Of interest is the BestFit program using the local homology algorithm of Smith and Waterman (*Advances in Applied Mathematics* 2: 482-489 (1981)) to determine sequence identity. The gap generation penalty will generally range from 1 to 5, usually 2 to 4 and in many embodiments will be 3. The gap extension penalty will generally range from about 0.01 to 0.20 and in many instances will be 0.10. The program has default parameters determined by the sequences inputted to be compared. Preferably, the sequence identity is determined using the default parameters determined by the program. This program is available also from Genetics Computing Group (GCG) package, from Madison, Wis., USA.

[0055] Another program of interest is the FastDB algorithm. FastDB is described in *Current Methods in Sequence Comparison and Analysis, Macromolecule Sequencing and Synthesis, Selected Methods and Applications*, pp. 127-149, 1988, Alan R. Liss, Inc. Percent sequence identity is calculated by FastDB based upon the following parameters: Mismatch Penalty: 1.00; Gap Penalty: 1.00; Gap Size Penalty: 0.33; and Joining Penalty: 30.0.

[0056] "Recombinant," as applied to a polynucleotide means that the polynucleotide is the product of various combinations of cloning, restriction or ligation steps, and other procedures that result in a construct that is distinct from a polynucleotide found in nature.

[0057] A "control element" or "control sequence" is a nucleotide sequence involved in an interaction of molecules that contributes to the functional regulation of a polynucleotide, including replication, duplication, transcription, splicing, translation, or degradation of the polynucleotide. The regulation may affect the frequency, speed, or specificity of the process, and may be enhancing or inhibitory in nature. Control elements known in the art include, for example, transcriptional regulatory sequences such as promoters and enhancers. A promoter is a DNA region capable under certain conditions of binding RNA polymerase and initiating transcription of a coding region usually located downstream (in the 3' direction) from the promoter.

[0058] "Operatively linked" or "operably linked" refers to a juxtaposition of genetic elements, wherein the elements are in a relationship permitting them to operate in the expected manner. For instance, a promoter is operatively linked to a coding region if the promoter helps initiate transcription of the coding sequence. There may be intervening residues between the promoter and coding region so long as this functional relationship is maintained.

[0059] An "expression vector" is a vector comprising a region which encodes a gene product of interest, and is used for effecting the expression of the gene product in an intended target cell. An expression vector also comprises control elements operatively linked to the encoding region to facilitate expression of the gene product in the target. The combination of control elements and a gene or genes to which they are operably linked for expression is sometimes referred to as an "expression cassette," a large number of which are known and available in the art or can be readily constructed from components that are available in the art.

[0060] As used herein, the terms "polypeptide," "peptide," and "protein" refer to polymers of amino acids of any length. The terms also encompass an amino acid polymer that has been modified; for example, to include disulfide bond formation, glycosylation, lipidation, phosphorylation, or conjugation with a labeling component.

[0061] As used herein, the term "antibody" means an isolated or recombinant binding agent that comprises the necessary variable region sequences to specifically bind an antigenic epitope. Therefore, an antibody is any form of antibody or fragment thereof that exhibits the desired biological activity, e.g., binding the specific target antigen. Thus, it is used in the broadest sense and specifically covers monoclonal antibodies (including full-length

monoclonal antibodies), polyclonal antibodies, human antibodies, humanized antibodies, chimeric antibodies, nanobodies, diabodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments including but not limited to scFv, Fab, and Fab₂, so long as they exhibit the desired biological activity.

[0062] "Antibody fragments" comprise a portion of an intact antibody, for example, the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (e.g., Zapata et al., Protein Eng. 8(10): 1057-1062 (1995)); single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen combining sites and is still capable of cross-linking antigen.

[0063] By "comprising," it is meant that the recited elements are required in, for example, the composition, method, kit, etc., but other elements may be included to form the, for example, composition, method, kit etc. within the scope of the claim. For example, an expression cassette "comprising" a gene encoding a therapeutic polypeptide operably linked to a promoter is an expression cassette that may include other elements in addition to the gene and promoter, e.g. poly-adenylation sequence, enhancer elements, other genes, linker domains, etc.

[0064] By "consisting essentially of," it is meant a limitation of the scope of the, for example, composition, method, kit, etc., described to the specified materials or steps that do not materially affect the basic and novel characteristic(s) of the, for example, composition, method, kit, etc. For example, an expression cassette "consisting essentially of" a gene encoding a therapeutic polypeptide operably linked to a promoter and a polyadenylation sequence may include additional sequences, e.g. linker sequences, so long as they do not materially affect the transcription or translation of the gene. As another example, a variant, or mutant, polypeptide fragment "consisting essentially of" a recited sequence has the amino acid sequence of the recited sequence plus or minus about 10 amino acid residues at the boundaries of the sequence based upon the full length naïve polypeptide from which it was derived, e.g. 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 residue less than the recited bounding amino acid residue, or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 residues more than the recited bounding amino acid residue.

[0065] By “consisting of,” it is meant the exclusion from the composition, method, or kit of any element, step, or ingredient not specified in the claim. For example, a polypeptide or polypeptide domain “consisting of” a recited sequence contains only the recited sequence.

[0066] An "expression vector" as used herein encompasses a vector, e.g. plasmid, minicircle, viral vector, liposome, and the like as discussed herein or as known in the art, comprising a polynucleotide which encodes a gene product of interest, and is used for effecting the expression of a gene product in an intended target cell. An expression vector also comprises control elements operatively linked to the encoding region to facilitate expression of the gene product in the target. The combination of control elements, e.g. promoters, enhancers, UTRs, miRNA targeting sequences, etc., and a gene or genes to which they are operably linked for expression is sometimes referred to as an "expression cassette." Many such control elements are known and available in the art or can be readily constructed from components that are available in the art.

[0067] A "promoter" as used herein encompasses a DNA sequence that directs the binding of RNA polymerase and thereby promotes RNA synthesis, i.e., a minimal sequence sufficient to direct transcription. Promoters and corresponding protein or polypeptide expression may be ubiquitous, meaning strongly active in a wide range of cells, tissues and species or cell-type specific, tissue-specific, or species specific. Promoters may be “constitutive,” meaning continually active, or “inducible,” meaning the promoter can be activated or deactivated by the presence or absence of biotic or abiotic factors. Also included in the nucleic acid constructs or vectors of the invention are enhancer sequences that may or may not be contiguous with the promoter sequence. Enhancer sequences influence promoter-dependent gene expression and may be located in the 5' or 3' regions of the native gene.

[0068] The term "native" or “wild-type” as used herein refers to a nucleotide sequence, e.g. gene, or gene product, e.g. RNA or protein, that is present in a wild-type cell, tissue, organ or organism. The term “variant” as used herein refers to a mutant of a reference polynucleotide or polypeptide sequence, for example a native polynucleotide or polypeptide sequence, i.e. having less than 100% sequence identity with the reference polynucleotide or polypeptide sequence. Put another way, a variant comprises at least one amino acid difference (e.g., amino acid substitution, amino acid insertion, amino acid deletion) relative to a reference polynucleotide sequence, e.g. a native polynucleotide or polypeptide sequence. For example, a variant may be a polynucleotide having a sequence identity of 50% or more, 60% or more, or 70% or more with a full length native polynucleotide sequence, e.g. an identity of 75% or 80% or more, such

as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full length native polynucleotide sequence. As another example, a variant may be a polypeptide having a sequence identity of 70% or more with a full length native polypeptide sequence, e.g. an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full length native polypeptide sequence. Variants may also include variant fragments of a reference, e.g. native, sequence sharing a sequence identity of 70% or more with a fragment of the reference, e.g. native, sequence, e.g. an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the native sequence.

[0069] As used herein, the terms "biological activity" and "biologically active" refer to the activity attributed to a particular biological element in a cell. For example, the "biological activity" of an R-spondin, or fragment or variant thereof refers to the ability to enhance Wnt signals. As another example, the biological activity of a polypeptide or functional fragment or variant thereof refers to the ability of the polypeptide or functional fragment or variant thereof to carry out its native functions of, e.g., binding, enzymatic activity, etc. As a third example, the biological activity of a gene regulatory element, e.g. promoter, enhancer, Kozak sequence, and the like, refers to the ability of the regulatory element or functional fragment or variant thereof to regulate, i.e. promote, enhance, or activate the translation of, respectively, the expression of the gene to which it is operably linked.

[0070] The terms "administering" or "introducing" or "providing", as used herein, refer to delivery of a composition to a cell, to cells, tissues and/or organs of a subject, or to a subject. Such administering or introducing may take place in vivo, in vitro or ex vivo.

[0071] The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof, e.g. reducing the likelihood that the disease or symptom thereof occurs in the subject, and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed

prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

[0072] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, human and non-human primates, including simians and humans; mammalian sport animals (e.g., horses); mammalian farm animals (e.g., sheep, goats, etc.); mammalian pets (dogs, cats, etc.); and rodents (e.g., mice, rats, etc.).

[0073] The various compositions and methods of the invention are described below. Although particular compositions and methods are exemplified herein, it is understood that any of a number of alternative compositions and methods are applicable and suitable for use in practicing the invention. It will also be understood that an evaluation of the expression constructs and methods of the invention may be carried out using procedures standard in the art.

[0074] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, molecular biology (including recombinant techniques), microbiology, biochemistry and immunology, which are within the scope of those of skill in the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Handbook of Experimental Immunology" (D. M. Weir & C. C. Blackwell, eds.); "Gene Transfer Vectors for Mammalian Cells" (J. M. Miller & M. P. Calos, eds., 1987); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987); "PCR: The Polymerase Chain Reaction", (Mullis et al., eds., 1994); and "Current Protocols in Immunology" (J. E. Coligan et al., eds., 1991), each of which is expressly incorporated by reference herein.

[0075] Several aspects of the invention are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the invention. One having ordinary skill in the relevant art, however, will readily recognize that the invention can be practiced without one or more of the specific details or with other methods. The present invention is not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated

acts or events are required to implement a methodology in accordance with the present invention.

[0076] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms “including”, “includes”, “having”, “has”, “with”, or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term “comprising”.

[0077] The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term “about” meaning within an acceptable error range for the particular value should be assumed.

[0078] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

[0079] It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely”, “only” and the like in connection with the recitation of claim elements, or the use of a “negative” limitation.

[0080] Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art and the practice of the present invention will employ, conventional techniques of microbiology and recombinant DNA technology, which are within the knowledge of those of skill of the art.

Tissue-Specific Wnt Signal Enhancing Molecules

[0081] In certain aspects, the present disclosure provides novel tissue-specific Wnt signal enhancing molecules capable of enhancing Wnt activity in a tissue- or cell-specific manner. In

certain embodiments, the tissue-specific Wnt signal enhancing molecules are bi-functional molecules comprising a first domain that binds to one or more ZNRF3 and/or RNF43 ligases, and a second domain that binds to one or more targeted tissue or cell type in a tissue- or cell-specific manner. Each of the first domain and the second domain may be any moiety capable of binding to the ligase complex or targeted tissue or cell, respectively. For example, each of the first domain and the second domain may be, but are not limited to, a moiety selected from: a polypeptide (e.g., an antibody or antigen-binding fragment thereof or a peptide or polypeptide different from an antibody), a small molecule, and a natural ligand or a variant, fragment or derivative thereof. In certain embodiments, the natural ligand is a polypeptide, a small molecule, an ion, an amino acid, a lipid, or a sugar molecule. The first domain and the second domain may be the same type of moiety as each other, or they may be different types of moieties. In certain embodiments, the tissue-specific Wnt signal enhancing molecules bind to a tissue- or cell-specific cell surface receptor. In particular embodiments, the tissue-specific Wnt signal enhancing molecules increase or enhance Wnt signaling by at least 50%, at least two-fold, at least three-fold, at least five-fold, at least ten-fold, at least twenty-fold, at least thirty-fold, at least forty-fold, or at least fifty-fold, e.g., as compared to a negative control.

[0082] Tissue-specific Wnt signal enhancing molecules may have different formats. Illustrative formats are depicted in FIG. 1A and FIG. 8. In particular embodiments, the tissue-specific Wnt signal enhancing molecules are fusion proteins comprising a first polypeptide sequence that binds to ZNRF3/RNF43 and a second polypeptide sequence that binds to one or more targeted tissue or cell type in a tissue- or cell-specific manner (see, e.g., FIG. 1A). In certain embodiments, the two polypeptide sequences may be fused directly or via a linker. In certain embodiments, the tissue-specific Wnt signal enhancing molecules comprise two or more polypeptides, such as dimers or multimers comprising two or more fusion proteins, each comprising the first domain and the second domain, wherein the two or more polypeptides are linked, e.g., through a linker moiety or via a bond between amino acid residues in each of the two or more polypeptides, e.g., an intermolecular disulfide bond between cysteine residues. In particular embodiments, a tissue-specific Wnt signal enhancing molecule is an antibody comprising antibody heavy and light chains (or antigen-binding fragments thereof) that constitute either the first domain or the second domain, wherein the other domain (i.e., the second domain or first domain) is linked to the antibody heavy chain or light chain, either as a fusion protein or via a linker moiety. In particular embodiments, the other domain is linked to the N-terminus of the heavy chain, the C-terminus of the heavy chain, the N-terminus of the

light chain, or the C-terminus of the light chain. Such structures may be referred to herein as appended IgG scaffolds or formats. For example, a tissue-specific Wnt signal enhancing molecule can be an antibody that binds ZNRF3/RNF43, wherein a binding domain that binds a tissue- or cell-specific receptor is fused or appended to either the heavy chain or light chain of the antibody that binds ZNRF3/RNF43. In another example, a tissue-specific Wnt signal enhancing molecule can be an antibody that binds a tissue- or cell-specific receptor, wherein a binding domain that binds ZNRF3/RNF43 is fused or appended to either the heavy chain or light chain of the antibody that binds the tissue- or cell-specific receptor. In particular embodiments, a liver-specific Wnt signal enhancing molecule is an antibody or antigen-binding fragment thereof that binds ASGR1 or ASGR2, wherein a binding domain that binds ZNRF3/RNF43 is fused or appended to either the heavy chain or light chain of the antibody or antigen-binding fragment thereof (see, e.g., FIG. 8). In particular embodiments, the binding domain that bind ZNRF3/RNF43 comprises Fu1 and Fu2 domains, wherein the Fu1 and Fu2 domains optionally comprise one or more amino acid modifications, including any of those disclosed herein, e.g., F105R and/or F109A.

[0083] In certain embodiments, the tissue-specific Wnt signal enhancing molecules comprise a first domain (“action module”) that binds ZNRF3/RNF43 and a second domain (“targeting module”) that binds a tissue- or cell-specific receptor, e.g., with high affinity. In certain embodiments, each of these two domains has substantially reduced activity or is inactive in enhancing Wnt signals by itself. However, when the tissue-specific Wnt signal enhancing molecules engage with target tissues that express the tissue-specific receptor, E3 ligases ZNRF3/RNF43 are recruited to a ternary complex with the tissue-specific receptors, leading them to be sequestered, and/or cleared from the cell surface via receptor-mediated endocytosis. The net result is to enhance Wnt signals in a tissue-specific manner.

[0084] In certain embodiments, the action module is a binder to ZNRF3/RNF43 E3 ligases, and it can be designed based on R-spondins, e.g., R-spondins-1-4, including but not limited to human R-spondins-1-4. In certain embodiments, the action module is an R-spondin, e.g., a wild-type R-spondin-1-4, optionally a human R-spondin-1-4, or a variant or fragment thereof. In particular embodiments, it is a variant of any of R-spondins-1-4 having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to the corresponding wild-type R-spondin-1-4 sequence. In certain embodiments, the action module comprises or consists of a Furin domain 1 of an R-spondin, e.g., any of R-spondins 1-4, which bind ZNRF3/RNF43. Extended versions of Furin domain 1 (including, but not limited to, those

with a mutated Furin domain 2 that no longer binds to LGR4-6 or has reduced binding to LGR4-6) or engineered antibodies or any other derivatives or any engineered polypeptides different from antibodies that are able to bind specifically to ZNRF3/RNF43 can also be used. In certain embodiments, the action module comprises one or more Furin domain 1 of an R-spondin. In certain embodiments, it does not comprise a Furin domain 2 of an R-spondin, or it comprises a modified or variant Furin domain 2 of an R-spondin, e.g., a Furin domain 2 with reduced activity as compared to the wild-type Furin domain 2. In certain embodiments, an action module comprises a Furin domain 1 but not a Furin domain 2 of R-spondin. In certain embodiments, an action module comprises two or more Furin domain 1 or multimers of a Furin domain 1. The action domain may comprise one or more wild-type Furin domain 1 of an R-spondin. In particular embodiments, the action module comprises a modified or variant Furin domain 1 of an R-spondin that has increased activity, e.g., binding to ZNRF3/RNF43, as compared to the wild-type Furin domain 1. Variants having increased binding to ZNRF3/RNF43 may be identified, e.g., by screening a phage or yeast display library comprising variants of an R-spondin Furin domain 1. Peptides or polypeptides unrelated to R-spondin Furin domain 1 but with increased binding to ZNRF3/RNF43 may also be identified through screening. Action modules may further comprise additional moieties or polypeptide sequences, e.g., additional amino acid residues to stabilize the structure of the action module or tissue-specific Wnt signal enhancing molecule in which it is present.

[0085] In certain embodiments, the action module comprises an antibody or antigen-binding fragment thereof that specifically binds ZNRF3 and/or RNF43. In particular embodiments, the action module is an antibody or an antigen-binding fragment thereof, comprising: a) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or b) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the action module is an antibody or an antigen-binding fragment thereof, comprising a nanobody, VH or VL sequence set forth in Table 2B or SEQ ID NOs:78-150, or a fragment or variant thereof.

[0086] In further embodiments, the action module comprises another inhibitory moiety, such as a nucleic acid molecule, which reduces or prevents ZNRF3/RNF43 activity or expression, such as, e.g., an anti-sense oligonucleotide; a small interfering RNA (siRNA); a short hairpin RNA (shRNA); a microRNA (miRNA); or a ribozyme. As used herein, “antisense” refers to a

nucleic acid sequence, regardless of length, that is complementary to a nucleic acid sequence. In certain embodiments, antisense RNA refers to single-stranded RNA molecules that can be introduced to an individual cell, tissue, or subject and results in decreased expression of a target gene through mechanisms that do not necessarily rely on endogenous gene silencing pathways. An antisense nucleic acid can contain a modified backbone, for example, phosphorothioate, phosphorodithioate, or others known in the art, or may contain non-natural internucleoside linkages. Antisense nucleic acid can comprise, e.g., locked nucleic acids (LNA). In particular embodiments, the other inhibitor moiety inhibits an activity of one or both of *ZNR3/RNF43*, or it inhibits the gene, mRNA or protein expression of one or both of *ZNR3/RNF43*. In certain embodiments, the inhibitory moiety is a nucleic acid molecule that binds to a *ZNR3/RNF43* gene or mRNA, or a complement thereof.

[0087] “RNA interference” as used herein refers to the use of agents that decrease the expression of a target gene by degradation of a target mRNA through endogenous gene silencing pathways (e.g., Dicer and RNA-induced silencing complex (RISC)). RNA interference may be accomplished using various agents, including shRNA and siRNA. “Short hair-pin RNA” or “shRNA” refers to a double stranded, artificial RNA molecule with a hairpin turn that can be used to silence target gene expression via RNA interference (RNAi). Expression of shRNA in cells is typically accomplished by delivery of plasmids or through viral or bacterial vectors. shRNA is an advantageous mediator of RNAi in that it has a relatively low rate of degradation and turnover. Small interfering RNA (siRNA) is a class of double-stranded RNA molecules, usually 20-25 base pairs in length, similar to miRNA, and operating within the RNA interference (RNAi) pathway. It interferes with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation. In certain embodiments, an siRNA is 18, 19, 20, 21, 22, 23 or 24 nucleotides in length and has a 2-base overhang at its 3' end. siRNAs can be introduced to an individual cell and/or culture system and result in the degradation of target mRNA sequences. “Morpholino” as used herein refers to a modified nucleic acid oligomer wherein standard nucleic acid bases are bound to morpholine rings and are linked through phosphorodiamidate linkages. Similar to siRNA and shRNA, morpholinos bind to complementary mRNA sequences. However, morpholinos function through steric-inhibition of mRNA translation and alteration of mRNA splicing rather than targeting complementary mRNA sequences for degradation.

[0088] In certain embodiments, the targeting module specifically binds to a cell-specific surface molecule, e.g., a cell-specific surface receptor, and can be, e.g., natural ligands, antibodies, or synthetic chemicals. In particular embodiments, the cell-specific surface molecule is preferentially expressed on a target organ, tissue or cell type, e.g., an organ, tissue or cell type in which it is desirable to enhance Wnt signaling, e.g., to treat or prevent a disease or disorder. In particular embodiments, the cell-specific surface molecule has increased or enhanced expression on a target organ, tissue or cell type, e.g., an organ, tissue or cell type in which it is desirable to enhance Wnt signaling, e.g., to treat or prevent a disease or disorder, e.g., as compared to one or more other non-targeted organs, tissues or cell types. In certain embodiments, the cell-specific surface molecule is preferentially expressed on the surface of the target organ, tissue or cell type as compared to one or more other organ, tissue or cell types, respectively. For example, in particular embodiments, a cell surface receptor is considered to be a tissue-specific or cell-specific cell surface molecule if it is expressed at levels at least two-fold, at least five-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100-fold, at least 500-fold, or at least 1000-fold higher in the target organ, tissue or cell than it is expressed in one or more, five or more, all other organs, tissues or cells, or an average of all other organs, tissue or cells, respectively. In certain embodiments, the tissue-specific or cell-specific cell surface molecule is a cell surface receptor, e.g., a polypeptide receptor comprising a region located within the cell surface membrane and an extracellular region to which the targeting module can bind. In various embodiments, the methods described herein may be practiced by specifically targeting cell surface molecules that are only expressed on the target tissue or a subset of tissues including the target tissue, or by specifically targeting cell surface molecules that have higher levels of expression on the target tissue as compared to all, most, or a substantial number of other tissues, e.g., higher expression on the target tissue than on at least two, at least five, at least ten, or at least twenty other tissues.

[0089] Tissue-specific and cell-specific cell surface receptors are known in the art. Examples of tissue- and cell-specific surface receptors include but are not limited to, ASGR1 (for liver specificity), ASGR2 (for liver specificity), TFR2 (for liver specificity), SLC10A1 (for liver specificity), PTH1R (for bone and kidney specificity), LYPD3 (for oral mucous specificity), DSG3 (for oral mucous specificity) etc. Additional receptors for liver delivery are described, e.g., by Yan et al., *Tumor Biology*, 2015; 36:55-67.

[0090] In certain embodiments, the targeting module comprises an antibody or antigen-binding fragment thereof that specifically binds ASGR1 and/or ASGR2. In particular

embodiments, the second polypeptide is an antibody or an antigen-binding fragment thereof, comprising: a) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or b) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the action module is an antibody or an antigen-binding fragment thereof, comprising a nanobody, VH or VL sequence set forth in Table 3B or SEQ ID NOs:47-77 or 151-154, or a fragment or variant thereof.

[0091] In particular embodiments, the tissue-specific Wnt signal enhancing molecule, or a pharmaceutically acceptable salt thereof, comprises a first domain that specifically binds one or more transmembrane E3 ubiquitin ligases selected from Zinc and Ring Finger 3 (ZNRF3) and Ring Finger Protein 43 (RNF43), and a second domain that specifically binds asialoglycoprotein receptor 1 (ASGR1) and/or asialoglycoprotein receptor 2 (ASGR2), wherein: (a) the first domain comprises an antibody or antigen-binding fragment thereof comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences; and/or (b) the second domain comprises an antibody or antigen-binding fragment thereof comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, it comprises a polypeptide having at least 90% identity to any of SEQ ID NOs:47-77 or 151-154. In particular embodiments, it is a liver-specific Wnt signal enhancing molecule comprising an antibody or antigen-binding fragment thereof comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

[0092] An action module or targeting module, e.g., an antibody or antigen-binding fragment thereof, that "specifically binds to" or is "specific for" a particular cell surface polypeptide or receptor is one that binds to that particular polypeptide or receptor without substantially binding to any other polypeptide or polypeptide epitope. In some embodiments, the action modules and targeting modules of the present disclosure specifically bind to ZNRF3/RNF43 or a tissue-specific cell surface molecule (e.g., receptor), respectively, with dissociation constants (K_d) equal to or lower than 1000 nM, equal to or lower than 100 nM, equal to or lower than 10 nM, equal to or lower than 1 nM, equal to or lower than 0.5 nM, equal to or lower than 0.1 nM, equal to or lower than 0.01 nM, equal to or lower than 0.005 nM, equal to or lower than 0.001 nM, or equal to or lower than 0.0005 nM, when measured at a temperature of about 4° C., 25° C, 37° C or 42° C. Affinities of binders, e.g., antibodies, can be readily determined using conventional techniques, for example, those described by Scatchard et al. (Ann. N. Y. Acad. Sci. USA 51:660 (1949), ELISA assays, biolayer interferometry (BLI) assays, and surface plasmon resonance (SPR) assays). Binding properties of an antibody to antigens, cells or tissues thereof may generally be determined and assessed using immunodetection methods including, for example, immunofluorescence-based assays, such as immuno-histochemistry (IHC) and/or fluorescence- activated cell sorting (FACS).

[0093] In certain embodiments, the action module and/or the targeting module of the tissue-specific Wnt signal enhancing molecule are polypeptides, whereas in other embodiments, the action module and/or the targeting module of the tissue-specific Wnt signaling molecule are small organic molecules. In certain embodiments, the action module and the targeting module are both polypeptides, e.g., antibodies or antigen binding fragments thereof. In certain embodiments, the action module and the targeting module of a tissue-specific Wnt signal enhancing molecule are covalently bound to each other. In certain embodiments, the action module and the targeting module of a tissue-specific Wnt signal enhancing fusion molecule are non-covalently bound to each other. In certain embodiments, the action module and the targeting module of a tissue-specific Wnt signal enhancing molecule are present within the same fusion protein. In other embodiments, the action module is present within a first polypeptide further comprising a first binding domain, and the targeting module is present within a second polypeptide further comprising a second binding domain, wherein the first and second binding domain bind to each other. In some embodiments, the first and second binding domain are the same or variants thereof, such as, e.g., an Fc polypeptide. In some embodiments, the first and second binding domain are different from each other. In particular embodiments,

the present invention includes the use of fragments or variants of any of the targeting modules or action modules described herein, including functional fragments or variants of the reference molecule.

[0094] In certain embodiments, a tissue-specific Wnt signal enhancing molecule (e.g., a fusion protein) has a formula selected from: R_1-L-R_2 , and R_2-L-R_1 , wherein R_1 is an action module that binds ZNRF3/RNF43, R_2 is a targeting module that binds a tissue-specific cell surface receptor, and L is a linker, and wherein L may be absent or present. Each of R_1 and R_2 may be any of the various action modules and targeting modules described herein, respectively. Each of R_1 and R_2 may be any moiety capable of binding to one or more of the E3 ligases (ZNRF3 or RNF43), or targeted tissue or cell, respectively. For example, each of R_1 and R_2 may be, but are not limited to, a moiety selected from: a polypeptide (e.g., an antibody or antigen-binding fragment thereof or a peptide or polypeptide different from an antibody), a small molecule, and a natural ligand or a variant, fragment or derivative thereof. In certain embodiments, the natural ligand is a polypeptide, a small molecule, an ion, an amino acid, a lipid, or a sugar molecule. The action module and the targeting module (i.e., R_1 and R_2) may be the same type of moiety as each other, or they may be different types of moieties. In particular embodiments, R_2 is an antibody or antigen-binding fragment thereof, and in certain embodiments, R_2 comprises an Fc protein or analog thereof.

[0095] In certain embodiments, a tissue-specific Wnt signal enhancing molecule comprises a single molecule (e.g., polypeptide), whereas in other embodiments, a Wnt signal enhancing fusion molecule comprises two or more molecules (e.g., polypeptides) bound to each other, e.g., non-covalently bound to each other. For example, in one embodiment, a tissue specific Wnt signal enhancing fusion comprises two molecules having formulas R_3-L_1 and R_4-L_2 , respectively, wherein R_3 is an action module, R_4 is a targeting module, and wherein the L_1 and L_2 groups bind to each other, e.g., to form a dimer. In various embodiments, the L_1 and L_2 groups are the same as each other or different from one another. One example of an L_1 or L_2 group is an Fc sequence, e.g., murine Fc2b or human Fc1, each of which is known in the art. Each of R_3 and R_4 may be any of the various action modules and targeting modules described herein, respectively. Each of R_3 and R_4 may be any moiety capable of binding to one or more of the E3 ligases (ZNRF3 and/or RNF43), or targeted tissue or cell, respectively. In particular embodiments, a tissue-specific Wnt signal enhancing molecule comprises an antibody or binding fragments thereof that binds one or more of the E3 ligases (ZNRF3 and/or RNF43), wherein the antibody heavy chain and/or the antibody light chain comprises an appended

binding domain that binds a targeted tissue or cell. In particular embodiments, a tissue-specific Wnt signal enhancing molecule comprises an antibody or binding fragments thereof that binds a targeted tissue or cell, wherein the antibody heavy chain and/or the antibody light chain comprises an appended binding domain that binds one or more of the E3 ligases (ZNRFB3 and/or RNF43). The appended binding domain may be directly fused to the N-terminus or C-terminus of the antibody, e.g., as a heavy chain or light chain fusion protein, or it may be appended to the heavy chain or light chain via a linker moiety, e.g., to the N-terminus, C-terminus, or an internal amino acid of the heavy chain or light chain. In certain embodiments, the antibody is an IgG.

[0096] In certain embodiments, the tissue-specific Wnt signal enhancing molecules (e.g., fusion proteins) increase Wnt signaling in a liver tissue or liver cell contacted with the fusion protein. In particular embodiments, Wnt signaling in the liver tissue or cell type is increased by at least 50%, at least two-fold, at least three-fold, at least four-fold, at least five-fold, or at least ten-fold.

[0097] Tissue-specific Wnt signal enhancing molecules may be produced by standard methods of organic synthesis and molecular biology known and available in the art. For example, a tissue-specific Wnt signal enhancing fusion protein may be generated by fusing a targeting module (e.g., an antibody or antigen-binding fragment thereof that bind ASGR1 or ASGR2) to an action module (e.g., human R-spondin 2 Furin domain 1 alone, corresponding to amino acid residues N37-R95, or human R-spondin 2 Furin domain 1 followed by a Furin domain 2, in which the Furin domain 2 interaction with the LGR proteins is abolished or compromised by point mutations, e.g., F105A and F109A, singly or in combination). In certain embodiments, the targeting module and action module are fused by a linker, e.g., a glycine-serine linker, with either domain located at the N-terminus of the tissue-specific Wnt signal enhancing molecule. In certain embodiments, the targeting module and action module are fused by a protein linker (e.g., albumin). Additional ways of “fusing” the targeting module with the action module include, but are not limited to, “knob-in-hole” or leucine zipper mediated dimerization, for example. DNA sequences encoding the targeting module, the action module (and, optionally, a linker) may be genetically engineered to encode the desired fusion protein.

[0098] For tissue-specific Wnt signal enhancing fusion molecules, including antibody heavy and light chains, the DNA sequences encoding different parts of the fusion proteins may be inserted into bacterial or eukaryotic expression vectors using standard molecular cloning techniques, and expressed in appropriate host cells. The expressed fusion proteins may be

purified to homogeneity using standard techniques in protein science such as affinity, ion-exchange, and size-exclusion chromatography. The present disclosure also includes functional fragments and variants of any of the polypeptide action modules, targeting modules, and fusion proteins described herein, including variants having at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% polypeptide sequence identity to an action module, targeting module, or fusion protein described herein. Such variants may comprise one or more amino acid modifications as compared to any of the sequences disclosed herein, e.g., one or more amino acid deletion, insertion or substitution. In particular embodiments, functional fragments and variants of tissue-specific Wnt signal enhancing fusion proteins have at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% at least 90% at least 100% or more Wnt signal enhancing activity as compared to the tissue-specific Wnt signal enhancing fusion protein from which they were derived. In certain embodiments, functional fragments and variants of polypeptide action modules have at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% at least 90% at least 100% or more Wnt signal enhancing activity as compared to the action module from which they were derived (when measured in the context of the entire tissue-specific Wnt signal enhancing molecule). In certain embodiments, functional fragments and variants of targeting modules have at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% at least 90% at least 100% or more binding activity as compared to the targeting module from which they were derived.

[0099] The present disclosure also includes polynucleotides or nucleic acid sequences that encode one or more tissue-specific Wnt signal enhancing molecules or components thereof, e.g., fusion proteins or variants thereof, described herein, and vectors comprising these polynucleotides, including expression vectors, and cells comprising these vectors. In certain embodiments, the polynucleotides or nucleic acid sequences are DNA or RNA. In particular embodiments, the RNA is messenger RNA (mRNA). In certain embodiments, the RNA is a modified mRNA comprising one or more modified nucleosides. Modified mRNAs comprising one or more modified nucleoside have been described as having advantages over unmodified mRNAs, including increase stability, higher expression levels and reduced immunogenicity. Non-limiting examples of modified mRNAs that may be used according to the present invention are described, e.g., in PCT Patent Application Publication Nos. WO2011/130624, WO2012/138453, WO2013052523, WO2013151666, WO2013/071047, WO2013/078199,

WO2012045075, WO2014081507, WO2014093924, WO2014164253, US Patent Nos: US 8,278,036 (describing modified mRNAs comprising pseudouridine), US 8,691,966 (describing modified mRNAs comprising pseudouridine and/or N1-methylpseudouridine), US 8,835,108 (describing modified mRNAs comprising 5-methylcytidine), US 8,748,089 (describing modified mRNAs comprising pseudouridine or 1-methylpseudouridine). In particular embodiments, the modified mRNA sequence encoding the tissue-specific Wnt signal enhancing polypeptide comprises at least one modification as compared to an unmodified A, G, U or C ribonucleoside. In particular embodiments, the at least one modified nucleosides include N1-methylpseudouridine and/or 5-methylcytidine. In particular embodiments, the modified mRNA comprises a 5' terminal cap sequence followed by a sequence encoding the tissue-specific Wnt signal enhancing polypeptide, following by a 3' tailing sequence, such as a polyA or a polyA-G sequence.

[0100] In particular embodiments, the polynucleotide is a vector, e.g., an expression vector, and the expression vector comprises a polynucleotide sequence encoding a tissue-specific Wnt signal enhancing fusion molecule (e.g., a fusion protein or one or both chains of an appended antibody) described herein operably linked to a promoter sequence, e.g., a promoter sequence that drives expression of the polynucleotide in a cell. In certain embodiments, the vector is a viral vector, e.g., a virus comprising a polynucleotide comprising an expression cassette comprising a promoter operably linked to a DNA or RNA sequence encoding the tissue-specific Wnt signal enhancing polypeptide. In particular embodiments, the expression cassette comprises 5' and/or 3' cellular or viral UTRs or the derivatives thereof.

[0101] The present disclosure also includes functional fragments and variants of the polynucleotides described herein, including variants having at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% polynucleotide sequence identity to a polynucleotide described herein. Such variants may comprise one or more nucleotide or nucleoside modifications as compared to any of the sequences disclosed herein, e.g., one or more nucleotide deletion, insertion or substitution. In particular embodiments, the polynucleotides described herein are codon-optimized, e.g., to enhance expression of the encoded polypeptide in a host cell. In particular embodiments, polynucleotide variants comprise one or more modified nucleotide or nucleoside.

[0102] The present disclosure also includes cells comprising a polynucleotide or vector that encodes a tissue-specific Wnt signal enhancing molecule, e.g., fusion protein, described herein. In certain embodiments, the cell is a host cell, such as, e.g., an HEK293 cell that may be used

to produce tissue-specific Wnt signal enhancing fusion proteins. In preparing the subject compositions, any host cells may be employed, including but not limited to, for example, mammalian cells (e.g. 293 cells), insect cells (e.g., SF9 cells), microorganisms and yeast. In certain embodiments, the cells are heterologous or autologous to a subject treated with a tissue-specific Wnt signal enhancing polypeptide described herein. In particular embodiments, the cells were obtained from the subject and transduced with a viral vector described herein. In particular embodiments, the transduced cells are delivered to the subject for treatment.

[0103] The present disclosure also includes pharmaceutical compositions comprising one or more tissue-specific Wnt signal enhancing molecules (e.g., fusion proteins), or one or more polynucleotides or vectors comprising sequences encoding a tissue-specific Wnt signal enhancing molecule.

[0104] Wnt signaling may be measured using techniques and assays known and available in the art. In certain embodiments, an increase in Wnt signaling is determined using a cell line corresponding to a target tissue or cell type. In particular embodiments, the cell line contains a reporter plasmid with a marker gene (e.g., a luciferase gene) under the control of a Wnt signal-responsive promoter. Enhanced reporter activity of the cells in response to Wnt3a, Wnt3a conditioned media, or recombinant sources of Wnt3a, by the addition of either Furin domain 1 alone (or together with Furin domain 2, with the F105A and/or F109A point mutations) as a negative control or functional R-spondin (full length or Furin domains 1 and 2) as a positive control may be determined. Reporter activity in response to the tissue-specific Wnt signal enhancing molecules may also be determined by contacting the reporter cell line with the tissue specific Wnt signal enhancing molecule. The negative control may be substantially, significantly, or completely negative for reporter activity, and the tissue-specific Wnt signal enhancing molecule and positive control should show an increase in Wnt signaling response as an increase in reporter activity. Additional controls may include an anti-ASGR1 antibody alone (negative), a fusion protein in which an anti-GFP antibody is used in place of an anti-ASGR1 antibody (negative), and intact Furin domain 1-Furin domain 2 protein (positive). Tissue specificity of the tissue-specific Wnt signal enhancing molecule may be determined by similarly measuring the reporter activity in response to treatment with the tissue-specific Wnt signal enhancing molecule in cell types or tissues other than those targeted. In certain embodiments, reporter activity is higher in the targeted tissue bound by the tissue-specific Wnt signal enhancing molecule as compared to non-targeted tissues, e.g., at least 50%, at least two-fold, at least three-fold, at least four-fold, at least five-fold, or at least ten-fold higher.

[0105] In particular embodiments, a tissue-specific Wnt signal enhancing polypeptide comprises any combination of action module and targeting module, including any combination of any of the action modules and targeting modules described herein. In particular embodiments, they are joined by a linker, e.g., albumin (e.g., human serum albumin), a peptidyl linker, or a non-peptidyl linker, where the targeting and action modules are on the N- and C-termini of the linker, e.g., Fc or albumin, peptidyl linker, or non-peptidyl linker.

[0106] The tissue-specific Wnt signal enhancing molecules can also be joined to a moiety such as a polyethylene glycol (PEG), Fc, albumin, etc. as known in the art to enhance stability in vivo.

[0107] Illustrative, non-limiting examples of tissue-specific Wnt signal enhancing molecules include the following:

[0108] a) a bone tissue specific Wnt signal enhancing polypeptide comprising an action module comprising a variant or fragment of an R-spondin (e.g., human R-spondin 2) having reduced ability to enhance Wnt signaling and a targeting module that specifically binds PTH1R, wherein the tissue specific Wnt signal enhancing polypeptide increases Wnt signaling in bone tissue and may be used to treat a disease or condition of bone tissue;

[0109] b) a liver tissue specific Wnt signal enhancing polypeptide comprising an action module comprising a variant or fragment of an R-spondin (e.g., human R-spondin 2) having reduced ability to enhance Wnt signaling and a targeting module that specifically binds ASGR1, ASGR2, TFR2, or SLC10A1, wherein the tissue specific Wnt signal enhancing polypeptide increases Wnt signaling in liver tissue and may be used to treat a disease or condition of liver tissue; or

[0110] c) an oral mucosal tissue specific Wnt signal enhancing polypeptide comprising an action module comprising a variant or fragment of an R-spondin (e.g., human R-spondin 2) having reduced ability to enhance Wnt signaling and a targeting module that specifically binds LYPDS3 or DSG3, wherein the tissue specific Wnt signal enhancing polypeptide increases Wnt signaling in oral mucosal tissue and may be used to treat a disease or condition of oral mucosal tissue

[0111] Illustrative, non-limiting examples of tissue-specific Wnt signal enhancing molecules include those described in the accompanying Examples and sequences, including but not limited to those described in Table 1. In particular embodiments, a tissue-specific Wnt signal enhancing molecule comprises two or more polypeptide sequences disclosed herein, e.g., in the appended IgG or antibody format. Polypeptides disclosed herein include but are not limited

to polypeptides comprising or consisting of a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity to any of the sequences set forth in Table 1 and fragments and variants thereof. In particular embodiments, polypeptides comprises the action module or targeting module present within any of the sequences set forth in Table 1 (e.g., they may lack tags (e.g., His tag or Flag tag) or other additional sequences), and fragments and variants thereof. In certain embodiments, the polypeptides have activity as an action module and/or a targeting module.

[0112] Illustrative, non-limiting examples of polynucleotides disclosed herein include any that encode for any of the polypeptides, variants and fragments described herein, including those described above. In certain embodiments, the polynucleotides encode polypeptides that have activity as a functional domain and/or a targeting module.

Table 1. Description of Sequence Identifiers

Figure	SEQ ID NO:	Brief Description
1	1	Full length human RSPO1 (PP)
1	2	Full length human RSPO2 (PP)
1	3	Full length human RSPO3 (PP)
1	4	Full length human RSPO4 (PP)
1, 2, 3	5 & 6	anti-GFP, RSPO2 wild type (PN & PP)
1, 2, 3	7 & 8	anti-GFP, RSPO2 (F105R/F109A) (PN & PP)
1, 2, 3	9 & 10	anti-GFP, RSPO2 (R65A/R69A/Q70A/F105A/F109A) (PN & PP)
1, 2, 3	11 & 12	anti-ASGR1, RSPO2 wild type (PN & PP)
1, 2, 3	13 & 14	anti-ASGR1, RSPO2 (F105R/F109A) (PN & PP)
1, 2, 3	15 & 16	anti-ASGR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) (PN & PP)
4	17 & 18	anti-TFR1, RSPO2 wild type (PN & PP)
4	19 & 20	anti-TFR1, RSPO2 (F105R/F109A) (PN & PP)
4	21 & 22	anti-TFR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) (PN & PP)
5, 9-15	23 & 24	Fc-RSPO2 (PN & PP)
		αGFP-RSPO2-RA-IgG
5, 6, 9, 13-15	25 & 26	anti-GFP light chain (PN & PP)
5, 6, 9, 13 & 15	27 & 28	RSPO2 (F105R/F109A), anti-GFP Heavy chain IgG2 (PN & PP)

		<u>αASGR1-RSPO2-RA-IgG</u>
5, 6, 9, 13 & 15	29 & 30	anti-ASGR1 light chain (PN & PP)
5, 6, 9, 13 & 15	31 & 32	RSPO2 (F105R/F109A), anti-ASGR1 Heavy chain IgG2 (PN & PP)
		<u>αGFP-IgG</u>
5 & 6	25 & 26	anti-GFP light chain (PN & PP)
5 & 6	33 & 34	anti-GFP Heavy chain IgG1 (PN & PP)
		<u>ASGR ECDs</u>
7 & 9	35 & 36	hASGR1 ECD
9	163 & 164	mASGR1 ECD
7	37 & 38	hASGR2 ECD
	39 & 40	cynoASGR1 ECD
	41 & 42	cynoASGR2 ECD
		<u>E3 ligase ECDs</u>
1 & 4	43 & 44	hRNF43 ECD
1 & 4	45 & 46	hZNRF3 ECD
		<u>anti-β-Gal</u>
9, 10, 13 & 15	155 & 156	anti- β -Gal light chain (PN & PP)
9	157 & 158	anti- β -Gal Heavy chain IgG1-LALAPG (PN & PP)
10, 13 & 15	159 & 160	anti- β -Gal Heavy chain IgG2 (PN & PP)
		<u>anti-ASGR1 Fab</u>
9	29 & 30	anti-ASGR1 light chain (PN & PP)
9	161 & 162	anti-ASGR1 VH-CH1 (PN & PP)
		<u>α-β-Gal-RSPO2-RA-IgG (C-HC appended)</u>
14	155 & 156	anti- β -Gal light chain (PN & PP)
14	186 & 187	anti- β -Gal Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>α-GFP-RSPO2-RA-IgG (C-HC appended)</u>
14	25 & 26	anti-GFP light chain (PN & PP)
14	188 & 189	anti-GFP Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-1F8-RSPO2-RA-IgG (C-HC appended)</u>
14	190 & 191	LP1-1F8 light chain (PN & PP)

14	192 & 193	LP1-1F8 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-1N15-RSPO2-RA-IgG (C-HC appended)</u>
14	194 & 195	LP1-1N15 light chain (PN & PP)
14	196 & 197	LP1-1N15 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-1P13-RSPO2-RA-IgG (C-HC appended)</u>
14	198 & 199	LP1-1P13 light chain (PN & PP)
14	200 & 201	LP1-1P13 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-1P5-RSPO2-RA-IgG (C-HC appended)</u>
14	202 & 203	LP1-1P5 light chain (PN & PP)
14	204 & 205	LP1-1P5 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-2E12-RSPO2-RA-IgG (C-HC appended)</u>
14	206 & 207	LP1-2E12 light chain (PN & PP)
14	208 & 209	LP1-2E12 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-2I13-RSPO2-RA-IgG (C-HC appended)</u>
14	210 & 211	LP1-2I13 light chain (PN & PP)
14	212 & 213	LP1-2I13 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-2I22-RSPO2-RA-IgG (C-HC appended)</u>
14	214 & 215	LP1-2I22 light chain (PN & PP)
14	216 & 217	LP1-2I22 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-3A24-RSPO2-RA-IgG (C-HC appended)</u>
14	218 & 219	LP1-3A24 light chain (PN & PP)
14	220 & 221	LP1-3A24 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-3E20-RSPO2-RA-IgG (C-HC appended)</u>
14	222 & 223	LP1-3E20 light chain (PN & PP)
14	224 & 225	LP1-3E20 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-6H3-RSPO2-RA-IgG (C-HC appended)</u>
14	226 & 227	LP1-6H3 light chain (PN & PP)

14	228 & 229	LP1-6H3 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-7B13-RSPO2-RA-IgG (C-HC appended)</u>
14	230 & 231	LP1-7B13 light chain (PN & PP)
14	232 & 233	LP1-7B13 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-7I20-RSPO2-RA-IgG (C-HC appended)</u>
14	234 & 235	LP1-7I20 light chain (PN & PP)
14	236 & 237	LP1-7I20 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-8M24-RSPO2-RA-IgG (C-HC appended)</u>
14	238 & 239	LP1-8M24 light chain (PN & PP)
14	240 & 241	LP1-8M24 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)

		<u>LP1-9C3-RSPO2-RA-IgG (C-HC appended)</u>
14	242 & 243	LP1-9C3 light chain (PN & PP)
14	244 & 245	LP1-9C3 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-9M16-RSPO2-RA-IgG (C-HC appended)</u>
14	246 & 247	LP1-9M16 light chain (PN & PP)
14	248 & 249	LP1-9M16 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-10C22-RSPO2-RA-IgG (C-HC appended)</u>
14	250 & 251	LP1-10C22 light chain (PN & PP)
14	252 & 253	LP1-10C22 Heavy chain IgG2, RSPO2 (F105R/F109A) (PN & PP)
		<u>LP1-1N15-RSPO2-RA, IgG1 N297G (N-HC appended)</u>
14-15	194 & 195	LP1-1N15 light chain (PN & PP)
14-15	254 & 255	RSPO2 (F105R/F109A), LP1-1N15 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-1P13-RSPO2-RA-IgG1 N297G (N-HC appended)</u>
14-15	198 & 199	LP1-1P13 light chain (PN & PP)
14-15	256 & 257	RSPO2 (F105R/F109A), LP1-1P13 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-2I13-RSPO2-RA-IgG1 N297G (N-HC appended)</u>

14-15	210 & 211	LP1-2I13 light chain (PN & PP)
14-15	258 & 259	RSPO2 (F105R/F109A), LP1-2I13 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-2I22-RSPO2-RA-IgG1 N297G (N-HC appended)</u>
14-15	214 & 215	LP1-2I22 light chain (PN & PP)
14-15	260 & 261	RSPO2 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-3A24-RSPO2-RA-IgG1 N297G (N-HC appended)</u>
14-15	230 & 231	LP1-7B13 light chain (PN & PP)
14-15	266 & 267	RSPO2 (F105R/F109A), LP1-7B13 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-8M24-RSPO2-RA-IgG1 N297G (N-HC appended)</u>
14-15	238 & 239	LP1-8M24 light chain (PN & PP)
14-15	268 & 269	RSPO2 (F105R/F109A), LP1-8M24 Heavy chain IgG1 N297G (PN & PP)
		<u>LP1-9M16-RSPO2-RA-IgG1 N297G (N-HC appended)</u>
14-15	246 & 247	LP1-9M16 light chain (PN & PP)
14-15	270 & 271	RSPO2 (F105R/F109A), LP1-9M16 Heavy chain IgG1 N297G (PN & PP)
15	29 & 30	Anti-ASGR1 light chain (PN&PP)
15	272 & 273	<u>Anti-ASGR1 heavy chain IgG2 (PN & PP)</u>

Action Modules

[0113] R-spondins are capable of amplifying Wnt signals. The minimal functional unit of R-spondin is composed of two Furin domains, Furin domain 1 that binds to ZNRF3/RNF43 E3 ligases, and Furin domain 2 that binds to LGR4-6, bringing together a ternary complex of R-spondin, LGR, and the E3 ligases. This results in internalization of the whole complex and removal of ZNRF3/RNF43 away from their targets of destruction. Furin domain 1 alone is not functional, but it is capable of binding to both ZNRF3 and RNF43.

[0114] The action module of the tissue-specific Wnt signal enhancing molecules described herein can be, but is not limited to, any functional moiety that can bind to the ZNRF3/RNF43 ligases, e.g., polypeptides or organic chemicals. In particular embodiments, the action module, for example a polypeptide comprising the Furin domain 1 of an R-spondin, either alone or together with the targeting module, is substantially inactive in non-target tissues, so as to minimize potential off-target effects. The action module is fused to or bound to a targeting

module in the context of a tissue-specific Wnt signal enhancing molecule, and when the tissue-specific Wnt signal enhancing molecule engages with target tissue that express the tissue-specific receptor, E3 ligases ZNRF3/RNF43 are recruited to a ternary complex with the tissue-specific receptors, leading them to be relocated on the cell surface, sequestered, and/or cleared from the cell surface.

[0115] In certain embodiments, the action module comprises a fragment or variant of an R-spondin polypeptide (e.g., any of R-spondins 1-4), or a functional fragment or variant thereof. In particular embodiments, the action module comprises a fragment of a wild-type R-spondin, and in other embodiments, the action module comprises a fragment of an R-spondin comprising one or more amino acid modifications. The R-spondin may be any R-spondin known in the art or a homolog thereof, including R-spondins from any animal species, including but not limited to mammalian species, such as human R-spondins. R-spondins have been identified and described, and their polypeptide and encoding polynucleotide sequences are known and available in the art. In particular embodiments, the R-spondin polypeptide is a human R-spondin or a homolog found in other vertebrates or non-vertebrates, e.g., a mouse R-spondin. Amino acid sequences of human R-spondin 1, human R-spondin 2, human R-spondin 3, and human R-spondin 4, and the Furin domains 1 thereof, are provided in FIG. 1 and SEQ ID NOs:1-4, respectively. Their homologues and variants are available from general database search, such as <https://www.ncbi.nlm.nih.gov/protein/>. The present invention includes (but is not limited to) action modules comprising or consisting of fragments and variants of any of these or other R-spondins. In various embodiments, variants of any of the R-spondin polypeptides and fragments thereof comprise one or more amino acid modifications, e.g., deletions, additions, or substitutions as compared to the wild-type R-spondin polypeptide. The modification(s) may be present in any region of the variant of R-spondin or a fragment thereof, including but not limited to a Furin domain 1 and/or a Furin domain 2. It is understood that amino acid modifications outside of the Furin domain 1 or Furin domain 2 may alter the resulting variant such that the resulting variant has reduced LGR4-6 binding activity as compared to the wild-type R-spondin or fragment thereof.

[0116] In certain embodiments, the action module comprises or consists of an R-spondin sequence, e.g., a full length or wild-type R-spondin-1, -2, -3 or -4, optionally a human R-spondin-1, -2, -3, or -4, or a variant or fragment thereof. In particular embodiments, it is a variant of any of R-spondins-1-4 having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to the corresponding wild-type R-spondin-1-4

sequence. In certain embodiments, the action module comprises or consists of a full length R-spondin (e.g., any of R-spondins-1-4) comprising one or more amino acid modifications, including but not limited to any of those disclosed herein. In certain embodiments, the action module comprises or consists of a fragment of a wild-type or modified R-spondin (e.g., any of R-spondins-1-4). In particular embodiments, the fragment is able to bind to ZNRF3 and/or RNF43. In certain embodiments, the action module comprises the Furin domain 1 of an R-spondin protein, or fragments or variants of R-spondin proteins. In certain embodiments, the action module comprises or consists of one or more (e.g., one, two or three or more Furin domain 1 of an R-spondin protein (e.g., R-spondin-1-4), or a variant thereof having at least 85%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to an R-spondin Furin domain 1. In certain embodiments, the action module comprises an R-spondin Furin 1 domain or variant or fragment thereof and an R-spondin Furin 2 domain or variant or fragment thereof. In certain embodiments, the action module comprises an antibody, or antigen binding fragment thereof, that bind ZNRF3/RNF43. In particular embodiments, the action module specifically binds to either ZNRF3 or RNF43.

[0117] In certain embodiments, the action module comprises one or more Furin domain 1 of an R-spondin, e.g., human R-spondin 1 or human R-spondin 2, or a variant thereof. In certain embodiments, the action module comprises one or more Furin domain 1 of an R-spondin, but it does not comprise a Furin domain 2 of an R-spondin. In certain embodiments, the action module comprises one or more Furin domain 1 of an R-spondin, and it comprises a modified or variant Furin domain 2 of an R-spondin, e.g., a Furin domain 2 with reduced activity as compared to the wild-type Furin domain 2. In certain embodiments, the action module comprises an R-spondin protein having a modified or variant Furin domain 2 of an R-spondin, e.g., a Furin domain 2 with reduced activity as compared to the wild-type Furin domain 2. In certain embodiments, an action module comprises two or more Furin domains 1, or variants thereof, or multimers of a Furin domain 1 or variant thereof. In certain embodiments, the action module comprises a variant R-spondin Furin 1 domain comprising one or more point mutations, e.g., at amino acid residues corresponding to K58, H76, S77, R86, and/or N91 of human R-spondin 2. In certain embodiments, the action module comprises a variant R-spondin Furin 2 domain comprising one or more point mutations, e.g., at amino acid residues corresponding to F105, F109 and/or K121 of human R-spondin 2. In particular embodiments, the action module comprises a modified or variant Furin domain 1 of an R-spondin that has increased activity, e.g., binding to ZNRF3/RNF43, as compared to the wild-type Furin domain

1. Action modules may further comprise additional moieties or polypeptide sequences, e.g., additional amino acid residues to stabilize the structure of the action module or tissue-specific Wnt signal enhancing molecule in which it is present. In certain embodiments, an action module comprises a peptide or polypeptide without obvious/strong sequence homology to R-spondins but has binding affinity to ZNRF3/RNF43 comparable to or higher than the binding affinity of R-spondins to ZNRF3/RNF43.

[0118] In certain embodiments, the action module comprises a Furin domain 1 of an R-spondin polypeptide (e.g., a human R-spondin), or a functional fragment or variant thereof, and a modified or variant Furin domain 2 of an R-spondin polypeptide (e.g., a human R-spondin), wherein the modified Furin domain 2 has reduced binding affinity to LGR4-6 as compared to the corresponding wild-type Furin domain 2 (see FIGS. 1 and 4). In certain embodiments, the Furin domain 2 comprises one or more point mutations, e.g., at amino acid residues corresponding to F105 and/or F109 of human R-spondin 2. The skilled artisan can readily determine the corresponding amino acid residues in other R-spondin polypeptides by comparing their amino acid sequences to human R-spondin 2. In certain embodiments, the action module comprises a Furin domain 1 or variant thereof and a Furin domain 2 or variant thereof, wherein the Furin domain 1 and/or Furin domain 2 comprises one or more point mutations. The one or more point mutations within the action module (as compared to the corresponding wild-type R-spondin sequence) may occur at any amino acid residues within the Furin domain 1 and/or Furin domain 2, including but not limited to, e.g., at amino acid residues K58, H76, S77, R86, N91, F105, F109, or K121 and other residues that can be modified to reduce the binding affinity to LGR4-6. Regions of the Furin domain 1 and Furin domain 2 of human R-spondin 1 that are important for its functional activity have been identified, including conserved hydrophilic residues S48, N51, R66, R70 and Q71, and less conserved, hydrophobic residues, L46, L54, I62 and L64, which are important for binding to the E3 ligases. In addition, in the human R-spondin 1 Furin domain 1, amino acid residues K59, S78, D85, R87, N88 and N92 form a hydrophilic interaction surface with LGR5, and the FSHNF amino acid sequence has been identified as a loop important for the hydrophobic surface. In particular embodiments, action modules comprising R-spondin Furin domain 1 and/or Furin domain 2 may comprise one or more mutations within any of these regions, surfaces or amino acid residues. In particular embodiments, action modules comprising R-spondin Furin domain 1 and/or Furin domain 2 may comprise one or more mutations or other alternations beyond these regions, surfaces or amino acid residues, which indirectly compromise LGR4-6 binding by affecting

the structure and/or stability of the binding surface. In certain embodiments, action modules comprising R-spondin Furin domain 1 and/or Furin domain 2 may comprise one or more mutations at any amino acid residues, including but not limited to any of those depicted in the accompanying Examples. In particular embodiments, the action module comprises a modified Furin domain 2 comprising amino acid substitutions at amino acid residues F105 and/or F109. In particular embodiments, the action module comprises a Furin 1 domain and a modified Furin domain 2 comprising amino acid substitutions at amino acid residues F105 and/or F109. In particular embodiments, the action module comprises a modified Furin 1 domain and a modified Furin 2 domain, where in certain embodiments, the modified Furin 1 domain comprises one or more amino acid modifications at amino acids R65, R69 and/or Q70, and the modified Furin domain comprises one or more amino acid modification at amino acids F105 and/or F109. In particular embodiments, the modified Furin domain 2 has binding affinity to LGR4-6 less than 80%, less than 50%, less than 20%, or less than 10% the binding of the corresponding wild-type Furin domain 2, e.g., in the context of the full length R-spondin protein.

[0119] In certain embodiments, the action module comprises a Furin domain 1 of an R-spondin polypeptide (e.g., a human R-spondin), or a functional fragment or variant thereof, and an unmodified Furin domain 2 of an R-spondin polypeptide (e.g., a human R-spondin). While in certain embodiments, a modified Furin domain 2 having reduced binding affinity to LGR4-6 as compared to the corresponding wild-type Furin domain 2 is more desirable to increase the specificity of tissue targeting, in particular embodiments, the unmodified Furin domain 2 combined with the targeting module has improved tissue targeting over wild-type R-spondin without targeting module, and has utility in certain contexts.

[0120] In certain embodiments, the action module comprises a wild-type or modified R-spondin Furin domain 1, e.g., from any of R-spondin-1, -2, -3, -4, optionally human R-spondins-1, -2, -3 or -4. In particular embodiments, the action module comprises the R-spondin Furin 1 domain and a wild-type or modified R-spondin Furin 2 domain, e.g., from any of R-spondin-1, -2, -3, -4, optionally human R-spondins-1, -2, -3 or -4. In particular embodiments, the action module comprises the first R-spondin Furin 1 domain and a second wild-type or modified R-spondin Furin 1 domain, e.g., from any of R-spondin-1, -2, -3, -4, optionally human R-spondins-1, -2, -3 or -4. In particular embodiments, the modified Furin domain 2 has comparable binding affinity to LGR4-6 or a binding affinity to LGR4-6 of less than 80%, less

than 50%, less than 20%, or less than 10% the binding of the corresponding wild-type Furin domain 2, e.g., in the context of the full length R-spondin protein.

[0121] In certain embodiments, the action module comprises an antibody or antigen-binding fragment thereof that specifically binds ZNRF3 and/or RNF43. In particular embodiments, the action module comprises an antibody or antigen-binding fragment thereof that binds to human RNF43 (hRNF43, NCBI reference sequence XP_011523257.1, residues 44-198; SEQ ID NO:43-44) or human ZNRF3 (hZNRF3; NCBI reference sequence NP_001193927.1, residues 56-219; SEQ ID NO:45-46). In particular embodiments, the action module is an antibody or an antigen-binding fragment thereof, comprising: a) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or b) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the isolated antibody, or antigen-binding fragment thereof comprises a heavy chain variable region, light chain, nanobody, or scFv sequence comprising an amino acid sequence having at least 90% identity to the heavy chain variable region, light chain, nanobody or scFv of any of these antibodies, e.g., any of SEQ ID NOs:78-154 or 165-170. VL indicates variable light chain, and VH indicates variable heavy chain sequences.

Table 2A: Clone IDs and CDR sequences of binders against hRNF43/ZNRF3

Clone ID	Specificity	CDRH1	SID NO.	CDRH2	SID NO.	CDRH3	SID NO.
020S-E06	RNF43	YTFTGYMH	329	GIINPSGGSTSYA	349	CARGRQGVWDYW	393
020S-F06	RNF43	YTFTSYLH	338	GWMNPNSGNTG YA	366	CARGDFWSGYYPY YYYYYGMDVW	388
028S-B01	RNF43	YTFTAYMH	327	GIINPNGGRTTY A	345	CARSFGVAGTLDY W	404
028S-E01	RNF43	YTFTSYDIN	336	GVINPGGSDTTY A	354	CARDGYYYGMDV W	379
028S-G01	RNF43	YTFTNYMH	332	GWINPHSGGTN YA	356	CAREDYNWNDGW FDPW	386
028S-H01	RNF43	GTFSNYAIS	318	GWINPNSGGTN YA	358	CAKDSGYCSSTSCY DGGYFDLW	376
028S-B02	RNF43	FTFSSYAMH	312	SAISGSGTYA	372	CARDQGHDYGDYE IDYW	383
028S-C02	RNF43	YTFTNYMH	332	GIINPSGGSANY A	348	CARDPVRGISAFDY W	382
024S-A02	RNF43, ZNRF3	YTFTSYAMH	335	GWINAGNGNTK YS	355	CARDLMVRGGPPF DYW	381
028S-D02	ZNRF3	DSVSSNSAA WY	306	GRYYRSKWYH DY A	353	CARVVRAVDAFDI W	407
020S-H06	ZNRF3	YTFTSYMH	339	GWMNPNSGNTG YA	366	CARGRVVRGVII SY GMDVW	397

020S-A07	ZNRF3	DTFTGYIHH	307	GGIPIFDAATYA	342	CTRARGQRSGYSY FDLW	409
020S-B07	ZNRF3	GTFTSTSGIT	321	GWMNPNTGGIK YS	367	CAKSRALKGSYTS W	377
020S-D07	RNF43, ZNRF3	GTFSNTDIN	317	GGIPIFGTANYA	344	CVGGRSGWIWYFD LW	410
020S-E07	ZNRF3	GTFSNYSLS	319	GIINPRRGSTRY A	347	CARDGLGVDAFDI W	378
020S-F07	RNF43, ZNRF3	FTFSNYAMG	311	SYISRSSSTIYYA	697	CARRRDGYNWGY W	402
028S-H02	ZNRF3	YTFTNYMH	332	GRIKPNNGTGY A	351	CARGRRSRGSSSLG YYYMDVW	395
028S-C03	ZNRF3	YTFSRYFMH	326	GWPNPNSGGTR YA	359	CARDQKKGSSSWF RFDPW	384
028S-A04	ZNRF3	YTFTNYKMH	331	GKINPSSGSTSY A	350	CARSGAGMWYFDL W	405
028S-B04	ZNRF3	YTFRRYPMH	325	GIINPSGGSTSYA	349	CARDKVGAIWY	380
028S-C04	ZNRF3	YTFTRYMH	334	GIINPSGGSTSYA	349	CARGGSGWLDYW	391
028S-D04	ZNRF3	GTFSYSAIS	320	GRISPNGGTTY A	352	CARDSWLRGAWG YW	385
028S-E04	ZNRF3	FTFNNFGMS	310	SGISASGRNTYY A	373	CARETRHGSDYW	387
028S-H04	ZNRF3	YTFIGYYMH	324	GWVNPKNIGHTG YA	368	CAKDLEHTGYSSG WAGFDYW	375
028S-B06	ZNRF3	YRFTNYMH	322	GWISPNSGATNY A	363	CARGGRTTVTTMA YW	390
028S-G06	ZNRF3	FAFSNFAMI	308	SAISGSGGSTYY A	370	CARLRANYGMDV W	400
028S-B07	ZNRF3	YTFTEYYMH	328	GWMNPNSGHA GSA	365	CARGRRSGLSPPAY W	394
028S-H07	ZNRF3	YTFTNYGIS	330	GWISADNGNTN YA	362	CARGRSGNWKFW	396
028S-D08	ZNRF3	YTFTSYMH	339	GWPNPNSGNTK YA	360	CARGSNMGMDVW	399
028S-E08	ZNRF3	FSFSNYAMS	309	SAISGSGRTTY A	371	CARRTSSFSLW	403
028S-F08	ZNRF3	GTFSNYAIS	318	GGIPIFDATNYA	343	CARRQYSGYDTHF DYW	401
028S-A09	ZNRF3	YRFTSYLH	323	GWMNPKSGGTN YA	364	CARGGRSYGYWYF DLW	389
028S-D09	ZNRF3	YTFTRHYMH	333	GIINPSGGSTSYA	349	CARGSLGYFDLW	398
028S-E10	ZNRF3	YTFTSYMH	339	GWPNPNTGGTK SA	361	CARVLRGSLGFDY W	406
028S-G10	ZNRF3	YTFTSYGVS	337	GIINPRGGSTSY A	346	CARYSSWSWPFY W	408
028S-A11	ZNRF3	GTFSGYMH	316	GWPNPNRGGTS YA	357	CARGMYSSSWLRY W	392
SC-01	RNF43	GFNIKDT	314	DPANGK	340	GGGYGMDY	411
SC-02	RNF43	GFNIKDD	313	DPENGD	341	SRTTALDY	412
NV-01	ZNRF3	GFTFSDY	315	KSKTDGGI	369	AIYYLEAFDV	374

Table 2A (cont.)

Clone ID	Specificity	CDRL1	SID NO.	CDRL2	SID NO.	CDRL3	SID NO.
020S-E06	RNF43	RSSQSIRTYLN	439	AASTLQS	448	CQQANSFPITF	473
020S-F06	RNF43	RVSQGISSYLN	441	AASTLQS	448	CQQSYGAPLTF	479
028S-B01	RNF43	RSSQSLHSHNGYNYLD	440	DASNLET	451	CMQTLHTPYTF	472
028S-E01	RNF43	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSDPITF	498
028S-G01	RNF43	RASENIHKYLN	417	AASSLQS	447	CQQGYSTPYTF	477
028S-H01	RNF43	RASQNIYDWLA	426	DASNLET	451	CQQTYSTPPTF	492
028S-B02	RNF43	RSSQSLHSHNGYNYLD	440	LGSYRAS	462	CMQALQTPLTF	468
028S-C02	RNF43	RASQSIRSYLN	428	AASSLQS	447	CLQDYDYPLTF	467
024S-A02	RNF43, ZNF3	RASQSVSSSYLA	437	GASSRAT	456	CQQYGSSPRTF	494
028S-D02	ZNRF3	RASQSVNSRYLA	434	GASSRAT	456	CQQYGSSRLTF	495
020S-H06	ZNRF3	RASQSVSSSNLA	436	ATSTRAT	450	CQQYGSSPITF	493
020S-A07	ZNRF3	RASQNIYSWLA	425	DASSLQR	454	CQQSYSTPPTF	487
020S-B07	ZNRF3	RAGQSISRFLN	416	AASSLQS	447	CQQSYSTPYTF	489
020S-D07	RNF43, ZNRF3	RASQSISRWLA	429	DASSLET	452	CQQAYSFPWTF	475
020S-E07	ZNRF3	QASQDISRYLN	415	AASSLQS	447	CQQSYSRPPTF	484
020S-F07	RNF43, ZNRF3	RASQDISNSLN	419	AASTLQS	448	CQQSYSPHPTF	483
028S-H02	ZNRF3	RASQFISTYLN	422	DASSLPS	453	CQQSYSTSWTF	490
028S-C03	ZNRF3	RSSQSLHSHNGYNYLD	440	LGSNRAS	461	CMQSLEAPLAF	471
028S-A04	ZNRF3	RASQDIYRYLN	421	AASSLHS	445	CQQSYTTPITF	491
028S-B04	ZNRF3	RASQGISNYLA	424	AASSLQR	446	CQQSYSTPLTF	486
028S-C04	ZNRF3	RASQSISTWLA	432	AASTLQS	448	CQQSYSSPLTF	485
028S-D04	ZNRF3	RASQSISRWLA	429	AASTLQS	448	CQQSFSTPYTF	478
028S-E04	ZNRF3	TSSQSVLHSSNNKNYLA	443	WASTRAS	464	CQQYHSTPYTF	496
028S-H04	ZNRF3	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSTPLTF	499
028S-B06	ZNRF3	RSSQSLHSHNGYNYLD	440	GASSLQS	455	CMQGTHWPRTF	469
028S-G06	ZNRF3	RASQSISSYLN	431	AASSLQS	447	CQQSYRTPYTF	481
028S-B07	ZNRF3	RASQSVSASLA	435	GASTRAT	457	CHQYFSPMTF	466

028S-H07	ZNRF3	RASQYIGSYLN	438	AASTLQS	448	CQQSYSPPTF	482
028S-D08	ZNRF3	RSSQSLLHSNGYNYLD	440	KASSLES	458	CMQGTHWPYAF	470
028S-E08	ZNRF3	RASQSINNWLA	427	KASSLES	458	CQQANTFPITF	474
028S-F08	ZNRF3	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSTPPTF	500
028S-A09	ZNRF3	RASQSVDSYLA	433	AASARAA	444	CQQYYRSPPTF	497
028S-D09	ZNRF3	RASQSISSWLA	430	AASSLQS	447	CQQSYSTPLTF	486
028S-E10	ZNRF3	RASQDISRYLA	420	AASTVES	449	CQQSYRSPYTF	480
028S-G10	ZNRF3	RASQGISNNLN	423	AASTLQS	448	CQQSYSTPTF	488
028S-A11	ZNRF3	RASQGISNYLA	424	AASSLQS	447	CQQGSSFPPLTF	476
SC-01	RNF43	RASESVDSYGNSFMH	418	LASNLES	459	QQNNEDPLT	502
SC-02	RNF43	KASQSVRPAVA	413	LASNRHT	460	LQHWNYPYT	501
NV-01	ZNRF3	SGDSLGSYYVH	442	RNKQRPS	463	QTYDWMYSSRV	503

Table 2B. Description of Sequence Identifiers

SID NO:	Brief Description	Sequence
78	020S-E06 VL	DIQMTQSPSSLSASVGDRVITICRSSQSIRTYLNWYQQKPGKAPKLLIY AASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPITFG GGTKVEIK
79	020S-E06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHVVRQAPGQGL EWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGRQGVWDYWGRTLVTVSS
80	020S-F06 VL	DIQMTQSPSSLSASVGDRVITICRVSQGISSYLNWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYGAPLT FGQGTKVEIK
81	020S-F06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYLHWVRQAPGQGLE WMGWMNPNSGNTGYAQNFGQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGDFWSGYYPYYYYYGMVDVWGQGTITVTVSS
82	028S-B01 VL	DIVMTQSPSLPVTTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQS PQLLIYDASNLETGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQT LHPTPTFGQGTKLEIK
83	028S-B01 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYMHVVRQAPGQGL EWMGIINPNGGRTTYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARSGFVAGTLDYWGQGTITVTVSS
84	028S-E01 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQ QYYSDPITFGQGTTRLEIK
85	028S-E01 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYDINWVRQAPGQGLE WMGVINPGGSDTTYAQKFQGRVTITADESTSTAYMELSSLRSEDTAV YYCARDGYYYGMVDVWGQGTITVTVSS
86	028S-G01 VL	DIQMTQSPSSLSASVGDRVITICRASENIHKYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGYSTPYT FGQGTKLEIK

87	028S-G01 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQGL EWMGWINPHSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARELYNWNWDGWFDPWGQGLTVTVSS
88	028S-H01 VL	DIQMTQSPSSLSASVGDRVITICRASQNIYDWLAWYQQKPGKAPKLLI YDASNLETGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQTYSTPFT FGPGTKVDIK
89	028S-H01 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSNYAISWVRQAPGQGLE WMGWINPNSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCAKDSGYCSSTSCYDGGYFDLWGRGTLTVTVSS
90	028S-B02 VL	DIVMTQSPSLPLVTPGEPASISCRSSQSLHNSGNYLDWYLQKPGQS PQLLIYLGSRASGVPRFSGSGSGTDFTLKISRVEAEDVGVYYCMQA LQTPLTFGGGTKVEIK
91	028S-B02 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVSAISGSGTYYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYY CARDQGHDIYGDYIDYWGQGLTVTVSS
92	028S-C02 VL	DIQMTQSPSSLSASVGDRVITICRASQSIRSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQDYDYPLT FGGGTKVEIK
93	028S-C02 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQGL EWMGIINPSGGSANYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARDPVRGISAFDYWGQGLTVTVSS
94	024S-D04 VHH	DVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSVINSGGGSTSYAESVKGRFIISRDNKNTLYLQMNSLKPEDTAV YYCARGTYYSGSYYYPALYYGMDYWGKGTQVTVSS
95	024S-A02 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRT FGQGTKVEIK
96	024S-A02 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRL EWMGWINAGNGNTKYSQTFQGRVTITRDTASTAYMELSSLRSED TAVYYCARDLMVRGGPPFDYWGQGLTVTVSS
97	028S-D02 VL	ETTLTQSPGTLSLSPGERATLSCRASQSVNSRYLAWYQQKPGQAPRLI IYGASSRATGIPDRLTGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSRL TFGGGTKVEIK
98	028S-D02 VH	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWYWRQSPSRGLE WLGRTYYRSKYHDYAVSVKSRITINADTSKNQFSLQLNSVTPEDTA VYYCARVVRAVDADFIDWGQGTMTVTVSS
99	020S-H06 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSSNLAWYQQKPGQAPRLI IYATSTRATGIPARFSGSGSGTEFTLTISLQSEDFATYYCQQYGSSPIT FGGGTKVEIK
100	020S-H06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGL EWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGRVVRGVIIISYGMVDVWGQGTTVTVSS
101	020S-A07 VL	DIQMTQSPSSLSASVGDRVITICRASQNIYDWLAWYQQKPGKAPKLLI YDASSLQRGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPPT FGQGTKLEIK
102	020S-A07 VH	QVQLVQSGAEVKKPGSSVKVSCKASGDTFTGYIHWVRQAPGQGLE WMGGIIPIDFAATYAAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCTRARGQRSGYSYFDLWGRGTLTVTVSS
103	020S-B07 VL	DIQMTQSPSSLSASVGDRVITICRASQSIYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPYT FGQGTKLEIK

104	020S-B07 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSTSGITWVRQAPGQGLE WMGWMNPNTGGIKYSQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAKSRALKGSYTSWGQGTLLTVSS
105	020S-D07 VL	DIQMTQSPSSLSASVGDRVITICRASQSISRWLAWYQQKPGKAPKLLI YDASSLETGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQAYSFPWT FGQGTKVEIK
106	020S-D07 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSTNTDINWVRQAPGQGLE WMGGIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCVGGRSGWIWYFDLWGRGTLTVSS
107	020S-E07 VL	DIQMTQSPSSLSASVGDRVITICQASQDISRYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYSPFT FGPGTKVDIK
108	020S-E07 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSTNYSLWVRQAPGQGLE WMGIINPRRGSTRYAQNQFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARDGLGVDAFDIWGQGTMTVTVSS
109	020S-F07 VL	DIQMTQSPSSLSASVGDRVITICRASQDISNSLNWYQQKPGKAPKLLI YAASTLQSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYSPHT FGGGTKVEIK
110	020S-F07 VH	EVQLLESQGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLE WVSYISRSSSTIYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVY YCARRRDGYNWGYWGQGTLLTVSS
111	028S-H02 VL	DIQMTQSPSSLSASVGDRVITICRASQFISTYLNWYQQKPGKAPKLLIY DASSLPSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYSTSWTF GQGTKVEIK
112	028S-H02 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGL EWMGRIKPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGRRSRGSSSLGYYYMDVWGKGTTTVTVSS
113	028S-C03 VL	DIVMTQSPLSLPVTGPGEASISCRSSQSLHSGNYLDWYLQKPGQS PQLLIYLGSRASGVPRFRSGSGSGTDFTLKISRVEAEDVGVYYCMQS LEAPLAFGQGTKLEIK
114	028S-C03 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFSRYFMHWVRQAPGQGL EWMGWINPNSGGTRYAQNQLQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARDQKKGSSSWFRFDPWGQGTLLTVTVSS
115	028S-A04 VL	DIQMTQSPSSLSASVGDRVITICRASQDIYRYLNWYQQKPGKAPKLLI FAASSLHSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPITF GQGTKVEIK
116	028S-A04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYKMHWRQAPGQGL EWMGKINPSSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARSGAGMWYFDLWGRGTLTVTVSS
117	028S-B04 VL	DIQMTQSPSSLSASVGDRVITICRASQGISNYLAWYQQKPGKAPKLLI YAASSLQRGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLT FGGGTKVEIK
118	028S-B04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFRRYPMHWVRQAPGQGL EWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARDKVGAIWYWGQGTLLTVTVSS
119	028S-C04 VL	DIQMTQSPSSLSASVGDRVITICRASQSISTWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSYSSPLT FGGGTKVEIK
120	028S-C04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYMHWRQAPGQGL EWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGGSGWLDYWGQGTLLTVTVSS
121	028S-D04 VL	DIQMTQSPSSLSASVGDRVITICRASQSISRWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQQSFSTPYT

		FGQGTKVEIK
122	028S-D04 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGRISPNRGGTKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARDSWLRGAWGYWGQGLTVTVSS
123	028S-E04 VL	DIVMTQSPDSLAVSLGERATINCTSSQSVLHSSNKKNYLAWYQQKPG QPPKLLIYWASTRASGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QYHSTPYTFGQGTKVEIK
124	028S-E04 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFNNFGMSWVRQAPGKGLE WVSGISASGRNTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDRAV YYCARETRHGS DYWGQGLTVTVSS
125	028S-H04 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLA WYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QYYSTPLTFGGG GTKVEIK
126	028S-H04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFIGYYMHWVRQAPGQGL EWLGWVNPKNIGHTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAKDLEHTGYSSGWAGFDYWGQGLTVTVSS
127	028S-B06 VL	DIVMTQSPLSLPVTPEPASISCRSSQSLHNSNGYNYLDWYLQKPGQS PQLLIYGASSLQSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQG THWPRTFGQGTKVDIK
128	028S-B06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYRFTNYYMHWVRQAPGQGL EWMGWISPNSGATNYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGGRITTVTMMAYWGQGLTVTVSS
129	028S-G06 VL	DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPYTF GQGTKLEIK
130	028S-G06 VH	EVQLLES GGGLVQPGGSLRLSCAASGFAFSNFAMIWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVY YCARLRANYGMDVWGQGTITVTVSS
131	028S-B07 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSASLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCHQYFSPPMT FGQGTRLEIK
132	028S-B07 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYYMHWVRQAPGQGL EWMGWMNPNSGHAGSAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGRRSGLSPPAYWGQGLTVTVSS
133	028S-H07 VL	DIQMTQSPSSLSASVGDRVITICRASQYIGSYLNWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSPPT FGQGTKVEIK
134	028S-H07 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLE WMGWISADNGNTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGRSGNWKFWGQGLTVTVSS
135	028S-D08 VL	DIVMTQSPLSLPVTPEPASISCRSSQSLHNSNGYNYLDWYLQKPGQS PQLLIYKASSLES GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQG THWPYAFGQGTRLEIK
136	028S-D08 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGL ELMGWINPNSGNTKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGSNGMDVWGQGTITVTVSS
137	028S-E08 VL	DIQMTQSPSSLSASVGDRVITICRASQSINNWLAWYQQKPGKAPKLLI YKASSLES GVPDRFSGSGSGTDFTLTISSLQPEDFATYYCQQANTFPITF GQGTRLEIK
138	028S-E08 VH	EVQLLES GGGLVQPGGSLRLSCAASGFSFSNYAMSWVRQAPGKGLE WVSAISGSGRTTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARRTSSFS LWGQGLTVTVSS
139	028S-F08 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLA WYQQKPG

		QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QYYSTPPTFGQGKLEIK
140	028S-F08 VH	QVQLVQSGAEVKKPGSSVKVSKASAGTFSNYAISWVRQAPGQGLE WMGGIIPFDATNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCARRQYSGYDTHFDYWGQGTLLVTVSS
141	028S-A09 VL	EIVMTQSPATLSVSPGERATLSCRASQSVDSYLAWYQQKPGQAPRL LIYAASARAAGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQYYRSP PTFGQGTRLEIK
142	028S-A09 VH	QVQLVQSGAEVKKPGASVKVSKASGYRFTSYLHWVRQAPGQGLE WMGWMNPKSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGGRSYGYWYFDLWGRGTLVTVSS
143	028S-D09 VL	DIQMTQSPSSLSASVGDRVITICRASQSISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLT FGGGTKVEIK
144	028S-D09 VH	QVQLVQSGAEVKKPGASVKVSKASGYTFTRHYMHWVRQAPGQGL EWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGSLGYFDLWGRGTLVTVSS
145	028S-E10 VL	DIQMTQSPSSLSASVGDRVITICRASQDISRYLAWYQQKPGKAPKLLI YAASTVESGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYRSPYT FGQGKLEIK
146	028S-E10 VH	QVQLVQSGAEVKKPGASVKVSKASGYTFTSYMHWVRQAPGQGL EWMGWINPNTGGTKSAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARVLRGSLGFDYWGQGTLLVTVSS
147	028S-G10 VL	DIQMTQSPSSLSASVGDRVITICRASQGISNNLNWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTF GQGKLEIK
148	028S-G10 VH	QVQLVQSGAEVKKPGASVKVSKASGYTFTSYGVSWVRQAPGQGLE WMGIINPRGGSTSYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARYSSSWSPFDYWGQGTLLVTVSS
149	028S-A11 VL	DIQMTQSPSSLSASVGDRVITICRASQGISNYLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGSSFPLT FGQGKVDIK
150	028S-A11 VH	QVQLVQSGAEVKKPGASVKVSKASGGTFSGYYMHWVRQAPGQGL EWMGWINPNRGGTSYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGMYSSSWLRYWGQGTLLVTVSS
165	SC-01 VL	DIVMTQSPDSLAVSLGERATINCRASEVDSYGNFMHWYQQKPGQP PKLLIYLASNLESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQN NEDPLTFGQGKLEIK
166	SC-01 VH	QVQLVQSGAEVKKPGASVKVSKASGFNIKDTYIHWVRQAPGQGLE WMGRIDPANGKANYDPKFQGRVTMTRDTSTSTFYMELSSLRSEDTA VYYCALGGGYGMDYWGQGTLLVTVSS
167	SC-02 VL	DIVMTQSQKFMSTSVGDRVSITCKASQSVRPAAWYQQKPGQSPKAL IYLASNRHTGVDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWNY YTFGGGKLEIK
168	SC-02 VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYIHWVKQRPEQGLEW IGWIDPENGDTKYASKFPKATMTADTSSNTAYLQLSSLTSEDTAVY YCTASRTTALDYWGPQTLLTVSS
169	NV-01 VL	DIELTQPPSVSVSPGQTASITCSGDSLGSYYVHWYQQKPGQAPVLVIY RNKQRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYDWMYS SRVFGGKLTVL
170	NV-01 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGIHWVRQAPGKGLEW VGRIKSKTDGGITEYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAV YYCARAIYYLEAFDVWGQGTLLVTVSS

Table 2C: Binding data for E3 ligase binders

Clone ID	Specificity	Octet KD (M)	Octet KD (M)
020S-E06	RNF43	Not Tested	Not Tested
020S-F06	RNF43	Not Tested	Not Tested
028S-B01	RNF43	Not Tested	Not Tested
028S-E01	RNF43	NB	NB
028S-G01	RNF43	Not Tested	Not Tested
028S-H01	RNF43	NB	NB
028S-B02	RNF43	NB	NB
028S-C02	RNF43	NB	NB
024S-A02	RNF43, ZNRF3	1.01E-05	*
028S-D02	ZNRF3	3.32E-06	*
020S-H06	ZNRF3	NB	NB
020S-A07	ZNRF3	NB	NB
020S-B07	ZNRF3	NB	NB
020S-D07	RNF43, ZNRF3	NB	NB
020S-E07	ZNRF3	NB	NB
020S-F07	RNF43, ZNRF3	NB	NB
028S-H02	ZNRF3	2.63E-06	*
028S-C03	ZNRF3	2.51E-08	***
028S-A04	ZNRF3	3.62E-08	***
028S-B04	ZNRF3	2.56E-07	**
028S-C04	ZNRF3	1.64E-07	**
028S-D04	ZNRF3	8.74E-07	**
028S-E04	ZNRF3	9.53E-08	***
028S-H04	ZNRF3	4.80E-08	***
028S-B06	ZNRF3	7.64E-07	**
028S-G06	ZNRF3	1.09E-07	**
028S-B07	ZNRF3	6.54E-08	***
028S-H07	ZNRF3	NB	NB

028S-D08	ZNRF3	1.39E-06	*
028S-E08	ZNRF3	3.90E-06	*
028S-F08	ZNRF3	1.04E-06	*
028S-A09	ZNRF3	1.25E-05	*
028S-D09	ZNRF3	3.54E-07	**
028S-E10	ZNRF3	4.16E-06	*
028S-G10	ZNRF3	6.84E-07	**
028S-A11	ZNRF3	2.03E-07	**
SC-01	RNF43	Not Tested	Not Tested
SC-02	RNF43	Not Tested	Not Tested
NV-01	ZNRF3	Not Tested	Not Tested

* Indicates $KD \geq 1 \mu M$, ** Indicates $1 \mu M > KD \geq 100 \text{ nM}$, *** Indicates $100 \text{ nM} > KD$, NB indicates Non Binding

Binding specificity was determined by ELISA

Targeting Modules

[0122] Specific cell types and cells within specific tissue may comprise one or more cell- or tissue-specific surface molecule, such as a cell surface receptor. As used herein, the molecule is said to be cell- or tissue-specific if a greater amount of the molecule is present on the specific cell or tissue type as compared to one or more other cell or tissue types, or any other cell or tissue type. In certain embodiments, the greater amount is at least two-fold, at least five-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold as compared to the amount in the one or more other cell or tissue types, or any other cell or tissue type. In particular embodiments, the cell-specific surface molecule has increased or enhanced expression on a target organ, tissue or cell type, e.g., an organ, tissue or cell type in which it is desirable to enhance Wnt signaling, e.g., to treat or prevent a disease or disorder, e.g., as compared to one or more other non-targeted organs, tissues or cell types. In certain embodiments, the cell-specific surface molecule is preferentially expressed on the surface of the target organ, tissue or cell type as compared to one or more other organ, tissue or cell types, respectively. For example, in particular embodiments, a cell surface receptor is considered to be a tissue-specific or cell-specific cell surface molecule if it is expressed at levels at least two-fold, at least five-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100-fold, at least 500-fold, or at least 1000-fold higher in the target organ, tissue or cell than it

is expressed in one or more, five or more, all other organs, tissues or cells, or an average of all other organs, tissue or cells, respectively. In certain embodiments, the tissue-specific or cell-specific cell surface molecule is a cell surface receptor, e.g., a polypeptide receptor comprising a region located within the cell surface membrane and an extracellular region to which the targeting module can bind. In various embodiments, the methods described herein may be practiced by specifically targeting cell surface molecules that are only expressed on the target tissue or a subset of tissues including the target tissue, or by specifically targeting cell surface molecules that have higher levels of expression on the target tissue as compared to all, most, or a substantial number of other tissues, e.g., higher expression on the target tissue than on at least two, at least five, at least ten, or at least twenty other tissues.

[0123] In particular embodiments, the targeting module binds to a tissue-specific surface molecule expressed on a target cell or tissue type of interest, i.e., a cell or tissue type wherein it is desired to enhance or increase Wnt signaling activity. The targeting modules that bind to each tissue-specific surface molecules can be, but are not limited to, antibodies or antigen-binding fragments thereof, peptides, natural ligands of tissue- or cell-specific receptors, or their derivatives, and synthetic small molecules, etc.

[0124] The targeted tissue bound by the targeting module may be any tissue, e.g., any mammalian tissue or cell type. In certain embodiments, the targeted tissue may be present in any organ. In certain embodiments, the target tissue is bone tissue, liver tissue, skin tissue, stomach tissue, intestine tissue, oral mucosa tissue, kidney tissue, central nervous system tissue, mammary gland tissue, taste bud tissue, ovary tissue, inner ear tissue (including cochlear and vestibular tissues), hair follicles, pancreas tissue, retina tissue, cornea tissue, heart tissue or lung tissue, and the targeting module binds to a tissue-specific cell surface molecule (e.g., a cell surface receptor) preferentially expressed on bone tissue, liver tissue, skin tissue, stomach tissue, intestine tissue, oral mucosa tissue, kidney tissue, central nervous system tissue, mammary gland tissue, taste bud tissue, ovary tissue, inner ear tissue (including cochlear and vestibular tissues), hair follicles, pancreas tissue, retina tissue, cornea tissue, heart tissue or lung tissue, respectively.

[0125] The targeting module may bind to any cell type, e.g., any cell within any tissue, organ or animal, including but not limited to mammals, such as humans. In certain embodiments, the tissue-specific Wnt signal enhancing molecule binds to specific cell types, e.g., specific cell types associated with a target tissue. For example, in liver tissue, the targeting module may bind to hepatocytes, precursors and stem cells of hepatocytes, biliary tract cells, and/or

endothelial or other vascular cells. For example, in bone tissue, the targeting module may bind osteoblasts, precursors of osteoblasts, mesenchymal stem cells, stem cells and precursor cells that give rise to bone, cartilage and/or other cells present in bone tissue. Cell types present in various tissues, including but not limited to the tissues described herein, are known in the art, and in various embodiments, the tissue-specific Wnt signal enhancing molecules described herein may bind any of them. In certain embodiments, the targeting module binds to liver tissue or liver cells.

[0126] The asialoglycoprotein receptor (ASGPR) is comprised of ASGR1 and ASGR2 (reviewed, for example by Stockert, Morell and Ashwell, 1991, Targeted Diagnostics and Therapy 4: 41-64). This receptor is a transmembrane protein that plays a critical role in serum glycoprotein homeostasis by mediating the endocytosis and lysosomal degradation of glycoproteins with exposed terminal galactose or N-acetylgalactosamine residues. Thus, natural and synthetic ligands of AGPR include, but are not limited to, galactosylated cholinesterase, galactose (Gal) and N-acetylgalactosamine (GalNAc), GalNAc containing molecules such as GalNAc-terminating glycoproteins, and mono-, oligo-, or poly-saccharide containing molecules or nano-particles (reviewed, for example, by D'Souza and Devarajan 2015, Journal of Controlled Release, 203:126-139).

[0127] The SLC10 family transport bile acids, sulphated solutes, and other xenobiotics in a sodium-dependent manner. The founding members, SLC10A1 (NTCP) and SLC10A2 (ASBT) function to maintain the enterohepatic circulation of bile acids. Examples of natural and synthetic ligands of SLC10A include, but are not limited to, cholate, Na(+)/bile acid, Na(+)/taurocholate, and the preS1 domain of hepatitis B virus and the fragments or variants thereof (reported, for example, by Yan et al., 2012 eLife, 1:e00049).

[0128] Transferrin receptor 2 (TFR2) is a homologue of transferrin receptor 1 (TFR1), the protein that delivers iron to cells through receptor-mediated endocytosis of diferric transferrin (Fe₂TF). TFR2 also binds Fe₂TF, but it seems to function primarily in the regulation of systemic iron homeostasis (reviewed, for example, by Worthen and Enns, 2014, Frontiers in Pharmacology 5:34). Examples of natural and synthetic ligands and binding partners of TFR2 include, but are not limited to, transferrin, such as diferric transferrin, and the hemochromatosis (HFE) protein and fragments and variants thereof.

[0129] The type 1 receptor (PTH1R) for parathyroid hormone (PTH) and PTH-related peptide (PTHrP) is highly expressed in bone and kidney (reviewed, for example, by Mannstadt, Juppner, and Gardella, 1999, American Journal of Physiology 277: F665-F675). Natural and

synthetic ligands of parathyroid hormone receptor 1 (PTH1R) include, but are not limited to, PTH, PTHrP, and fragments and variants thereof.

[0130] Ly6/PLAUR domain-containing protein 3 (LYPD3) is a GPI-anchored protein exhibiting highly specific expression in stratified squamous epithelium found in tissues such as oral mucosa, skin and esophagus. LYPD3 expression was also seen upregulated in migrating keratinocytes during wound healing as well as various cancers (reviewed, e.g., by Jacobsen, Kriegbaum, Santoni-Rugiu and Ploug, 2014, *World Journal of Clinical Oncology*, 5(4):621-32). Even though LYPD3 expression has been reported, its exact function remains unclear, since animals lacking LYPD3 gene are viable, fertile and no obvious defect in development of squamous epithelia. Various molecules have been identified as binding partners of LYPD3. Laminin1, laminin5, and galectin-3 associate with LYPD3 to promote cell migration (Paret, Bourouba, Beer, Miyazaki, Schnölzer, Fiedler and Zöller. *International Journal of Cancer*. 2005 Jul 10;115(5):724-33). Anterior gradient 2, AGR2, interacts with LYPD3 and promotes cancer growth, metastasis and resistance to therapy in pancreatic ductal adenocarcinoma (PDAC) (Arumugam, Deng, Bover, Wang, Logsdon and Ramachandran. *Molecular Cancer Therapeutics*. 2015 Apr;14(4):941-51). Under hypoxic condition, LYPD3 forms a complex with $\alpha 6\beta 4$ integrin and matrix metalloproteinase 14 (MMP14), which promotes cancer cell motility through focalized laminin 332 degradation. (Ngora, Galli, Miyazaki and Zöller. *Neoplasia*. 2012 Feb;14(2):95-107).

[0131] Desmoglein 3 (DSG3) encodes a calcium-binding transmembrane glycoprotein that is a member of cadherin cell adhesion molecule superfamily of proteins. DSG3 is expressed in desmosomes, special structure for cell to cell adhesion, in epithelium and mucosa. DSG3 has five extracellular cadherin domains (ECDs) containing Ca^{2+} -binding sites that are required for DSG3 intercellular interaction (reviewed, e.g., by Thomason, Scothern, McHarg and Garrod, 2010, *Biochemical Journal*, 429 (3): 419-433). DSG3 intercellular interaction is mediated by trans-homophilic interaction near their N-termini. The loss of DSG3 in animals causes very severe erosion in oral mucosa and hair loss at weaning, indicating how important this gene is for the integrity of epithelial cells in these tissues. Single molecule atomic force microscopy experiment has shown a homophilic trans DSG3-binding via extracellular cadherin domains (Heupel, Zillikens, Drenckhahn and Waschke. *Journal of Immunology*. August 1, 2008, 181 (3) 1825-1834).

[0132] In various embodiments, the tissue-specific surface molecules are tissue-specific cell surface receptors. For liver, these include, but are not limited to, ASGR1, ASGR2, TFR2,

SLC10A1, etc. In certain embodiments, the targeting module is a natural ligand, or functional variant or fragment thereof, or an antibody, or antigen-binding fragment thereof, that binds ASGR1, ASGR2, TFR2, SLC10A1, LYPD3, or DSG3. For bone or kidney, such tissue-specific cell surface receptors include, but are not limited to, parathyroid hormone receptor 1 (PTH1R), etc. In certain embodiments, the targeting module is a natural ligand, or a functional variant or fragment thereof, or an antibody, or antigen-binding fragment thereof, that binds PTH1R. For oral mucosa, such tissue-specific cell surface receptors include, but are not limited to, LYPD3 and DSG3. In certain embodiments, the targeting module is a natural ligand, or a functional variant or fragment thereof, or an antibody, or antigen-binding fragment thereof, that binds LYPD3 or DSG3.

[0133] In particular embodiments, the targeting module binds to human ASGR1 (hASGR1; NCBI reference sequence NP_001662.1, residues 62-291; SEQ ID NO:35-36), human ASGR2 (hASGR2; NCBI reference sequence NP_550436.1, residues 66-292; SEQ ID NO:37-38), cynomolgus ASGR1 (cynoASGR1, sequence ID XP_005582755.1, residues 62-291; SEQ ID NO:39-40), or cynomolgus ASGR2 (cynoASGR2; SEQ ID NO:41-42).

In certain embodiments, the targeting module comprises an antibody or antigen-binding fragment thereof, comprising the CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies listed in Table 3A; and/or CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the isolated antibody, or antigen-binding fragment thereof comprises a heavy chain variable region, light chain, nanobody, or scFv sequence comprising an amino acid sequence having at least 90% identity to the heavy chain variable region, light chain, nanobody or scFv of any of these antibodies, e.g., any of SEQ ID NOs: 47-77, 151-154, 171-179, 180-185 or 274-305 (see, e.g. Table 3B or 3C).

Table 3A: Clone IDs and CDR sequences of binders against hASGR1/2

Clone ID	Specificity	CDRH1	SID NO.	CDRH2	SID NO.	CDRH3	SID NO.
024S-D03	ASGR1	DSVSSNSAAWN	505	GRTYYRSKWYNDYA	551	CARWNHEEHYFDYW	589
024S-E03	ASGR1	ASVSSNSAAWN	504	GRTYYRSKWYNDYA	551	CARWNHEEHYFDYW	589
024S-A04	ASGR1	DSVSSNSVAWN	505	GRTYYRSKWYYDYA	552	CASWTRGAFDIW	594
020S-A05	ASGR2	GTFSSYAIS	517	GGIPIFGTANYA	544	CAVSDGYDLDYW	596

020S-C05	ASGR2	GTFSSY AIS	517	GGIIPFGTANYA	544	CASFGVGAPDYW	591
020S-G06	ASGR2	YTFTSYGIS	533	GWISAYNGNTNYA	561	CASAGGGYW	590
020S-A06	ASGR2	YTFTGYHMH	530	GGIIPVFGAPNYA	546	CARDGGYGMDVW	576
020S-B06	ASGR2	YTFTGYMH	531	GIINPSGGGTSYA	548	CARDTGATAEYFQHW	580
020S-C06	ASGR2	YSFTGNYMH	520	GGIIPMFGTVKYA	545	CAKDRGYRFDLW	570
020S-D06	ASGR2	FTFSSYAMS	508	SYISSYNSHTNDA	568	CARWAVAAGGQYYMDVW	588
020S-C07	ASGR2	YTFSNYMH	525	GWINPKSGGTKYA	559	CARDRGITMVRGVM DYW	579
028S-H09	ASGR2	YTFTTYMH	535	GWINPNGGGTNYA	560	CAKDRTAMAPEGAFDIW	571
028S-C11	ASGR2	YTFSDYYVH	524	GIINPRNGRTSYA	547	CARDHLYGMDVW	577
028S-D11	ASGR2	FTVSSNYMS	514	SAISGSGGSTYYA	565	CAKDSPIVRRGERGRYYGMDVW	572
028S-G11	ASGR2	YTFTDYNMH	527	GWMNPNTGNTAYA	562	CARDKNYYGMDVW	578
020S-H05	ASGR2	HTFSSYAMG	518	AAISQSGYVRYYA	536	CNARWGAGSLFASW	599
Abv-3D11	ASGR2	GFSFNTY	515	RSKSNNYA	564	PRYDYWYFDV	605
Abv-10B8	ASGR2	GFTFSSY	516	SSGGDY	567	EGTGGMDY	604
RO-01	ASGR1	GFTFSSY	516	SGSGGS	566	DFSSRRWYLEY	603
RO-02	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSWYLPGRGFDYW	575
RO-03	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSSFTFGRYFDYW	574
RO-04	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSSFSYLRAF DYW	573
LP1-1F8	ASGR1	FTFSTYTMS	511	ATISSIGVNTYYP	541	CARHVDYDGISFDYW	583
LP1-1N15	ASGR1	YTFTDYMN	529	GRVIPSNGGTNYN	554	CARGMDYW	582
LP1-1P13	ASGR1	YSFTDYFMN	519	GRFNPFGQTIFYN	550	CARRGRYDVYYVLDYW	586
LP1-1P5	ASGR1	YTFLTYWMN	523	GQIFPATGITYYS	549	CARRRAYHSNFFDYW	587
LP1-2E12	ASGR1	YSITSGYYWN	522	GSIGYDDTNHYN	557	CAGDYPFAFW	569
LP1-2I13	ASGR1	FTFSDYGMH	507	AYISSGSSTIYYA	542	CSRKGGFGDYEKSYAMDYW	600
LP1-2I22	ASGR1	YSFTGYFMN	521	GRFNPFGQTIFYN	550	CARRGRYDVYYALDYW	585
LP1-3A24	ASGR1	YTFTDYYIN	528	GRVIPSNGGSNYN	553	CATQLGRW	595
LP1-3E20	ASGR1	YTFTSYWIH	534	GYINPSSGYAEYN	563	CARESYYSFDYTMDYW	581
LP1-6H3	ASGR1	YTFSRFDMH	526	GVIYPGNGDTSYN	558	CASSYYGNPW	593
LP1-7B13	ASGR1	FTFTDYYMN	512	GRVNPSNDDTRYN	556	CTRWYFYFDYW	601
LP1-7I20	ASGR1	FTFTDYYMS	513	ALIRNKANGYTT EYS	539	CAVTYGAYW	597

LP1-8M24	ASGR1	YTFTNYGIN	532	GEIFPRSDNTFYN	543	CARKGRDYGTSHYF DYW	584
LP1-9C3	ASGR1	FSLSTSYM VS	506	AHIFWDDDKRYN	537	CGGPYYPFTYW	598
LP1-9M16	ASGR1	YTFTDYMN	529	GRVNPNNNGGS N	555	CASRNFDVW	592
LP1-10C22	ASGR1	FTFSSYGMS	510	ASISSGGSYTYYP	540	CVRHEEYGKSGFAY W	602

Table 3A (cont.)

Clone ID	Specificity	CDRL1	SID NO.	CDRL2	SID NO.	CDRL3	SID NO.
024S-D03	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
024S-E03	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
024S-A04	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
020S-A05	ASGR2	RASQSVGSYLA	625	DASNRAT	643	CQQRSNWPLTF	685
020S-C05	ASGR2	RASQSVSSYLA	626	DASNRAT	643	CQQRSNWVPTF	686
020S-G06	ASGR2	RSSQSLHSDGHNY LQ	630	LGSYRAS	651	CMQATHWPPTF	670
020S-A06	ASGR2	RASQNIYTYLN	618	AASSLQS	638	CQQYNYNYPITF	692
020S-B06	ASGR2	RASQGISSWLA	617	AASSLQS	638	CQQAYDFPLTF	682
020S-C06	ASGR2	RASQSISSWLA	623	AATTLQS	640	CQQSYSTPLTF	688
020S-D06	ASGR2	RASQGIATWLA	616	DASNLQS	641	CQQANSFPVTF	681
020S-C07	ASGR2	RASQISRYLN	622	DASNLRS	642	CQQGYTIPITF	684
028S-H09	ASGR2	RASQSISSYLN	624	QASNKDT	655	CQQGYSTPLTF	683
028S-C11	ASGR2	RASQSINNYLN	619	AASSLQS	638	CQQANSFPLTF	680
028S-D11	ASGR2	RSSQSLHSDNGYNY LD	631	AASNLQS	636	CMQALQTPLTF	669
028S-G11	ASGR2	RASQISNWLA	620	AASRLQS	637	CQQTYAIPLTF	689
020S-H05	ASGR2						
Abv-3D11	ASGR2	KSSQSLDSDGKTY LN	611	LVSKLDS	652	WQGTHFPYT	696
Abv-10B8	ASGR2	SASSSVSSSFLH	634	RTSNLAS	658	QQWSGYPYT	695
RO-01	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	NSLERIGYLSYV	694
RO-02	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	CNSRLRSGKMV VF	673
RO-03	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	CNSRKSSSKNV VF	672
RO-04	ASGR1	QGDSLRSYYAS	613	GRNNRPS	649	CNSRDRRGYSV F	671
LP1-1F8	ASGR1	KSSQSLFNSRTRKN YLA	610	WASTRES	661	CKQSYLLTF	663
LP1-1N15	ASGR1	KASQDINSHLS	606	RANRLVD	657	CLQYDEFPTF	667
LP1-1P13	ASGR1	RTSENIYSNLA	632	AATNLAD	639	CQHFWGSTWTF	674
LP1-1P5	ASGR1	KASQNVGTNVA	609	SASYRYS	659	CQQYNSYPLTF	691
LP1-2E12	ASGR1	RSSQSLANSYGNTY LS	629	GISNRFS	647	CLQGTHQPLTF	665
LP1-2I13	ASGR1	RASENIYSYLV	615	NAKTLAE	653	CQHHYGTWTF	678
LP1-2I22	ASGR1	RASENIYSNLA	614	GATNLAD	646	CQHFWGTTWTF	676
LP1-3A24	ASGR1	KASQNVGSNVA	608	SSSYRYS	660	CQQYNSFPLTF	690
LP1-3E20	ASGR1	KASQDINSYLS	607	RANRLVD	657	CLQYDDLWTF	666
LP1-6H3	ASGR1	KSSQSLDSDGKTY LN	612	LVSKLDS	652	CWQGTHFPHTF	693
LP1-7B13	ASGR1	RASQISNYLH	621	FASQIS	645	CQQSNSWPLTF	687
LP1-7I20	ASGR1	RTSENIYSYLA	633	NAKTLAK	654	CQHHYGTPTYTF	677
LP1-8M24	ASGR1	RISENIYSNLA	627	AAINLAD	635	CQHFWGTPPTF	675

LP1-9C3	ASGR1	RSSQSLANSYGNTY LS	629	GISNRFS	647	CLQATHQPWTF	664
LP1-9M16	ASGR1	KASQDINSYLS	607	RANRLAD	656	CLQYDEFPLTF	668
LP1-10C22	ASGR1	RSSQGIVHSNGNIYL E	628	KVSNRFS	650	CFQGSHVPPTF	662

Table 3B. Description of Sequence Identifiers (ASGR targeting modules)

SID NO:	Brief Description	Sequence
47	024S-D03 VL	EIVLTQSPATLSFSPGERATLSCRASQSVGSYLA WYQQRPGQAPRPLIY DATNRATGIPTRFSGSGSGTDFTLT ISSLEPEDFATYY CQHRRTFGRGTKLEIK
48	024S-D03 VH	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSA AWNWMRQSPSRGLE WLGRTYYRSKWYNDYAVSVKSRMTINPDTSR NQF SLQLNSVTLEDTAVYYCARWNHEEHYFDYWGQ GTLVTVSS
49	024S-E03 VL	DVVMTQSPATLSFSPGERATLSCRASQSVGSYLA WYQQRPGQAPRPLI YDATNRATGIPTRFSGSGSGTDFTLT ISSLEPEDFAT YYCQHRRTFGRGTKLEIK
50	024S-E03 VH	QVQLQQSGPGLVKPSQTLSTCAISGASVSSNSA AWNWMRQSPSRGLE WLGRTYYRSKWYNDYAVSVKSRITINPDTSKN QFSLQLNSVTPGDTAVYYCARWNHEEHYFDYWG QGTLMVTVSS
51	024S-A04 VL	DIQLTQSPATLSFSPGERATLSCRASQSVGSYLA WYQQRPGQAPRPLIY DATNRATGIPTRFSGSGSGTDFTLT ISSLEPEDF ATYYCQHRRTFGRGTKLEIK
52	024S-A04 VH	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSV AWNWMRQSPSRGLE WLGRTYYRSKWYNDYAVSVKSRITINPDTSKN QFSLQLNSVTPEDTAVYYCASWTRGAFDIWGQ GTMVTVSS
53	020S-A05 VL	EIVMTQSPATLSLSPGERATLSCRASQSVGSYLA WYQQKPGQAPRLLIY DASNRTGIPARFSGSGSGTDFTLT ISSLEPEDF AVYYCQQRSNWPLTFGGGTKVEIK
54	020S-A05 VH	EVQLVESGAEVKKPGSSVKVSKASGGTFSSYA ISWVRQAPGQGLEW MGGIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCAVSDGYDLDYWGQGT LTVTVSS
55	020S-C05 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIH DASNRTGIPARFSGSGSGTDFTLI SSLEPEDF AVYYCQQRSNWPVTFGGGTKVEIK
56	020S-C05 VH	EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYA ISWVRQAPGQGLEW MGGIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCASFGVGAPDYWGQGT LTVTVSS
57	020S-G06 VL	DVVMTQSPSLPVTGPGEASISCRSSQSLHSDGH NYLQWYLQKPGQS PQLLILLGSYRASGVPDRFSGSGSGTDFTLKIS R VEAEDVGVYYCMQATHWPPTFGQGTKVEIK
58	020S-G06 VH	EVQLVQSGAEVKKPGATVKVSKASGYTFTSYGI SWVRQAPGQGLEW MGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCASAGGGYWGQGT LTVTVSS
59	020S-A06 VL	DIQMTQSPSSLSASVGDRVITICRASQNIYTYL NWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDF ATYYCQYYNYPIITFGQGTREIK
60	020S-A06 VH	QVQLVQSGAEVKKPGSSVKVSKASGYTFTGYH MHWVRQAPGQGLE WVGGIIPVFGAPNYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDGGYGM DVWGQGTMTVTVSS
61	020S-B06 VL	DIQMTQSPSSLSASVGDRVITICRASQGISSWLA WYQQKPGKAPKLLIY

		AASSLQSGVPSRFSGSGSGTDFTLTISLQPED FATYYCQQAYDFPLTFGGGKVEIK
62	020S-B06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQAPGQGLE WMGIINPSGGGTSYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDNAVYYCARDTGATAEYFQHWGQGLTVTVSS
63	020S-C06 VL	DIQMTQSPSSLSASVGDRVITICRASQSISSWLAWYQQKPGKAPKLLIY AATTLQSGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQSYSTPLTFGQGTKLEIK
64	020S-C06 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSTGNMHWRQAPGQGLE WMGGIIPMFGTVKYAQKFQGRVTITADESTSTAYM ELSSLRSEDNAVYYCAKDRGYRFDLWGRGTLTVTVSS
65	020S-D06 VL	DIQMTQSPSSLSASVGDRVITICRASQGIATWLAWYQQKPGKAPKLLIY YDASNLQSGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQANSFPVTFGPGTKVDIK
66	020S-D06 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSYISSYNSHTNDADSVKGRFTISRDN SKNTLYLQ MNSLRAEDNAVYYCARWAVAAGGQYYMDVWGKGT TVTVSS
67	020S-C07 VL	DIQMTQSPSSLSASVGDRVITICRASQSI SRYLNWYQQKPGKAPKLLIY DASNL RSGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQGYTIPITFGQGTKVEIK
68	020S-C07 VH	QVQLVQSGAEVKKTGASVKVSCKASGYTFSNYYMHWRQAPGQGLE WMGWINPKSGGTKYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDNAVYYCARDRGITMVRGVMDYWGQGLTVTVSS
69	028S-H09 VL	DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIY QASNKDTGVPSRFSGSGSGTDFTLTISLQPEDFAT YYCQQGYSTPLTFGGGKVEIK
70	028S-H09 VH	QVQLVQSGAEVKKPGATVKVSCKASGYTFTTYMHWRQAPGQGLE WMGWINPNGGNTYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDNAVYYCAKDRTAMAPEGAFDIWGQGTMTVTVSS
71	028S-C11 VL	DIQMTQSPSSLSASVGDRVITICRASQSINNYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCQQANSFPLTFGGGKVEIK
72	028S-C11 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFS DYYVHWVRQAPGQGLE WMGIINPRNGRTSYAQR FQGRVTMTRDTSTSTVYME LSSLRSEDNAVYYCARDHLYGMDVWGQGT TVTVSS
73	028S-D11 VL	DIVMTQSPLSLPVTPEPASISCRSSQSLLSNGYNYLDWYLQKPGQSP QLLIYAASN LQSGVPDRFSGSGSGTDFTLKISRVEAE DVG VYYCMQALQTPLTFGGGKVEIK
74	028S-D11 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQM NSLRAEDNAVYYCAKDSPIVRRGERGRYYGMDVWGQGT TVTVSS
75	028S-G11 VL	DIQMTQSPSSLSASVGDRVITICRASQSI SNWLAWYQQKPGKAPKLLIY AASRLQSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCQQTYAIPLTFGGGKVEIK
76	028S-G11 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHWRQAPGQGLE WMGWMNPNTGNTAYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDNAVYYCARDKNYYGMDVWGQGT TVTVSS
77	020S-H05 nAb	EVQLVES GGGLVQAGDSLRLSCTASGHTFSSYAMGWFRQAPGKERE VAAISQSGYVRYADSVKGRFTISRDN AKNTVY LQMN SLKPDDTNAVYYCNARWGAGSLFASWGQGTQVTVSS
151	Abv-3D11 VL	EVVMTQTPLTSLVTIGQPASISCKSSQSLDSDGKTYLNWLLQRPQSP KRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDL GVYYCWQGTHFPYTFGGGKVEIK

152	Abv-3D11 VH	EVQLVESGGGLVQPKGSLKLSCAASGFSFNTYAMNWVRQAPGKGLE WVARIRSKSNYYATYYADSVKDRFTISRDDSEMLYL QMNNLKTEDTAMYYCVRPRYDYWYFDVWGTGTTVTVSS
153	Abv-10B8 VL	ENVLTQSPAIMAASLGQKVTMTCSASSSVSSSFLHWYQQKSGASPKPLI HRTSNLASGVPARFSGSGSGTSYSLTISSVEAED DATYYCQQWSGYPTYFGGGTKLEIK
154	Abv-10B8 VH	DVKLVESGGLVQPGGSLKLSCAASGFTFSSYAMSWVRQTPEKRLEW VAYISSGGDIYYVDTVKGRFTISRDNARNTLYL QMSSLKSEDTAVYYCTREGTGGMDYWGQGTSTVTVSS
171	RO-01v VL	DIELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSLERIGYLSYVFGGGTKLTVL
172	RO-01 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDE ADYYCNSLERIGYLSYVFGGGTKLTVL
173	RO-01 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCAKDFSSRRWLEYWGQGT LTVTVSS
174	RO-02 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRLRSGKMVVF GG GTKLTVL
175	RO-02 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCAKSWYLPGRGFDYWGQGT LTVTVSS
176	RO-03 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRKSSSKNVVF GG GTKLTVL
177	RO-03 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCAKSSFTFGRYFDYWGQGT LTVTVSS
178	RO-04 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GRNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRDRRGYSVF GG GTKLTVL
179	RO-04 VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCAKSSFSYLRAF DYWGQGT LTVTVSS
274	LP1-1F8 VL	DIVMSQSPSSLAVSAGEKVTMSCKSSQSLFNSRTRKNYLA WYQQKPG QSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTI SSVQAEDLAVYYCKQSYLLTFGAGTKLELK
275	LP1-1F8 VH	EVKLVESGGGLVQPKGSLKLSCAASGFTFSTYTMSWVRQTPAKRLEW VATISSIGVNTYYPDSVKGRFTISRDNARNTLYL QVSSLRSED TAMY YCARHVDY YDGISFDYWGQGTTLTVSS
276	LP1-1N15 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSHLSWFQQKPGKSPKTLIIR ANRLVDGVPSRFSGSGSGQDYSLTISPEYEEM GIYYCLQYDEFPTFGGGTKLEIK
277	LP1-1N15 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDY YMNWVKQSHGESLE WIGRVIPSNGGTNYNQKFKGKATLTVDKSLTTA YMQLNSLTSEDSAVYFCARGMDYWGPGT SVTVSS
278	LP1-1P13 VL	DIQMTQSPASLSASVGQTVIITCRTSENIYSNLAWYQQKQKSPQLLVY AATNLADGVPSRFSGSGSGTQYYLKINSLQSED FGSY YCQHFWGSTWTFGGGT KLDIK
279	LP1-1P13 VH	EVQLQQSGPELVKPGASVKISCKASGYSTFDYFMNWVKQSHGKSLEW IGRFNPFNGQTFYNQEFKGKATLTVDKSSSTA H

		MELRSLTSEDSAVYYCARRGRYDVYYVLDYWGQGTSTVSS
280	LP1-1P5 VL	DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKA LIYSASYRYSVGPDRFTGSGSGTDFTLTISNVQSE DLAEYFCQQYNSYPLTFGAGTKLELK
281	LP1-1P5 VH	QVQLQQSGPELVRPGTSVKISCKASGYTFLTYWMNWVKQRPQGGL WIGQIFPATGITYYSEMFKDKATLTEDTSSTAY MQLSSLTSEATAVYFCARRRAYHSNFFDYWGQGTTLTVSS
282	LP1-2E12 VL	DVVVTQTPLSLPVSFGRVSISSCRSSQSLANSYGNTYLSWYLHKPGQSP QLLIYGISNRFSGVPDRFSGSGSGTDFTLKISTIKP EDLGMYYCLQGTHQPLTFGAGTKLELK
283	LP1-2E12 VH	DVQLQESGPELVKPSQSLTCSVTGYSTSGYYWNWIRQFPGNKLEW MGSIGYDDTNHYNPSLKNRISITRDTSKNQFFLK LNSVTTEDTATYYCAGDYPFAFWGQGTTLTVSA
284	LP1-2I13 VL	DIQMTQSPASLSASVGETVTITCRASENIYSYLWVYQQKQKSPQLLV YNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPED FGSYQCQHHYGTWTFGGGIKLEIK
285	LP1-2I13 VH	EVQLVESGGGLVKPGGSRKLSAASGFTFSDYGMHWVRQAPEKGL WVAYISSGSSTIYYADTVKGRFTISRDNKNTL FLQMTSLRSEDAMYYCSRKGFGDYEKSYAMDYWGQGTSTVSS
286	LP1-2I22 VL	DIQMTQSPASLSASVGETVTITCRASENIYSNLAWYQQKQKSPQLLV GATNLADGVTSRFSGSGSGTQFSLKIDSLQSE DFGSYYCQHFHWGTTWTFGGGKLEIK
287	LP1-2I22 VH	EVQLQQSGPELVKPGASVKISCKASGYSTGYFMNWVKQSHGKSLEW IGRFNPFNGQTFYNQEFK GKATLTVDKSSDTAH MELRSLTSEDSAVYYCARRGRYDVYYALDYWGQGTSTVSS
288	LP1-3A24 VL	DIVMTQSQKFMSTSVGDRVSVTCKASQNVGSNVAWFQQKPGQSPKAL IYSSSYRYSVGPDRFTGSGSGTDFTLTITNVQSE DLAEYFCQQYNSFPLTFGAGTKLELK
289	LP1-3A24 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLEW IGRVIPSNNGGSNNYQKFKGKATLTVDKSLSTAY MHLNSLTSEDSAVYYCATQLGRWGQGTTLTVSA
290	LP1-3E20 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIY RANRLVDGVPSRFSGSGSGQDYSLTISSEYEDM GIYYCLQYDDLWTFGGGKLEIK
291	LP1-3E20 VH	QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPQGGL WIGYINPSSGYAEYNQKFKVRATLTADKSSSTAY MQLSSLTSEDSAVYYCARESYYSFDYTMDYWGQGTSTVSS
292	LP1-6H3 VL	DVVMVTQTPLTSLVTIGQPASISCKSSQSLDSDGKTYLNWLLQRPQSP KRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISRV EAEDLGVYYCWQGTHFPHTFGSGTKLEIK
293	LP1-6H3 VH	QAYLQQSGAELVRPGASVKMSCKASGYTFSRFDMHVVKQTPRQGL WIGVIYPGNGDTSYNQKFRDKASLTVDKSSSTAY MQLSSLTSEDSAVYFCASSYYGNPWGQGTTLTVSS
294	LP1-7B13 VL	DIVLTQSPATLSVTPGDRVSLSCRASQSIYNLHWYQQKSHESPRLLIKF ASQSIGIPSRFSGSGSGTDFTLTINSVETEDFG MYFCQQSNSWPLTFGAGTKLELK
295	LP1-7B13 VH	EVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYYMNWVKQGHGKSLE WIGRVNPSNDDTRYNQKFKGKATLTVDKSLST AYMQLNSLTSEDSAVYYCTRWFYFDYWGQGTTLTVSS
296	LP1-7I20 VL	DIQMTQSPASLSASVGETVTITCRTSENIYSYLAWYQQKQKSPQLLV YNAKTLAKGVPSRFSGSGSGTQFSLKINGLQPED FGNYCQHHYGTPTYTFGGGKVEIK
297	LP1-7I20 VH	EVKLVESGGGLVQPGGSLSLSCAASGFTFTDYYMSWVRQPPGKALEW

		LALIRNKANGYTTEYSASVKGRFTISRDNQSIL YLQMNALRAEDSATYYCAVTY GAYWGQGLTVTSA
298	LP1-8M24 VL	DIQMTQSPASLSVSVGETVTITCRISENIYSNLAWYQQKQKSPHLLVY AAINLADGVPSRFSGSGSGTQF SLKINSLQSEDFGSYYCQHFHWGTPFTFGSGGTKLEIK
299	LP1-8M24 VH	QVQLQQSGAELARPGASVKLSCKASGYTFTNYGINWVKQRTGQGLE WIGEIFPRSDNTFYNEKFKGKATLTADKS STTAYMELRSLTSEDSAVYFCARKGRDYGTSHYFDYWGQGTTLTVSS
300	LP1-9C3 VL	DVVVTQTPLSLPVSGDQVSISCRSSQSLANSYGNTYLSWYLHKPGQSP QLLIYGISNRFSGVPDRFSGSGSGTDFTL KISTIKPEDLGIYYCLQATHQPWTFGGGTCKLEIK
301	LP1-9C3 VH	QVTLKESGPGILQPSQTLSTCSFSGFSLSTSYMGVSWIRKPSGKGLEW LAHIFWDDDKRYNPSLKSRLTISKDTSSN QVFLMITSVETADTATYYCGGPYPFTYWGQGLTVTSA
302	LP1-9M16 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIY RANRLADGVPSRFSGSGSGQDYSLTISNL EYEDMGIYYCLQYDEFPLTFGAGTKLELK
303	LP1-9M16 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYMNWVKQSHGKSLE WIGRVNPNNGGSNYNQKFKGKATLTVDK SLSTAYMQLNSLTSEDSAVYYCASRNFDVWGAGTTVTSS
304	LP1-10C22 VL	DVLTMTQTPLSLPVSLGDQASISCRSSQGIVHSNGNIYLEWYLQKPGQSP KLLIYKVSNRFSGVPDRFSGSGSGTDFTLK ISRVEAEDLGVIYCFQGSHVPPTFGGGTKLEIK
305	LP1-10C22 VH	EVQLVESGGDLVKPGGSLKLSCAASGFTFSYGMWVRQTPDKRLEW VASISSGGSYTYYPDSVKGRFTISRDNAN TLYLQMSSLKSEDTAMYYCVRHEEYGKSGFAYWGQGLTITSA

Table 3C. Description of Sequence Identifiers (Alternative targeting modules)

SID NO:	Brief Description	Sequence
180	GT-01 (TFR1) VH	QVQLQQSGPELVKPGVSVKISCKGSGYTFTDYAMHWVKQSHAKS LEWIGGISTYFGRNTYNQKFKGRATMTVDKSSSTAYMELARLTSE DSALYYCARGLSGNYVMDYWGQGTSTVTVSS
181	GT-01 (TFR1) VL	DIVLFQSPASLAVSLGQRATISCRASESVDDYGNFSFMHWYQQKPG QPPKLLIYRASNLSEGPAPRFSGSGSRTDFTLTINPVEADDVATYYC QQSNEAPPTFGGGTKLEIK
182	BA-01 (LYPD3) VH	EVQLLES GGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKG LEWVSYISSSGSTIYYADSVKGRFTISRDNKNTLYLQMNSLRAED TAVYYCAREGLWAFDYWGQGLTVTVTS
183	BA-01 (LYPD3) VL	QSVLTQPPSASGTPGQRTISCTGSSSNIGAGYVHVHWYQQLPGTA PKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLASEDEADYYCA AWDDRLNGPVFGGGTKLTVL
184	FR-01 (DSG3) VH	EVQLQQSGTVLARPASVKMSCKASGYTFASYWIHWVKQRPGQ GLEWIGSIYPGNSDTTYNQKFKGKAKLTVVTSASSAYMELSSLTN EDSAVYYCTEPTYYSYDDYYAMDYWGQGTSTVTVSS
185	FR-01 (DSG3) VL	EIVLTQSPALMAASPGEKVTITCSVSSSISSNLHWYQQKSGTSPKP WIYGTSNLAGVPPVRFSGSGSGTSYSLTISTMEAEDAATYYCQQW SSYPLTFGAGTKLELK

[0134] Illustrative, non-limiting examples of tissue-specific Wnt signal enhancing molecules include fusion proteins comprising: 1) a first domain comprising an R-spondin Furin domain 1

or variant thereof and a second domain comprising an antibody or fragment thereof that specifically binds ASGR1 or ASGR2; 2) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising an antibody or fragment thereof that specifically binds SLC10A1; 3) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising an antibody or fragment thereof that specifically binds TFR2; 4) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds PTH1R; 5) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds LYPD3; 6) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds DSG3; and 7) a first domain comprising an R-spondin Furin domain 1 or variant thereof and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds TFR1. Additional, illustrative, non-limiting examples of tissue-specific Wnt signal enhancing molecules include fusion proteins comprising: 1) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising an antibody or fragment thereof that specifically binds ASGR1 or ASGR2; 2) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising an antibody or fragment thereof that specifically binds SLC10A1; 3) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising an antibody or fragment thereof that specifically binds TFR2; 4) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds PTH1R; 5) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds LYPD3; 6) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds DSG3; and 7) a first domain comprising an antibody or fragment thereof that specifically binds ZNRF3 and/or RNF43, and a second domain comprising a ligand derivative, an antibody or fragment thereof that specifically binds TFR1. In particular embodiments, the first domain comprises an antibody comprising any of the sets of heavy chain or light chain

CDR sequences set forth in Table 2, and/or the second domain comprises an antibody comprising any of the sets of heavy chain or light chain CDR sequences set forth in Table 3. In particular embodiments, the two domains are joined via a linker, e.g., a polypeptide linker. In certain embodiments, the linker is albumin, e.g., human serum albumin, where the targeting and action modules are on the N- and C- termini of albumin. In particular embodiments, the tissue-specific Wnt signal enhancing molecules have an appended antibody (e.g., IgG) format comprising an antibody heavy chain and an antibody light chain (or fragments or variants thereof of either or both chains), wherein one or both chains further comprises one or more additional binding domain. In particular embodiments, the tissue-specific Wnt signal enhancing molecules have an appended antibody (e.g., IgG) format, wherein the second domain comprises an antibody heavy chain and an antibody light chain (or fragments or variants thereof of either or both chains), and wherein a first domain comprising an R-spondin Furin domain 1 or variant is appended to one or both of the antibody heavy and/or light chains, e.g., at either or both the N-terminus and/or C-terminus of either or both chains. In particular embodiments, the first domain is appended or fused to the heavy chain, e.g., at either the N-terminus or C-terminus. In particular embodiments, the first domain is appended or fused to the light chain, e.g., at either the N-terminus or C-terminus).

Linkers

[0135] In certain embodiments, the targeting module and the action module are bound or fused directly to each other, whereas in other embodiments, they are separated by a linker, e.g., a polypeptide linker, or a non-peptidyl linker, *etc.* In particular embodiments, a linker is an Fc linker, e.g., a region of an antibody Fc domain capable of dimerizing with another Fc linker, e.g., via one or more disulfide bonds. In another particular embodiment, a linker is albumin, e.g., human serum albumin, where the targeting and action modules are on the N- and C-termini of albumin.

[0136] In certain embodiments, particularly when joining two polypeptides, the linker is made up of amino acids linked together by peptide bonds. In particular embodiments, the linker comprises, in length, from 1 up to about 40 amino acid residues, from 1 up to about 20 amino acid residues, or from 1 to about 10 amino acid residues. In certain embodiments, the amino acid residues in the linker are from among the twenty canonical amino acids, and in certain embodiments, selected from cysteine, glycine, alanine, proline, asparagine, glutamine, and/or serine. In certain embodiments, a linker comprises one or more non-natural amino acids. In some embodiments, a peptidyl linker is made up of a majority of amino acids that are sterically

unhindered, such as glycine, serine, and alanine linked by a peptide bond. Certain linkers include polyglycines, polyserines, and polyalanines, or combinations of any of these. Some exemplary peptidyl linkers are poly(Gly)1-8, particularly (Gly)3, (Gly)4 (SEQ ID NO:698), (Gly)5 (SEQ ID NO:699) and (Gly)7 (SEQ ID NO:700), as well as, poly(Gly)4 Ser (SEQ ID NO:701), poly(Gly-Ala)2-4 and poly(Ala)1-8. Other specific examples of peptidyl linkers include (Gly)5Lys (SEQ ID NO:702), and (Gly)5LysArg (SEQ ID NO:703). To explain the above nomenclature, for example, (Gly)3Lys(Gly)4 (SEQ ID NO:704) means Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly (SEQ ID NO:704). Other combinations of Gly and Ala are also useful. Additionally, a peptidyl linker can also comprise a non-peptidyl segment such as a 6 carbon aliphatic molecule of the formula --CH₂--CH₂--CH₂--CH₂--CH₂--CH₂--. The peptidyl linkers can be altered to form derivatives as described herein.

[0137] Illustrative non-peptidyl linkers include, for example, alkyl linkers such as --NH--(CH₂)_s--C(O)--, wherein s=2-20. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C1-C6) lower acyl, halogen (e.g., Cl, Br), CN, NH₂, phenyl, etc. Non-peptide portions of the inventive composition of matter, such as non-peptidyl linkers or non-peptide half-life extending moieties can be synthesized by conventional organic chemistry reactions. Chemical groups that find use in linking binding domains include carbamate; amide (amine plus carboxylic acid); ester (alcohol plus carboxylic acid), thioether (haloalkane plus sulfhydryl; maleimide plus sulfhydryl), Schiff's base (amine plus aldehyde), urea (amine plus isocyanate), thiourea (amine plus isothiocyanate), sulfonamide (amine plus sulfonyl chloride), disulfide; hydrazone, lipids, and the like, as known in the art.

[0138] The linkage between domains may comprise spacers, e.g. alkyl spacers, which may be linear or branched, usually linear, and may include one or more unsaturated bonds; usually having from one to about 300 carbon atoms; more usually from about one to 25 carbon atoms; and may be from about three to 12 carbon atoms. Spacers of this type may also comprise heteroatoms or functional groups, including amines, ethers, phosphodiester, and the like. Specific structures of interest include: (CH₂CH₂O)_n where n is from 1 to about 12; (CH₂CH₂NH)_n, where n is from 1 to about 12; [(CH₂)_n(C=O)NH(CH₂)_m]_z, where n and m are from 1 to about 6, and z is from 1 to about 10; [(CH₂)_nOPO₃(CH₂)_m]_z where n and m are from 1 to about 6, and z is from 1 to about 10. Such linkers may include polyethylene glycol, which may be linear or branched.

[0139] In certain embodiments, the domains may be joined through a homo- or heterobifunctional linker. Illustrative entities include: azidobenzoyl hydrazide, N-[4-(p-azidosalicylamino)butyl]-3'-[2'-pyridyldithio]propionamide), bis-sulfosuccinimidyl suberate, dimethyladipimide, disuccinimidyltartrate, N- γ -maleimidobutyryloxysuccinimide ester, N-hydroxy sulfosuccinimidyl-4-azidobenzoate, N-succinimidyl [4-azidophenyl]-1,3'-dithiopropionate, N-succinimidyl [4-iodoacetyl]aminobenzoate, glutaraldehyde, NHS-PEG-MAL; succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate; 3-(2-pyridyldithio)propionic acid N-hydroxysuccinimide ester (SPDP); N, N'-(1,3-phenylene) bismaleimide; N, N'-ethylene-bis-(iodoacetamide); or 4-(N-maleimidomethyl)-cyclohexane-1-carboxylic acid N-hydroxysuccinimide ester (SMCC); m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), and succinimide 4-(p-maleimidophenyl)butyrate (SMPB), an extended chain analog of MBS. In certain embodiments, the succinimidyl group of these cross-linkers reacts with a primary amine, and the thiol-reactive maleimide forms a covalent bond with the thiol of a cysteine residue.

[0140] Other reagents useful include: homobifunctional cross-linking reagents including bismaleimidohexane ("BMH"); p,p'-difluoro-m,m'-dinitrodiphenylsulfone (which forms irreversible cross-linkages with amino and phenolic groups); dimethyl adipimide (which is specific for amino groups); phenol-1,4-disulfonylchloride (which reacts principally with amino groups); hexamethylenediisocyanate or diisothiocyanate, or azophenyl-p-diisocyanate (which reacts principally with amino groups); disdiazobenzidine (which reacts primarily with tyrosine and histidine); O-benzotriazolyloxy tetramethuluronium hexafluorophosphate (HATU), dicyclohexyl carbodiimide, bromo-tris (pyrrolidino) phosphonium bromide (PyBroP); N,N-dimethylamino pyridine (DMAP); 4-pyrrolidino pyridine; N-hydroxy benzotriazole; and the like.

Antibodies and Uses Thereof

[0141] In various embodiments, the present invention provides anti-RNF43, anti-ZNRF3, and anti-ASGR1/2 antibodies and antigen-binding fragments thereof and related methods of use.

[0142] In one embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds to RNF43, ZNRF3, ASGR1, or ASGR2 (optionally human), comprising a sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A or 3A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A or 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications,

wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence having at least 90% identity to the amino acid sequence set forth in Table 2B or Table 3B or a heavy chain variable region comprising the amino acid sequence set forth in Table 2B or Table 3B. In particular embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region comprising an amino acid sequence having at least 90% identity to the amino acid sequence set forth in Table 2B or Table 3B or a light chain variable region comprising the amino acid sequence set forth in Table 2B or Table 3B.

[0143] In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, are humanized. In certain embodiments, any of the antibodies, or antigen-binding fragments thereof, are a single chain antibody, a scFv, a univalent antibody lacking a hinge region, a nanobody, or a minibody. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, are a VHH nanobody. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, are a Fab or a Fab' fragment.

[0144] In certain embodiments, any of the antibodies, or antigen-binding fragments thereof, are a fusion protein.

[0145] In a related embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that competes with any of the antibodies disclosed herein for binding to its target ZNRF3, RNF43 or ASGR1/2. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, bind to its target with a KD of 50 μ M or lower.

[0146] In one embodiment, the invention comprises an isolated antibody or antigen-binding fragment thereof that binds to human ASGR and inhibits ASGR binding to ligand. In another embodiment, the invention comprises an isolated antibody or antigen-binding fragment thereof that binds to human ASGR-1 and inhibits ASGR-1 binding to ligand and/or ASGR-1 interaction with ASGR-2. In another embodiment, the invention comprises an isolated antibody or antigen-binding fragment thereof that binds to human ASGR-2 and inhibits ASGR-2 binding to ligand and/or ASGR-2 interaction with ASGR-1. In yet another embodiment, the invention comprises an isolated antibody or antigen-binding fragment thereof that binds to human ASGR-1 and human ASGR-2, and inhibits ASGR-1 and/or ASGR-2 binding to ligand. In some embodiments, the isolated antibody or antigen-binding fragment thereof binds specifically to human ASGR, ASGR-1 and/or ASGR-2.

[0147] In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, modulate a Wnt signaling pathway in a cell, optionally a mammalian cell. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof increase signaling via a Wnt signaling pathway in the cell. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof decrease signaling via a Wnt signaling pathway in the cell. In certain embodiments, the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway.

[0148] In a further related embodiment, the present disclosure provides an isolated polynucleotide encoding an antibody, or antigen-binding fragment thereof, disclosed herein. In certain embodiments, the present disclosure provides an expression vector comprising the isolated polynucleotide and an isolated host cell comprising the expression vector.

[0149] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, disclosed herein.

[0150] The present disclosure provides methods for detecting the presence of or expression levels of ZNRF3, RNF43 or ASGR1/2 polypeptides, e.g., in a biological sample (e.g., cells or tissue), comprising contacting the biological sample with an antibody or antigen-binding fragment thereof disclosed herein that specifically binds the target polypeptide. In certain embodiments, the antibody or antigen-binding fragment thereof is detectable labeled, e.g., by a fluorescent tag. Accordingly, the antibodies may be used to stain cells expressing the antibody target polypeptides. For example, the anti-ASGR1/2 antibodies and antigen-binding fragments thereof may be used to detect or stain hepatocytes.

[0151] The antibodies or antigen-binding fragments thereof disclosed herein may also be used to deliver drugs to the cells that they bind. For example, the anti-ASGR1/2 antibodies and antigen-binding fragments thereof may be conjugated to a therapeutic agent to deliver the therapeutic agent to liver cells, e.g., normal or cancer liver cells.

[0152] In a further embodiment, the present disclosure provides a method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell with an isolated antibody, or antigen-binding fragment thereof, disclosed herein that increases Wnt signaling. In another embodiment, the present disclosure provides a method for inhibiting a Wnt signaling pathway in a cell, comprising contacting the cell with the isolated antibody, or antigen-binding fragment thereof, disclosed herein the inhibits Wnt signaling.

[0153] In another embodiment, the present disclosure includes a method for treating a subject having a disease or disorder associated with reduced Wnt signaling, comprising administering to the subject an effective amount of a pharmaceutical composition comprising an isolated antibody, or antigen-binding fragment thereof, disclosed herein that is an agonist of a Wnt signaling pathway. In particular embodiments, the disease or disorder is any of those described herein as being treated by a tissue-specific Wnt signal enhancing molecule.

[0154] In some embodiments, the disclosure includes a method of decreasing the risk of acquiring coronary artery disease or having an MI comprising administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2. In some embodiments, the relative risk reduction of coronary artery disease or MI is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60% in the treated subject as compare to an untreated subject.

[0155] In some embodiments, the disclosure provides a method of reducing blood LDL cholesterol levels in a subject comprising administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2. In some embodiments, the blood LDL cholesterol level in the treated subject is reduced by at least about 15%, as compared to a predose level of blood LDL cholesterol in the subject. In some embodiments of this aspect of the invention, the blood LDL cholesterol level of said subject is lowered by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90% as compared to a predose level of blood LDL cholesterol in the subject.

[0156] In some embodiments, the disclosure provides a method of reducing non-HDL cholesterol levels in a subject comprising administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof

disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2. In some embodiments, the non-HDL cholesterol level in the subject is reduced by at least about 5%, as compared to a predose level of non-HDL cholesterol in the subject. In some embodiments of this aspect of the invention, the non-HDL cholesterol level of said patient is lowered by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90% as compared to a predose level of non-HDL cholesterol in the patient.

[0157] In some embodiments, the disclosure provides a method of increasing ALP levels through inhibition of ASGR activity, in a patient comprising administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2. In some embodiments, the ALP level in the patient is increased by at least about 30%, as compared to a predose level of ALP in the patient. In some embodiments of this aspect of the invention, the ALP level of said subject is increased by at least about at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90% as compared to a predose ALP level in the subject. In some embodiments, ALP levels are increased at least about 1.25-fold, 1.5-fold, 2-fold, 2.5-fold, 3-fold, 3.5-fold, 4-fold, 4.5-fold, and 5-fold over pretreatment.

[0158] In some embodiments, the disclosure provides a method of antagonizing ASGR, ASGR-1 and/or ASGR-2 in a subject, comprising administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2.

[0159] In some embodiments, a method of treating or preventing a cardiovascular disease is provided and comprises administering to a subject in need thereof a therapeutically effective dose of an anti-ASGR antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, the antibody binds ASGR-1, and in some embodiments, the antibody binds

ASGR-2. In some embodiments, the antibody is an inhibitor of ASGR-1 and/or ASGR-2. In some embodiments, the relative risk reduction of a cardiovascular event is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60% in the patient.

Wnt Molecules, Norrin Molecules, and Wnt Signal Enhancing Molecules

[0160] The present disclosure further relates to Wnt polypeptides, Norrin polypeptides, and Wnt signaling agonist molecules and their use to increase Wnt signaling and treat or prevent Wnt-related diseases or disorders, including those described herein. In certain embodiments, the Wnt polypeptides, Norrin polypeptides and Wnt signaling agonist molecules are provided to a subject alone or in combination with one or more tissue-specific Wnt signal enhancing molecules described herein.

[0161] Wnt polypeptides and Wnt-encoding polynucleotide sequences are known in the art and include any and all Wnt polypeptides or polynucleotides, including those of any and all species, including mammalian Wnt polypeptides and polynucleotides, such as human Wnt polypeptides and polynucleotides. Illustrative Wnt polypeptides include Wnt1, Wnt2, Wnt2B, Wnt3, Wnt3A, Wnt4, Wnt5A, Wnt5B, Wnt6, Wnt7A, Wnt7B, Wnt8A, Wnt8B, Wnt9A, Wnt9B, Wnt10A, Wnt10B, Wnt11, and Wnt16, and functional variants and fragments of any of the foregoing. Wnt polypeptide encompasses native Wnt polypeptides, Wnt polypeptide variants, Wnt polypeptide fragments and chimeric Wnt polypeptides. In particular embodiments, a Wnt polypeptide is a native human full length mature Wnt protein.

[0162] For example, human native sequence Wnt proteins of interest in the present application include but are not limited to the following: Wnt1 (GenBank Accession No. NM_005430); Wnt-2 (GenBank Accession No. NM_003391); Wnt2B (Wnt-13) (GenBank Accession No. NM_004185 (isoform 1), NM_024494.2 (isoform 2)), Wnt3 (RefSeq.: NM_030753), Wnt3A (GenBank Accession No. NM_033131), Wnt4 (GenBank Accession No. NM_030761), Wnt5A (GenBank Accession No. NM_003392), Wnt5B (GenBank Accession No. NM_032642), Wnt6 (GenBank Accession No. NM_006522), Wnt7A (GenBank Accession No. NM_004625), Wnt7B (GenBank Accession No. NM_058238), Wnt8A (GenBank Accession No. NM_058244), Wnt8B (GenBank Accession No. NM_003393), Wnt9A (Wnt-14) (GenBank Accession No. NM_003395), Wnt9B (Wnt15) (GenBank Accession No. NM_003396), Wnt1 OA (GenBank Accession No. NM_025216), Wnt10B (GenBank Accession No. NM_003394), Wnt11 (GenBank Accession No.

NM_004626), Wnt16 (GenBank Accession No. NM_016087)). Although each member has varying degrees of sequence identity with the family, all encode small (i.e., 39-46 kD), acylated, palmitoylated, secreted glycoproteins that contain 23-24 conserved cysteine residues whose spacing is highly conserved (McMahon, A P et al., Trends Genet. 1992; 8: 236-242; Miller, J R. Genome Biol. 2002; 3(1): 3001.1-3001.15). Other native sequence Wnt polypeptides of interest include orthologs of the above from any mammal, including domestic and farm animals, and zoo, laboratory or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, rats, mice, frogs, zebra fish, fruit fly, worm, etc.

[0163] Norrin polypeptides and Norrin-encoding polynucleotide sequences are also known in the art and include any species of Norrin polypeptide or polynucleotide, including mammalian Norrin polypeptides and polynucleotides, such as human Norrin polypeptides and polynucleotides, and functional variants and fragments thereof.

[0164] Wnt signaling agonist molecules include any type of molecule that agonizes Wnt signaling. In particular embodiments, the Wnt signaling agonist molecule is described in PCT Patent Application Publication No. WO 2016/040895. A Wnt signaling agonist can be any molecule, e.g. protein or pharmaceutical (e.g., small organic molecule), in certain embodiments water soluble, which directly activates the canonical Wnt signaling through binding to one or more Fzd proteins and to Lrp5/6. In particular embodiments, they are small molecules, which may be less than about 15 Kd. In other embodiments, they are polypeptides. In addition, certain Wnt signaling agonists may comprise both a polypeptide region or domain and a non-polypeptide region or domain.

[0165] In some embodiments of the invention, the Wnt signaling agonist molecule is a polypeptide, which can comprise separate or contiguous binding domains or elements for Fzd, and for Lrp5/6. A polypeptide Wnt signaling agonist may be a single chain, dimer, or higher order multimer. The Fzd binding domain/element and the Lrp5/6 binding domain/element may be directly joined, or may be separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, etc.

[0166] In polypeptide embodiments, the Fzd binding domain may be selected from any domain that binds Fzd at high affinity, e.g. a KD of at least about 1×10^{-7} M, at least about 1×10^{-8} M, at least about 1×10^{-9} M, or at least about 1×10^{-10} M. Suitable Fzd binding domains include, without limitation, de novo designed Fzd binding proteins, antibody derived binding proteins, e.g. scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins; nanobody derived binding domains; knottin-based engineered scaffolds;

Norrin and engineered binding fragments derived therefrom, naturally occurring Fzd binding domains, and the like.

[0167] In some embodiments the Fzd binding domain binds to one, two, three, four, five or more different frizzled proteins, e.g. one or more of human frizzled proteins Fz1, Fz2, Fz3, Fz4, Fz5, Fz6, Fz7, Fz8, Fz9, Fz10. In some embodiments the antibody based signaling agonist binds to Fz1, Fz2, Fz5, Fz7 and Fz8. In other embodiments the frizzled binding moiety is selective for one or more frizzled protein of interest, e.g. having a specificity for the one or more desired frizzled protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other frizzled proteins.

[0168] In certain embodiments, the frizzled binding domain comprises the six CDR regions of the pan specific frizzled antibody OMP-18R5 (vantictumab). In certain embodiments, the frizzled binding domain is an scFv comprising the six CDR regions of the pan-specific frizzled antibody OMP-18R5 (vantictumab). See, for example, U.S. Patent no. 8507442, herein specifically incorporated by reference. For example, the CDR sequences of OMP-18R5 include a heavy chain CDR1 comprising GFTFSHYTLS (SEQ ID NO:705), a heavy chain CDR2 comprising VISGDGSYTTYADSVKG (SEQ ID NO:706), and a heavy chain CDR3 comprising NFIKYVFAN (SEQ ID NO:707), and (ii) a light chain CDR1 comprising SGDKLGKKYAS (SEQ ID NO:708) or SGDNIQSFYVH (SEQ ID NO:709), a light chain CDR2 comprising EKDNRPSPG (SEQ ID NO:710) or DKSNRPSPG (SEQ ID NO:711), and a light chain CDR3 comprising SSFAGNSLE (SEQ ID NO:712) or QSYANTLSL (SEQ ID NO:713). In particular embodiments, the frizzled binding domain is an antibody or derivative thereof, including without limitation ScFv, minibodies, nanobodies and various antibody mimetics comprising CDR sequences of OMP-18R5. In certain embodiments, these CDR sequences comprise one or more amino acid modifications as compared to the CDR sequences of OMP-18R5.

[0169] In other embodiments, the Fzd binding domain comprises a variable region sequence, or the CDRs thereof, from any of a number of frizzled specific antibodies, which are known in the art and are commercially available, or can be generated de novo. Any of the frizzled polypeptides can be used as an immunogen or in screening assays to develop an antibody. "Fz", "Fz proteins" and "Fz receptors" is used herein to refer to proteins of the Frizzled receptor family. These proteins are seven-pass transmembrane proteins (Ingham, P. W. (1996) Trends Genet. 12: 382-384; Yang-Snyder, J. et al. (1996) Curr. Biol. 6: 1302-1306; Bhanot, P. et al. (1996) Nature 382: 225-230) that comprise a CRD domain. There are ten known members of

the Fz family (Fz1 through Fz10), any of which can serve as receptors of Wnts. The Genbank accession numbers of human frizzled reference sequences are as follows: FZD1 (NM_003505); FZD2 (NM_001466); FZD3 (NM_145866); FZD4 (NM_012193); FZD5 (NM_003468); FZD6 (NM_003506); FZD7 (NM_003507); FZD8 (NM_031866); FZD9 (NM_003508); FZD10 (NM_007197). [0076] Non-limiting examples of frizzled binding domains include antibodies available from Biolegend, e.g. Clone CH3A4A7 specific for human frizzled 4 (CD344); Clone W3C4E11 specific for human Fz9 (CD349); antibodies available from Abcam, e.g. ab64636 specific for Fz7; ab83042 specific for human Fz4; ab77379 specific for human Fz7; ab75235 specific for human Fz8; ab102956 specific for human Fz9; and the like. Other examples of suitable antibodies are described in, inter alia, US Patent application 20140105917; US Patent application 20130230521 ; US Patent application 20080267955; US Patent application 20080038272; US Patent application 20030044409.

[0170] The frizzled binding moiety of the surrogate may be an engineered protein that is selected for structural homology to the frizzled binding region of a Wnt protein. Such proteins can be identified by screening a structure database for homologies. The initial protein thus identified, for example the microbial Bh1478 protein. The native protein is then engineered to provide amino acid substitutions that increase affinity, and may further be selected by affinity maturation for increased affinity and selectivity in binding to the desired frizzled protein. Non-limiting examples of frizzled binding moieties include the Fz27 and Fz27-B12 proteins illustrated in Figure 1 of PCT Patent Application Publication No. WO 2016/040895.

[0171] In certain polypeptide embodiments, the Lrp5/6 binding domain or element may be selected from any domain that binds Lrp5/6 at high affinity, e.g. a K_D of at least about 1×10^{-7} M, at least about 1×10^{-8} M, at least about 1×10^{-9} M, at least about 1×10^{-10} M. Suitable Lrp5/6 binding domains include, without limitation, de novo designed Lrp5/6 binding proteins, antibody derived binding proteins, e.g. scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins; nanobody derived binding domains; knottin-based engineered scaffolds; naturally occurring Lrp5/6 binding proteins or polypeptides, including without limitation, Norrin, DKK1, DKK2, DKK3, DKK4, sclerostin; and the like. In certain embodiments the Lrp5/6 binding domain is a C-terminal portion of DKK1.

[0172] An Lrp5/6 binding domain may be selected from any domain that binds Lrp5 or Lrp6 at high affinity, e.g. with a K_D of at least about 1×10^{-7} M, at least about 1×10^{-8} M, at least about 1×10^{-9} M, at least about 1×10^{-10} M. "LRP", "LRP proteins" and "LRP receptors" is used herein to refer to proteins of the low density lipoprotein receptor-related protein family.

These receptors are single-pass transmembrane proteins that bind and internalize ligands in the process of receptor-mediated endocytosis. LRP proteins LRP5 (GenBank Accession No. NM 002335.2) and LRP6 (GenBank Accession No. NM 002336.2) are included in the Wnt receptor complex.

[0173] Suitable Lrp5/6 binding domains include, without limitation, de novo designed Lrp5/6 binding proteins, antibody derived binding proteins, e.g., scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins; nanobody derived binding domains; knottin-based engineered scaffolds; naturally occurring Lrp5/6, including without limitation, DKK1, DKK2, DKK3, DKK4, sclerostin; Wnt; fusions proteins comprising any of the above; derivatives of any of the above; variants of any of the above; and biologically active fragments of any of the above, and the like. A Lrp5/6 binding domain may be affinity selected to enhance binding.

[0174] Members of the Dickkopf (Dkk) gene family (see Krupnik et al. (1999) Gene 238(2):301-13) include Dkk-1, Dkk-2, Dkk-3, and Dkk-4, and the Dkk-3 related protein Soggy (Sgy). hDkks 1-4 contain two distinct cysteine-rich domains in which the positions of 10 cysteine residues are highly conserved between family members. Exemplary sequences of human Dkk genes and proteins are publicly available, e.g., Genbank accession number NM_014419 (soggy-1); NM_014420 (DKK4); AF177394 (DKK-1); AF177395 (DKK-2); NM_015881 (DKK3); and NM_014421 (DKK2). In some embodiments of the invention, the Lrp6 binding moiety is a DKK1 peptide, including without limitation the C-terminal domain of human DKK1. As shown in Figure 5, the C-terminal domain may comprise the sequence KMYHTKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLE IFQRC YCGEGLSCRIQKDDHHQASNSSRLHTCQRH (SEQ ID NO:714) (see Genbank accession number NP_036374) or a biologically active fragment thereof.

[0175] Binding of DKK proteins to LRP5/6 are discussed, for example in Brott and Sokol Mol. Cell. Biol. 22 (17), 6100-6110 (2002); and Li et al. J. Biol. Chem. 277 (8), 5977-5981 (2002), each herein specifically incorporated by reference. The corresponding region of human DKK2 (Genbank reference NP_055236) may comprise the sequence KMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGLEI FQRCDCAKGLSCKVWKDATYSSKARLHVCQK (SEQ ID NO:715) or a biologically active fragment thereof.

[0176] Antibodies that specifically bind to Lrp5 or Lrp6 are known in the art and are commercially available, or can be generated de novo. Lrp5, Lrp6 or fragments thereof can be

used as an immunogen or in screening assays to develop an antibody. Examples of known antibodies include, without limitation, those described in Gong et al. (2010) PLoS One. 5(9):e12682; Ettenberg et al. (2010) Proc Natl Acad Sci U S A. 107(35): 15473-8; and those commercially available from, for example Santa Cruz biotechnology antibody clone 1A12, which was raised against synthetic LRP5/6 of human origin and binds to both the full length and proteolytic fragment of LRP 6 and LRP 5 of mouse and human origin; the monoclonal antibody 2B11; Cell Signaling Technology antibody specific for LRP5 (D80F2), catalog number 5731; etc.

[0177] Polypeptides and binding domains may also include derivatives, variants, and biologically active fragments of polypeptides described above. A "variant" polypeptide means a biologically active polypeptide as defined below having less than 100% sequence identity with a provided sequence. Such variants include polypeptides comprising one or more amino acid modifications, e.g., insertions, deletions or substitutions, as compared to the provided sequence, e.g., wherein one or more amino acid residues are added at the N- or C-terminus of, or within, the native sequence; from about one to forty amino acid residues are deleted, and optionally substituted by one or more amino acid residues; and derivatives of the above polypeptides, wherein an amino acid residue has been covalently modified so that the resulting product has a non-naturally occurring amino acid. In certain embodiments, a biologically active variant will have an amino acid sequence having at least about 90% amino acid sequence identity with a native sequence polypeptide, at least about 95%, or at least about 99%. A "functional variant" of a sequence is a compound having a qualitative biological property in common with an initial sequence. "Functional variants" include, but are not limited to, fragments of a sequence and variants of a sequence, provided that they have a biological activity in common. The term "variant" encompasses both amino acid sequence variants of polypeptide and covalent modifications thereof.

[0178] The Fzd binding domain and the Lrp5/6 binding domain may be contiguous within one globular domain, or separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, etc., including but not limited to any of those described herein. The length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt signaling agonist. The enforced distance between binding domains can vary, but in certain embodiments may be less than about 100 angstroms, less than about 90 angstroms, less than about 80 angstroms, less than about 70 angstroms, less than about 60 angstroms, or less than about 50 angstroms.

[0179] In some embodiments the linker is a rigid linker, in other embodiments the linker is a flexible linker. Where the linker is a peptide linker, in certain embodiments, it may be from about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more amino acids in length, and is of sufficient length and amino acid composition to enforce the distance between binding domains. In some embodiments the linker comprises or consists of one or more glycine and/or serine residues.

[0180] The present disclosure also includes polynucleotides or nucleic acid sequences that encode one or more Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule, and vectors comprising these polynucleotides, including expression vectors, and cells comprising these vectors. In certain embodiments, the polynucleotides or nucleic acid sequences are DNA or RNA. In particular embodiments, the RNA is messenger RNA (mRNA). In certain embodiments, the RNA is a modified mRNA comprising one or more modified nucleosides. Modified mRNAs comprising one or more modified nucleoside have been described as having advantages over unmodified mRNAs, including increase stability, higher expression levels and reduced immunogenicity. Non-limiting examples of modified mRNAs that may be used according to the present invention are described, e.g., in PCT Patent Application Publication Nos. WO2011/130624, WO2012/138453, WO2013052523, WO2013151666, WO2013/071047, WO2013/078199, WO2012045075, WO2014081507, WO2014093924 WO2014164253, US Patent Nos: US 8,278,036 (describing modified mRNAs comprising pseudouridine), US 8,691,966 (describing modified mRNAs comprising pseudouridine and/or N1-methylpseudouridine), US 8,835,108 (describing modified mRNAs comprising 5-methylcytidine), US 8,748,089 (describing modified mRNAs comprising pseudouridine or 1-methylpseudouridine). In particular embodiments, the modified mRNA sequence encoding the Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule comprises at least one modification as compared to an unmodified A, G, U or C ribonucleoside. In particular embodiments, the at least one modified nucleosides include N1-methylpseudouridine and/or 5-methylcytidine. In particular embodiments, the modified mRNA comprises a 5' terminal cap sequence followed by a sequence encoding the Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule, following by a 3' tailing sequence, such as a polyA or a polyA-G sequence.

[0181] In particular embodiments, the polynucleotide is a vector, e.g., an expression vector, and the expression vector comprises a polynucleotide sequence encoding a Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule described herein operably linked to a

promoter sequence, e.g., a promoter sequence that drives expression of the polynucleotide in a cell. In certain embodiments, the vector is a viral vector, e.g., a virus comprising a polynucleotide comprising an expression cassette comprising a promoter operably linked to a DNA or RNA sequence encoding the Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecules. In particular embodiments, the expression cassette comprises 5' and/or 3' cellular or viral UTRs.

[0182] The present disclosure also includes functional fragments and variants of the polynucleotides described herein, including variants having at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% polynucleotide sequence identity to a polynucleotide described herein. Such variants may comprise one or more nucleotide or nucleoside modifications as compared to any of the sequences disclosed herein, e.g., one or more nucleotide deletion, insertion or substitution. In particular embodiments, the polynucleotides described herein are codon-optimized, e.g., to enhance expression of the encoded polypeptide in a host cell. In particular embodiments, polynucleotide variants comprise one or more modified nucleotide or nucleoside.

[0183] The present disclosure also includes cells comprising a polynucleotide or vector that encodes a Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule described herein. In certain embodiments, the cell is a host cell, such as, e.g., an HEK293 cell that may be used to produce Wnt polypeptides, Norrin polypeptides, or Wnt signaling agonist molecules. In preparing the subject compositions, any host cells may be employed, including but not limited to, for example, mammalian cells (e.g. 293 cells), insect cells (e.g., SF9 cells), microorganisms and yeast. In certain embodiments, the cells are heterologous or autologous to a subject treated with a Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule described herein. In particular embodiments, the cells were obtained from the subject and transduced with a viral vector described herein. In particular embodiments, the transduced cells are delivered to the subject for treatment. The present disclosure also includes pharmaceutical compositions comprising one or more Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecules, or one or more polynucleotides or vectors comprising sequences encoding a Wnt polypeptide, Norrin polypeptide, or Wnt signaling agonist molecule.

Pharmaceutical Compositions

[0184] Pharmaceutical compositions comprising a tissue-specific Wnt signal enhancing molecule or antibody or antigen-binding fragment thereof described herein and one or more

pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules described herein.

[0185] In further embodiments, pharmaceutical compositions comprising a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule or antibody or antigen-binding fragment thereof described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more polynucleotides comprising a nucleic acid sequence encoding a Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules as described herein. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same polynucleotide.

[0186] In further embodiments, pharmaceutical compositions comprising an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule or antibody or antigen-binding fragment thereof described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules as described herein. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same polynucleotide, e.g., expression cassette.

[0187] The present invention further contemplates a pharmaceutical composition comprising a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid encoding a tissue-specific Wnt signal enhancing molecule or antibody or antigen-binding fragment thereof described herein and one or

more pharmaceutically acceptable diluent, carrier, or excipient. In particular embodiments, the pharmaceutical composition further comprises a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid sequence encoding a Wnt polypeptide, a Norrin polypeptide or a Wnt signaling agonist molecules as described herein. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same polynucleotide, e.g., expression cassette and/or in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

[0188] The present disclosure contemplates pharmaceutical compositions comprising a first molecule for delivery of a tissue-specific Wnt signal enhancing molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist as a second active agent. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

[0189] The subject molecules, alone or in combination, can be combined with pharmaceutically-acceptable carriers, diluents and reagents useful in preparing a formulation that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for mammalian, e.g., human or primate, use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. Examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Supplementary active compounds can also be incorporated into the formulations. Solutions or suspensions used for the formulations can include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as

ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates; detergents such as Tween 20 to prevent aggregation; and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. In particular embodiments, the pharmaceutical compositions are sterile.

[0190] Pharmaceutical compositions may further include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, or phosphate buffered saline (PBS). In some cases, the composition is sterile and should be fluid to the extent that easy syringability exists. In certain embodiments, it is stable under the conditions of manufacture and storage and is preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be, e.g., a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the internal compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0191] Sterile solutions can be prepared by incorporating the tissue-specific Wnt signal enhancing molecule in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0192] In one embodiment, the pharmaceutical compositions are prepared with carriers that will protect the fusion protein against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art.

[0193] It may be advantageous to formulate the pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0194] The pharmaceutical compositions can be included in a container, pack, or dispenser, e.g. syringe, e.g. a prefilled syringe, together with instructions for administration.

[0195] The pharmaceutical compositions of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal comprising a human, is capable of providing (directly or indirectly) the biologically active tissue-specific Wnt signal enhancing molecule.

[0196] The present invention includes pharmaceutically acceptable salts of the tissue-specific Wnt signal enhancing molecules described herein. The term “pharmaceutically acceptable salt” refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. A variety of pharmaceutically acceptable salts are known in the art and described, e.g., in “Remington’s Pharmaceutical Sciences”, 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the “Encyclopaedia of Pharmaceutical Technology”, 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in J.

Pharm. Sci. 66: 2 (1977). Also, for a review on suitable salts, see “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, 2002).

[0197] Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Metals used as cations comprise sodium, potassium, magnesium, calcium, and the like. Amines comprise N-N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., “Pharmaceutical Salts,” J. Pharma Sci., 1977, 66, 119). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

[0198] In some embodiments, the pharmaceutical composition provided herein comprise a therapeutically effective amount of a tissue-specific Wnt signal enhancing molecule described herein in admixture with a pharmaceutically acceptable carrier, diluent and/or excipient, for example saline, phosphate buffered saline, phosphate and amino acids, polymers, polyols, sugar, buffers, preservatives and other proteins. Exemplary amino acids, polymers and sugars and the like are octylphenoxy polyethoxy ethanol compounds, polyethylene glycol monostearate compounds, polyoxyethylene sorbitan fatty acid esters, sucrose, fructose, dextrose, maltose, glucose, mannitol, dextran, sorbitol, inositol, galactitol, xylitol, lactose, trehalose, bovine or human serum albumin, citrate, acetate, Ringer's and Hank's solutions, cysteine, arginine, carnitine, alanine, glycine, lysine, valine, leucine, polyvinylpyrrolidone, polyethylene and glycol. Preferably, this formulation is stable for at least six months at 4° C.

[0199] In some embodiments, the pharmaceutical composition provided herein comprises a buffer, such as phosphate buffered saline (PBS) or sodium phosphate/sodium sulfate, tris buffer, glycine buffer, sterile water and other buffers known to the ordinarily skilled artisan such as those described by Good et al. (1966) Biochemistry 5:467. The pH of the buffer may be in the range of 6.5 to 7.75, preferably 7 to 7.5, and most preferably 7.2 to 7.4.

Methods For Increasing Wnt Activity or Wnt Receptor Cell Surface Expression

[0200] Tissue-specific Wnt signal enhancing molecules, exemplified herein with respect to fusion proteins, may be used to increase Wnt signaling in a targeted tissue or cell type. In

particular embodiments, the Wnt signaling is canonical Wnt signaling. Thus, in some aspects, the present invention provides a method for increasing or enhancing Wnt signaling in a target tissue or cell, comprising contacting the target tissue or cell with an effective amount of a tissue-specific Wnt signal enhancing molecule disclosed herein, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo, e.g., the subject tissue-specific Wnt signal enhancing molecule is administered or provided to a subject. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro.

[0201] In certain embodiments, the method comprises further contacting the target tissue or cell with one or more Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules described herein. The present disclosure contemplates contacting a target tissue or cell with a first molecule for delivery of a tissue-specific Wnt signal enhancing molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist as a second active agent. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

[0202] In related aspects, the present invention provides a method for increasing Wnt signaling in a target tissue or cell, comprising contacting the target tissue or cell with an effective amount of a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule disclosed herein, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the target tissue or cell is also contacted with a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a

promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same polynucleotide.

[0203] In related aspects, the present invention provides a method for increasing Wnt signaling in a target tissue or cell, comprising contacting the target tissue or cell with an effective amount of a vector comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule of the present invention, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the target tissue or cell is also contacted with a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same vector, e.g., in the same expression cassette.

[0204] In related aspects, the present invention provides a method for increasing Wnt signaling in a target tissue, comprising contacting the target tissue with an effective amount of a cell comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule of the present invention, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the target tissue is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the tissue-specific Wnt signal enhancing molecule or the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

[0205] Any of the methods described herein for increasing Wnt signalling may also be used to increase the number of Frizzled (Fz) receptors on the surface of targeted cells, e.g., liver tissue cells. In certain embodiments, the number of Fz receptors of the surface of the targeted cells is increase by at least 10%, at least 20%, at least 30%, at least 40%, at elast 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least two-fold, at least five-fold, or at least 10-fold. In particular embodiments, the Fz receptors include one or more of human frizzled proteins Fz1, Fz2, Fz3, Fz4, Fz5, Fz6, Fz7, Fz8, Fz9, Fz10. For example, the disclosure provides a method for increasing Fz receptors on the surface of targeted cells, comprising contacting the cells with an effective amount of a tissue- or cell-specific Wnt signal enhancing molecule disclosed herein, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In particular embodiments, the cells are liver cells, and the targeting module binds ASGR1 or ASGR2. In certain embodiments, the targeting module comprises an antibody or antigen-binding fragment thereof disclosed herein. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo, e.g., the tissue-specific Wnt signal enhancing molecule is administered or provided to a subject. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro. In certain embodiments, the targeted cell or tissue is initially contacted with the Wnt signal enhancing molecule directly, whereas in other related embodiments, the cell is initially contacted with a polynucleotide encoding the Wnt signal enhancing molecule, e.g., an expression vector, whereby the cell takes up the polynucleotide and expresses the Wnt signal enhancing molecule. In certain embodiments, the method comprises further contacting the targeted tissue or cell with one or more Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules described herein.

[0206] Any of the methods described herein for increasing Wnt signalling may also be used to increase Ki-67 on targeted cells, e.g., liver tissue cells.

Methods For Treating Diseases and Disorders

[0207] Tissue-specific Wnt signal enhancing molecules, exemplified herein with respect to fusion proteins, may be used in to treat a disease, disorder or condition, for example, by increasing Wnt signaling in a targeted cell, tissue or organ. Thus, in some aspects, the present invention provides a method for treating a disease or condition in a subject in need thereof, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting the subject with an effective amount of a composition of the present disclosure. In particular embodiments, the

composition is a pharmaceutical composition comprising any of: a tissue-specific Wnt signal enhancing molecule, e.g., a small molecule or a polypeptide; a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule, e.g., a DNA or mRNA, optionally a modified mRNA; a vector comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule, e.g., an expression vector or viral vector; or a cell comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule, e.g., a cell transduced with an expression vector or viral vector encoding a tissue-specific Wnt signal enhancing molecule. In particular embodiments, the disease or condition is a pathological disease or disorder, or an injury, e.g., an injury resulting from a wound. In certain embodiments, the wound may be the result of another therapeutic treatment. In certain embodiments, the disease or condition comprises impaired tissue repair, healing or regeneration, or would benefit from increased tissue repair, healing or regeneration. In some embodiments, contacting occurs in vivo, i.e., the subject composition is administered to a subject.

[0208] In certain embodiments, the method comprises further contacting the subject with a pharmaceutical composition comprising one or more Wnt polypeptides, Norrin polypeptides or Wnt signaling agonist molecules described herein. The present disclosure contemplates contacting a subject with a first molecule for delivery of a tissue-specific Wnt signal enhancing molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist as a second active agent. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

[0209] In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule of the present invention, wherein the molecule comprises a targeting

module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same polynucleotide.

[0210] In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule of the present invention, wherein the molecule comprises a targeting module that binds to a cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same vector, e.g., in the same expression cassette.

[0211] In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a cell comprising a nucleic acid sequence encoding a tissue-specific Wnt signal enhancing molecule of the present invention, wherein the molecule comprises a targeting module that binds to a

cell surface receptor on the target tissue or cell in a tissue- or cell-specific manner. In certain embodiments, the subject is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide, Norrin polypeptides or Wnt signaling agonist. In certain embodiments, the nucleic acid sequence encoding the tissue-specific Wnt signal enhancing molecule and the nucleic acid sequence encoding the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the tissue-specific Wnt signal enhancing molecule or the Wnt polypeptide, Norrin polypeptide or Wnt signaling agonist molecule. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

[0212] Wnt signaling plays key roles in the developmental process and maintenance of stem cells. Reactivation of Wnt signals is associated with regeneration and repair of most tissues after injuries and diseases. Tissue-specific Wnt signal enhancing molecules may provide benefit of healing and tissue repair in response to injuries and diseases. Causes of tissue damage and loss include but are not limited to aging, degeneration, hereditary conditions, infection and inflammation, traumatic injuries, toxins/metabolic-induced toxicities, or other pathological conditions. Wnt signals and enhancers of Wnt signals have been shown to activate adult, tissue-resident stem cells. In some embodiments, the compounds of the invention are administered for use in treating diseased or damaged tissue, for use in tissue regeneration and for use in cell growth and proliferation, and/or for use in tissue engineering.

[0213] Human diseases associated with mutations of the Wnt pathway provide strong evidence for enhancement of Wnt signals in the treatment and prevention of diseases. Preclinical in vivo and in vitro studies provide additional evidence of involvement of Wnt signals in many disease conditions and further support utilization of tissue-specific Wnt signal enhancing molecules in various human diseases. For example, compositions of the present invention may be used to promote or increase bone growth or regeneration, bone grafting, healing of bone fractures, treatment of osteoporosis and osteoporotic fractures, spinal fusion, osseointegration of orthopedic devices, tendon-bone integration, tooth growth and regeneration, dental implantation, periodontal diseases, maxillofacial reconstruction, and osteonecrosis of the jaw. They may also be used in the treatment of alopecia; enhancing regeneration of sensory organs, e.g. treatment of hearing loss including regeneration of the inner and outer auditory hair cells, treatment of vestibular

hypofunction, treatment of macular degeneration, treatment of retinopathies including vitreoretinopathy, diabetic retinopathy, or other diseases of retinal degeneration, Fuchs' dystrophy, other cornea disease, etc.; treatment of stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis and other conditions affecting the degeneration or integrity of the blood brain barrier; treatment of spinal cord injuries, other spinal cord diseases. The compositions of this invention may also be used in treatment of oral mucositis, intestinal mucositis, treatment of short bowel syndrome, inflammatory bowel diseases (IBDs), including but not limited to Crohn's Disease (CD) and ulcerative colitis (UC), in particular, CD and UC with fistula formation; other gastrointestinal disorders; treatment of metabolic syndrome; treatment of diabetes, treatment of pancreatitis, conditions where exocrine or endocrine pancreas tissues are damaged; conditions where enhanced epidermal regeneration is desired, e.g., epidermal wound healing, treatment of diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, etc., conditions where angiogenesis is beneficial; treatment of myocardial infarction, coronary artery disease, heart failure; enhanced growth of hematopoietic cells, e.g. enhancement of hematopoietic stem cell transplants from bone marrow, mobilized peripheral blood, treatment of immunodeficiencies, graft versus host diseases, etc.; treatment of acute kidney injuries, chronic kidney diseases; treatment of lung diseases, chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, enhanced regeneration of lung tissues, in particular, proliferation and differentiation of pulmonary stems cells (e.g., AT2 and AT1 cells). The compositions of the present invention may also be used in enhanced regeneration of liver cells, e.g. liver regeneration, treatment of cirrhosis, enhancement of liver transplantations, treatment of acute liver failure, treatment of chronic liver diseases with hepatitis (A, B, or C) virus infection or post-antiviral drug therapies, alcoholic liver diseases, including alcoholic hepatitis, non- alcoholic liver diseases with steatosis or steatohepatitis, and the like. The compositions of this invention may treat diseases and disorders including, without limitation, conditions in which regenerative cell growth is desired.

[0214] Human genetics involving loss-of-function or gain-of-function mutations in Wnt signaling components show strong evidence supporting enhancing Wnt signals for bone growth. Conditions in which enhanced bone growth is desired may include, without limitation, fractures, grafts, ingrowth around prosthetic devices, osteoporosis, osteoporotic fractures, spinal fusion, osteonecrosis of the jaw, dental implantation, periodontal diseases, maxillofacial reconstruction, and the like. Tissue-specific Wnt signal enhancing molecules enhance and

promote Wnt signals which are critical in promoting bone regeneration. Methods for regeneration of bone tissues benefit from administration of the compounds of the invention, which can be systemic or localized. In some embodiments, bone marrow cells are exposed to molecules of the invention, such that stem cells within that marrow become activated.

[0215] In some embodiments, bone regeneration is enhanced by contacting a responsive cell population, e.g. bone marrow, bone progenitor cells, bone stem cells, etc. with an effective dose of a molecule of the invention. Methods for regeneration of bone tissues benefit from administration of the compounds of the invention, which can be systemic or localized. In some such embodiments, the contacting is performed *in vivo*. In other such embodiments, the contacting is performed *ex vivo*. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include, without limitation, absorbable collagen sponges, ceramics, hydrogels, polymeric microspheres, nanoparticles, bone cements, and the like.

[0216] Compositions comprising one or more of the molecules of the invention can be used for the *in vivo* treatment of skeletal tissue deficiencies. By "skeletal tissue deficiency", it is meant a deficiency in bone or other skeletal connective tissue at any site where it is desired to restore the bone or connective tissue, no matter how the deficiency originated, e.g. whether as a result of surgical intervention, removal of tumor, ulceration, implant, fracture, or other traumatic or degenerative conditions. The compositions of the present invention can be used as part of a regimen for restoring cartilage function to a connective tissue, for the repair of defects or lesions in cartilage tissue such as degenerative wear and arthritis, trauma to the tissue, displacement of torn meniscus, meniscectomy, a luxation of a joint by a torn ligament, malalignment of joints, bone fracture, or by hereditary disease.

[0217] The compositions of the invention may also be used for treatment of periodontal diseases. Periodontal diseases are a leading cause of tooth loss and are linked to multiple systemic conditions. In some embodiments, tooth or underlying bone regeneration is enhanced by contacting a responsive cell population. In some such embodiments, the contacting is performed *in vivo*. In other such embodiments, the contacting is performed *ex vivo*, with subsequent implantation of the activated stem or progenitor cells. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include,

without limitation, absorbable collagen sponges, ceramics, hydrogels, bone cements, polymeric microspheres, nanoparticles, and the like.

[0218] Studies have shown that biology of Wnt signaling and R-spondins are capable of promoting sensory hair cell regeneration in the inner ear following injuries, aging, or degeneration. Loss of sensory hair cells in the inner ear involved in hearing loss or vestibular hypofunction may also benefit from the compositions of the invention. In the inner ear, the auditory organ houses mechanosensitive hair cells required for translating sound vibration to electric impulses. The vestibular organs, comprised of the semicircular canals (SSCs), the utricle, and the saccule, also contain sensory hair cells in order to detect head position and motion. Compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the ear for enhancement of auditory regeneration.

[0219] The compositions of this invention may also be used in regeneration of retinal tissue. In the adult mammalian retina, Muller glia cells are capable of regenerating retinal cells, including photoreceptors, for example after neurotoxic injury in vivo. Wnt signaling and enhancers of Wnt signals can promote proliferation of Muller glia-derived retinal progenitors after damage or during degeneration. The compositions of the invention may also be used in the regeneration of tissues and other cell types in the eye. For examples age-related macular degeneration (AMD), other retina degenerative diseases, cornea diseases, Fuchs' dystrophy, vitreoretinopathy, hereditary diseases, etc. can benefit from the compositions of the present inventions. AMD is characterized by progressively decreased central vision and visual acuity. Fuchs' dystrophy is characterized by progressive loss of cornea endothelial cells. Wnt signal and enhancing of Wnt signal can promote regeneration of cornea endothelium, retina epithelium, etc. in the eye tissue. In other embodiments, compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the eye for retinal regeneration and treatment of macular degeneration.

[0220] Specific populations of proliferating cells for homeostatic renewal of hepatocytes have been identified through lineage tracing studies, for example Axin2-positive cells in peri-central region. Lineage tracing studies also identified additional potential liver progenitor cells, including but not limited to Lgr-positive cells. The self-renewing liver cells and other populations of potential progenitor cells, including Lgr5-positive and Axin2-positive cells, are identified to be capable of regeneration responding to Wnt signals and/or R-spondins following injuries. Numerous preclinical models of acute liver injury and failure and chronic liver

diseases showed recovery and regeneration of hepatocytes benefit from enhancing Wnt signals. In certain embodiments, the compositions of this invention may be used in treatment of, e.g., acute liver failure (of all causes), acute alcoholic liver injuries, chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, chronic alcoholic liver diseases, non-alcoholic fatty liver diseases (NAFLD)(fatty liver), non-alcoholic steatohepatitis (NASH), cirrhosis, severe chronic liver diseases of all causes, acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases, chronic liver failure (of all causes), liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, liver surgery, liver injury, liver transplantation, “small for size” syndrome in liver surgery and transplantation, congenital liver disease and disorders, any other liver disorder or defect resulting from genetic diseases, degeneration, aging, drugs, or injuries. They may also be used to enhance regeneration of liver cells, *in vivo* or *in vitro*. Methods for regeneration of liver tissue benefit from administration of the compounds of the invention, which can be systemic or localized. These include, but are not limited to, methods of systemic administration and methods of localized administration, e.g., by injection into the liver tissue, by injection into veins or blood vessels leading into the liver, by implantation of a sustained release formulation, and the like.

[0221] The compositions of the present invention may be used to treat end stage liver disease (ESLD). ESLD or chronic liver failure is often the result of severe liver cirrhosis and the resultant liver fibrosis. ESLD is manifested by the development of ascites, variceal hemorrhage, hepatic encephalopathy and/or liver function impairment (e.g., decompensated liver disease). Common diseases or disorders associated with ESLD include: alcoholic hepatitis, chronic hepatitis C infection, chronic hepatitis B infection, chronic hepatitis D infection, non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), and inherited diseases such as cystic fibrosis, alpha-1 anti-trypsin deficiency, hemochromatosis, Wilson disease, galactosemia, and glycogen storage disease. Prolonged exposure to drugs, toxic chemicals, parasitic infections, and repeated heart failures with liver congestion can also result in ESLD.

[0222] Wnt signals play an important role in regeneration of various epithelial tissues. Various epidermal conditions benefit from treatment with the compounds of the present invention. Mucositis occurs when there is a breakdown of the rapidly divided epithelial cells lining the gastro-intestinal tract, leaving the mucosal tissue open to ulceration and infection.

The part of the epithelial lining that covers the mouth, called the oral mucosa, is one of the most sensitive parts of the body and is particularly vulnerable to chemotherapy and radiation. Oral mucositis is probably the most common, debilitating complication of cancer treatments, particularly chemotherapy and radiation. In addition, the compositions of the invention may also benefit treatment of intestinal mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), or other gastrointestinal disorders. Other epidermal conditions include epidermal wound healing, diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, and the like. Molecules of the present invention may be used in all these conditions, where regenerative cells are contacted with compounds of the invention. Methods for regeneration of epithelial tissues benefit from administration of the compounds of the invention, which can be systemic or localized. Contacting can be, for example, topical, including intradermal, subdermal, in a gel, lotion, cream etc. applied at targeted site, etc.

[0223] In addition to skin and gastrointestinal tract, Wnt signals and enhancement and promotion of Wnt signals also play an important role in repair and regeneration of tissues including pancreas, kidney, and lung in preclinical models. Tissue-specific Wnt signal enhancing molecules may benefit various disease conditions involving exocrine and endocrine pancreas, kidney, or lung. The compositions of the invention may be used in treatment of metabolic syndrome; treatment of diabetes, treatment of acute or chronic pancreatitis, exocrine pancreatic insufficiency, treatment of acute kidney injuries, chronic kidney diseases, treatment of lung diseases, including but not limited to chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, other conditions that cause loss of lung epithelial tissues. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

[0224] Epidermal Wnt signaling, in coordination with signaling via other development factors, is critical for adult hair follicle regeneration. Hair loss is a common problem, and androgenetic alopecia, often called male pattern baldness, is the most common form of hair loss in men. In some embodiments, hair follicle regeneration is enhanced by contacting a responsive cell population with a molecule of the present invention. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo. The molecule may be localized to the site of action, e.g. topical lotions, gels, creams and the like.

[0225] Stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis and other conditions affecting the blood brain barrier (BBB) may be treated with tissue-specific Wnt

signal enhancing molecules of the invention. Angiogenesis is critical to ensure the supply of oxygen and nutrients to many tissues throughout the body, and is especially important for the CNS as the neural tissue is extremely sensitive to hypoxia and ischemia. CNS endothelial cells which form the BBB differ from endothelial cells in non-neural tissue, in that they are highly polarized cells held together by tight junctions and express specific transporters. Wnt signaling regulates CNS vessel formation and/or function. Conditions in which the BBB is compromised can benefit from administration of the compounds of the invention, which can be systemic or localized e.g. by direct injection, intrathecal administration, implantation of sustained release formulations, and the like. In addition, Wnt signal is actively involved in neurogenesis and plays a role of neuroprotection following injury. The compositions of the present invention may also be used in treatment of spinal cord injuries, other spinal cord diseases, stroke, traumatic brain injuries, etc.

[0226] Wnt signals also play a role in angiogenesis. Tissue-specific Wnt signal enhancing molecules may benefit conditions where angiogenesis is beneficial, treatment of myocardial infarction, coronary artery disease, heart failure, etc., and conditions from hereditary diseases. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

[0227] In certain embodiments, methods of the present invention promote tissue regeneration, e.g., in a tissue subjected to damage or tissue or cell reduction or loss. The loss or damage can be anything which causes the cell number to diminish, including diseases or injuries. For example, an accident, an autoimmune disorder, a therapeutic side-effect or a disease state could constitute trauma. Tissue regeneration increases the cell number within the tissue and preferably enables connections between cells of the tissue to be re-established, and more preferably the functionality of the tissue to be regained.

[0228] In particular embodiments, a composition is administered parenterally, e.g., intravenously, orally, rectally, or by injection. In some embodiments, it is administered locally, e.g., topically or intramuscularly. In some embodiments, a composition is administered to target tissues, e.g., to bone, joints, ear tissue, eye tissue, gastrointestinal tract, skin, a wound site or spinal cord. Methods of the invention may be practiced in vivo or ex vivo. In some embodiments, the contacting of a target cell or tissue with a tissue-specific Wnt signal enhancing molecule is performed ex vivo, with subsequent implantation of the cells or tissues, e.g., activated stem or progenitor cells, into the subject. The skilled artisan can determine an appropriate site of and route of administration based on the disease or disorder being treated.

[0229] The dose and dosage regimen may depend upon a variety of factors readily determined by a physician, such as the nature of the disease or disorder, the characteristics of the subject, and the subject's history. In particular embodiments, the amount of tissue-specific Wnt signal enhancing molecule, e.g., fusion protein, administered or provided to the subject is in the range of about 0.01 mg/kg to about 50 mg/kg, 0.1 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 50 mg/kg of the subject's body weight.

[0230] In certain embodiments, the subject may be any mammal, e.g. human, rodent (e.g. mice, rats, gerbils), rabbit, feline, canine, goat, ovine, pig, equine, bovine, or primate.

[0231] In some embodiments, the subject method results in a therapeutic benefit, e.g., preventing the development of a disorder, halting the progression of a disorder, reversing the progression of a disorder, etc. In some embodiments, the subject method comprises the step of detecting that a therapeutic benefit has been achieved. The ordinarily skilled artisan will appreciate that such measures of therapeutic efficacy will be applicable to the particular disease being modified, and will recognize the appropriate detection methods to use to measure therapeutic efficacy.

[0232] In certain embodiments, the disclosure provides a method for treating or preventing a disease or disorder associated with reduced Wnt signaling or that would benefit from increased Wnt signaling activity in bone tissue, such as, for example, any of the conditions disclosed herein wherein bone growth is desirable, comprising providing to a subject in need thereof a pharmaceutical composition comprising a Wnt signal enhancing molecule comprising a targeting module that binds bone tissue, e.g., a targeting module that specifically binds to PTH1R, wherein the Wnt signal enhancing molecule increases or enhances Wnt signaling in the subject's bone tissue. In certain embodiments, the pharmaceutical composition is administered orally or systemically, e.g., parenterally. In particular embodiments, the Wnt signal enhancing molecule comprises an action module comprising an R-spondin Furin domain 1 or a fragment or variant thereof and, optionally, a mutated Furin domain 2 or a fragment or variant thereof.

[0233] In certain embodiments, the disclosure provides a method for treating or preventing a disease or disorder associated with reduced Wnt signaling or that would benefit from increased Wnt signaling activity in liver tissue, such as, for example, any of the diseases or disorders disclosed herein that would benefit from liver regeneration, comprising providing to a subject in need thereof a pharmaceutical composition comprising a Wnt signal enhancing molecule comprising a targeting module that binds liver tissue, e.g., a targeting module that specifically

binds to ASGR1, ASGR2, TFR2 or SLC10A1, wherein the Wnt signal enhancing molecule increases or enhances Wnt signaling in the subject's liver tissue. In certain embodiments, the pharmaceutical composition is administered orally or systemically, e.g., parenterally. In particular embodiments, the Wnt signal enhancing molecule comprises an action module comprising an R-spondin Furin domain 1 or a fragment or variant thereof and, optionally, a mutated Furin domain 2 or a fragment or variant thereof.

[0234] In certain embodiments, the disclosure provides a method for treating or preventing a disease or disorder associated with reduced Wnt signaling or that would benefit from increased Wnt signaling activity in oral mucosa tissue, such as, for example, oral mucositis, comprising providing to a subject in need thereof a pharmaceutical composition comprising a Wnt signal enhancing molecule comprising a targeting module that binds oral mucosa tissue, e.g., a targeting module that specifically binds to LYPD3 or DSG3, wherein the Wnt signal enhancing molecule increases or enhances Wnt signaling in the subject's oral mucosa tissue. In certain embodiments, the pharmaceutical composition is administered orally or systemically, e.g., parenterally. In particular embodiments, the Wnt signal enhancing molecule comprises an action module comprising an R-spondin Furin domain 1 or a fragment or variant thereof and, optionally, a mutated Furin domain 2 or a fragment or variant thereof.

[0235] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

[0236] From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

EXAMPLES

[0237] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts,

temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0238] General methods in molecular biology, cell biology and biochemistry can be found in such standard textbooks as “Molecular Cloning: A Laboratory Manual, 3rd Ed.” (Sambrook et al., Harbor Laboratory Press 2001); “Short Protocols in Molecular Biology, 4th Ed.” (Ausubel et al. eds., John Wiley & Sons 1999); “Protein Methods” (Bollag et al., John Wiley & Sons 1996); “Nonviral Vectors for Gene Therapy” (Wagner et al. eds., Academic Press 1999); “Viral Vectors” (Kaplift & Loewy eds., Academic Press 1995); “Immunology Methods Manual” (I. Lefkovits ed., Academic Press 1997); and “Cell and Tissue Culture: Laboratory Procedures in Biotechnology” (Doyle & Griffiths, John Wiley & Sons 1998), the disclosures of which are incorporated herein by reference. Reagents, cloning vectors, and kits for genetic manipulation referred to in this disclosure are available from commercial vendors such as BioRad, Stratagene, Invitrogen, Sigma-Aldrich, and ClonTech.

[0239] Materials and methods employed in the following Examples include the following.

[0240] **Published ASGR1 Binders:** The prototypical anti-ASGR1 binder (RO-01) and several others (RO-02, -03, and -04) were selected from PCT Patent Application Publication No. WO2014/023709. The anti-TFR1 sequence was selected from PCT Patent Application Publication No. WO2016/081640. The anti-LYPD3 sequence was selected from PCT Patent Application Publication No. WO2017/0158775. The anti-DSG3 sequence was selected from PCT Patent Application Publication No. WO2010/092457. ZNRF3 binder SC-01 and SC-02 were selected from PCT Patent Application Publication No. WO2015/164392. RNF43 binder NV-01 was selected from PCT Patent Application Publication No. WO 2013/054307.

[0241] **Protein production:** All recombinant proteins were produced in Expi293F cells (Thermo Fisher Scientific) by transient transfection unless otherwise specified. All scFv-containing fusions contain a FLAG-His tag and were first purified using cOmplete his-tag purification resin (Sigma-Aldrich) following vendor recommended procedures. All IgG-based and Fc-containing constructs were first purified with Protein-A resin and eluted with 0.1 M glycine pH 3.5. All proteins were then polished by a size exclusion column in HBS buffer (10 mM HEPES pH 7.2, 150 mM NaCl). Proteins were supplemented with glycerol to 10% for long term storage at -80°C. For *in vitro* receptor binding analyses, extracellular domains of human RNF3 (Q44-D198) and ZNRF3 (K56-M219) and ASGR1 (Q62-L291) were expressed with a His-Avi tag at the N-terminus, and mouse ASGR1 (Q61-N284) was expressed with a

His-Avi tag at the C-terminus. They were purified by His-tag resin, biotinylated as described (Janda et al., 2017; Nature 545:234), then further purified by size exclusion chromatography. For affinity measurement Fab version of the ASGR1 binder was made with a (His)₆ tag at the C-terminus of human IgG1 CH1 domain following a 5-mer linker (GSGSG), and purified by His-tag resin followed by size exclusion chromatography. All proteins tested were examined by SDS-polyacrylamide electrophoresis and estimated to be at least 90% pure.

[0242] SuperTop Flash (STF) assay: Wnt signaling activity was measured using cell lines containing a luciferase gene controlled by a Wnt-responsive promoter (Super Top Flash reporter assay, STF) as reported (Janda et al., 2017; Nature 545:234). In brief, cells were seeded at a density of 10,000 per well in 96-well plates 24 hr prior to treatment, then treated by RSPO or mimetic proteins overnight either alone or together with 30% Wnt3a-conditioned media. Wnt3a conditioned media was prepared from ATCC-CRL-2647 Wnt3a secreting L cells following vendor recommended conditions. Cells were lysed with Luciferase Cell Culture Lysis Reagent (Promega) and activity was measured with Luciferase Assay System (Promega) using vendor suggested procedures. Data were plotted as average $\pm$ standard deviation of triplicates and fitted by non-linear regression using Prism (GraphPad Software). For over expression of exogenous receptors, cells were transiently transfected with plasmids containing receptors of interest under eukaryotic expression promoters (*ASGR1* was clone OHU03658D from GenScript, *ASGR2* was in-house cloned isoform d/NP_001188281.1, and *TFRC* was clone HG11020-UT from SinoBiologicals), then split into 96-well plates (20,000 cells per well) for STF assay 24 hr post transfection.

[0243] Affinity measurement: Binding kinetics of the RSPO-derived proteins to LGR5, RNF43, or ZNRF3, and binding of the anti-ASGR Fabs to human and/or mouse ASGR1 were determined by bio-layer interferometry (BLI) using Octet Red 96 (PALL ForteBio, Fremont, CA) instruments at 30°C, 1000 rpm with either streptavidin (SA) or anti-hIgG Fc capture (AHC) biosensors. Biotinylated extracellular domain (ECD) of RNF43 or ZNRF3 or ASGR1 and Fc portion of human IgG1-fused LGR5-ECD (R&D systems) were diluted to 50 nM in the running buffer (PBS, 0.05% Tween-20, 0.5% BSA, pH 7.2) captured to the SA biosensor and the AHC biosensor, respectively, until coupling level reached $\sim$ 1.0 nm. Following capture of ECDs of RNF43, ZNRF3 or LGR5, the biosensors were dipped into wells containing the relevant test molecules at 7 different concentrations in running buffer plus a well with only running buffer as a reference channel. K_D was determined by steady-state analysis based on the average responses between 140 to 145 seconds of association phase, for binding to LGR5,

RNF43, and ZNRF3. For the binding to ASGR, K_D was determined by curve model fitting using the Octet® Red data analysis software (Fortebio)

[0244] Cell flow cytometry: HEK293 cells transiently transfected with a plasmid overexpressing *ZNRF3* (GenScript OHu22977), alone or together with *ASGR1*, and were treated for 24 hours with RSPO derivative molecules at 10 nM final concentration with or without 10% Wnt3a conditioned media. Cells were dissociated using Gibco enzyme-free dissociation buffer, washed, and resuspended in FACS buffer (1X PBS with 1% BSA with 0.02% sodium azide). Cells were incubated with 1 nM 18R5 IgG (pan-frizzled) for 1 hour. After washing, the cells were incubated with goat anti-human IgG Alexa Fluor 647 (Invitrogen) for 40 minutes. Cells were washed with FACS buffer and subjected to multi-channel analysis using a BD Accuri C6 Plus Flow Cytometer. Data were processed with FlowJo software and fluorescence signals were displayed in histogram plots.

[0245] Western blot analysis of cellular proteins: Cells were lysed with RIPA buffer (50 mM Tris-HCl pH7.4, 150 mM NaCl, 1% IGEPAL CA630, 0.5% sodium deoxycholate, 0.1% SDS and 1 mM EDTA) supplemented with protease and phosphatase inhibitors. Cell lysates were spun at 15,000 rpm at 4°C for 5 min and supernatants were resolved by SDS-PAGE, transferred to nitrocellulose membranes and probed with primary antibody followed by HRP-conjugated secondary antibody and ECL film detection. The anti-LRP6, anti-phospho-LRP6 (Ser 1490) and anti-DLV2 primary antibodies were from Cell Signaling Technology. Anti- α tubulin antibody was from Sigma-Aldrich.

[0246] Semi-quantitative PCR analysis of gene expression: RNA from human cell cultures (HEK293, Huh-7 and A431) were extracted using the Qiagen RNeasy Micro Kit (Qiagen, 74004). cDNA was produced using the SuperScript™ VILO™ cDNA Synthesis Kit (ThermoFisher, 11754050). Human *ASGR1*, *ASGR2* and *TFRC* expression were measured by using TaqMan® Fast Advanced Master Mix (ThermoFisher, 4444963) and the Hs01005019_m1 *ASGR1*, the Hs00154160_m1 *ASGR2* and the Hs00951083_m1 *TFRC* probes (ThermoFisher, 4331182). Values were normalized to expression of constitutive *Actin B* gene using the Hs01060665_m1 probe (ThermoFisher, 4331182). RNA from mouse tissues (liver and small intestine samples) was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (ThermoFisher, A27828). cDNA was produced using the high-Capacity cDNA Reverse Transcription Kit (ThermoFisher, 43-688-14) or the SuperScript™ IV VILO™ Master Mix (ThermoFisher, Cat. No. 11756050). Mouse *Axin2* and *Ki67* mRNA expression were measured by using TaqMan® Fast Advanced Master Mix (ThermoFisher, 4444963) and the

Mm00443610_m1 *Axin2*, Mm01278617_m1 *Ki67*, Mm01300555_g1 *wnt1*, Mm00470018_m1 *wnt2*, Mm00437336_m1 *wnt3*, Mm01194003_m1 *wnt4*, Mm00437347_m1 *wnt5a*, Mm01183986_m1 *wnt5b*, Mm00437353_m1 *wnt6*, Mm00437356_m1 *wnt7a*, Mm01301717_m1 *wnt7b*, Mm01157914_g1 *wnt8a*, Mm00457102_m1 *wnt9b*, Mm00442104_m1 *wnt10b*, Mm00437327_g1 *wnt11*, Mm00446420_m1 *wnt16*, Mm00507077_m1 *rspo1*, Mm00555790_m1 *rspo2*, Mm01188251_m1 *rspo3*, and Mm00615419_m1 *rspo4* probes (ThermoFisher, 4331182). Values were normalized to expression of constitutive *Actin B* gene using the Mm02619580_g1 probe (ThermoFisher, 4351368).

[0247] Animal studies: Six-week old C57Bl/6J male mice were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and were group-housed. All animal experimentation was in accordance with the criteria of the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences. Protocols for animal experimentation were approved by the Surrozen Institutional Animal Care and Use Committee. Mice were acclimatized a minimum of two days prior to initiating experiments. Mice had unlimited access to purified, laboratory-grade acidified water and were fed *ad libitum* (2018 Teklad global 18% protein rodent diet). Mice were kept on a 12/12-hour light/dark cycle in a 30% to 70% humidity environment and room temperature ranging from 20°C to 26°C.

[0248] In cases where the mice were humanized for human *ASGR* gene expression, each mouse was dosed with 1×10^{11} ssAAV8-CAG-h*ASGR1* genome copies (Vector Biolabs, Malvern, PA) intravenously on day 0. On day 7, mice were injected intraperitoneally (i.p.) with α GFP, Fc-RSPO2-WT, α GFP-RSPO2-RA or α ASGR1-RSPO2-RA. At indicated times after protein dosing, mice were anesthetized with isoflurane and blood was removed by cardiac puncture. A portion of the left liver lobe and duodenum were collected for analysis.

EXAMPLE 1

CHARACTERIZATION OF TISSUE-SPECIFIC WNT SIGNALING ENHANCING MOLECULES

[0249] To create a tissue-specific RSPO-like Wnt signaling enhancer molecule, the asialoglycoprotein receptor (ASGR) was targeted. ASGR is a hetero-oligomer composed of two polypeptides, ASGR1 and ASGR2, that are predominantly expressed on hepatocytes and goes through rapid endocytosis. An ASGR1 antibody (e.g., RO-01) was converted into the scFv format and fused it to the N-terminus of different RSPO2 variants to create α ASGR1-RSPO2-WT, α ASGR1-RSPO2-RA, or α ASGR1-RSPO2-5mut (SEQ ID NOs: 11-16, FIG. 1B, right

panel). In this design, the antibody part of the fusion functions as a “targeting module” guiding the cell/tissue specificity, while the RSPO2 component functions as an “action module” interacting with the E3 ligases (FIG. 1B). To abolish LGR binding, point mutations were introduced into two highly conserved hydrophobic residues within the Fu2 domain of RSPO2 that are reported to be critical for binding to LGR proteins, F105R and F109A, were introduced (FIG. 1B, named α ASGR1-RSPO2-RA). To verify the involvement of Fu1 domain in E3 ligase interaction, additional point mutations in Fu1 domain reported to be critical for this interaction (R65A/R69A/Q70A) were also added (FIG. 1B, α ASGR1-RSPO2-5mut which contains all 5 mutations, F105R/F109A/R65A/R69A/Q70A in both Fu1 and Fu2). As a negative control for the targeting module, a scFv antibody against green fluorescent protein (GFP) was fused to the same human Rspo2 fragments and mutants (α -GFP-Rspo2-WT, α -GFP-Rspo2-RA, and α -GFP-Rspo2-5mut; SEQ ID NOs: 5-10, FIG. 1B; left panel).

[0250] The impact of the Fu1 and Fu2 mutations on LGR and E3 ligase binding were verified using bio-layer interferometry on an Octet system. The binding of wild type (α GFP-RSPO2-WT), or mutants (α GFP-RSPO2-RA or α GFP-RSPO2-5mut) to recombinant LGR5 protein were measured, and the binding of the wild type was observed but not the two Fu2 mutant RSPO variants (FIG. 1C). The effect of the Fu2 mutations are specific to LGR interaction as the binding of α GFP-RSPO2-RA to E3 ligases, ZNRF3 and RNF3, were not affected (FIG. 1D), while the α GFP-RSPO2-5mut containing mutations in the Fu1 domain additionally affected interaction with E3 ligases (FIG. 1D).

[0251] The impact of the Fu1 and Fu2 mutations on the ability of RSPO2 to enhance Wnt signaling was tested in HEK293 and Huh-7 Wnt responsive STF cells. As shown in Fig. 2B, right panels, in the absent of any added Wnt, none of the RSPO2 proteins activated Wnt signaling. In the presence of Wnt3a conditioned media (CM), α GFP-RSPO2-WT enhanced Wnt3a activity in a dose responsive matter, however, mutations in either Fu1 (α GFP-RSPO2-RA) or Fu1+Fu2 (α GFP-RSPO2-5mut) were completely inactive, consistent with the expectation that RSPO2 activity depends on the ability to engage both E3 ligases and LGR proteins.

[0252] Switching the targeting module from anti-GFP to anti-ASGR1 had no apparent effect on the interaction of RSPO2 to E3 ligases or LGR5 proteins. α ASGR1-RSPO2-WT bound to both E3 ligases and LGR5, α ASGR1-RSPO2-RA lost the ability to interact with LGR5, and α ASGR1-RSPO2-5mut lost the ability to interact with both LGR5 and E3 ligases (FIGS. 1C and 1D).

[0253] The ability of these molecules to modulate Wnt signaling was also assessed in both HEK293 STF and Huh-7 STF Wnt responsive reporter cells. In HEK293 STF cells, since they do not express ASGR1 (as verified by semi-quantitative PCR analysis, FIG. 2A), the anti-ASGR1-RSPO2 fusion proteins behaved almost identically to their anti-GFP counterparts (Fig. 2B). In the absence of added Wnt, none of the α ASGR1-RSPO2 proteins activated Wnt signaling (FIG. 2B right panel). In the presence of Wnt3a conditioned media (CM), α ASGR1-RSPO2-WT enhanced Wnt3a activity in a dose responsive matter similar to α GFP-RSPO2-WT, while α ASGR1-RSPO2-RA and α ASGR1-RSPO2-5mut were inactive (FIG. 2B). In contrast, in Huh-7 STF cells, a human hepatoma cell line which expresses ASGR1, the fusion of α ASGR1 scFv significantly rescued the ability of RSPO2-RA mutant to enhance Wnt3a induced signaling (FIG. 2B, lower left panel). The α ASGR1-RSPO2-5mut remained inactive, demonstrating that the activity observed with α ASGR1-RSPO2-RA depends on its ability to engage E3 ligases. Interestingly, α ASGR1 scFv fusion to WT RSPO2, α ASGR1-RSPO2-WT, also showed a significant, ~6-fold left shift in the dose response curve compared to α GFP-RSPO2-WT (FIG. 2B), suggesting that the attachment of the new targeting module, α ASGR1 scFv, may have synergized with LGR to further enhance the WT RSPO2 function.

[0254] In addition to the STF reporter system, Wnt signaling activity was also examined directly by Western blot analysis. As shown in FIG. 2C, while the treatment of Huh-7 cells with 10% Wnt3a CM did not induce a significant change, the addition of α GFP-RSPO2-WT enhanced the Wnt3a response and significantly increased both the phosphorylated LRP6 and DVL2 proteins in addition to increasing the total levels of LRP6 protein. The mutations in Fu2 abolished this enhancement activity as seen in the α GFP-RSPO2-RA treated cells. However, the fusion to α ASGR scFv, α ASGR1-RSPO2-RA, rescued the loss of function phenotype with α GFP-RSPO2-RA, slightly increased the total LRP6 protein as well as significantly increased the phosphorylated levels LRP6 and, to a lesser extent, DVL2 (FIG. 2C).

[0255] To further confirm the cell-type specific activity of the anti-ASGR1 RSPO2-RA fusion protein is dependent on the presence of the targeted receptor, ASGR, we transiently transfected HEK293 cells with a plasmid encoding a full length human *ASGR1* cDNA. Since ASGR1 and ASGR2 form a complex, co-transfection of both of the *ASGR* cDNAs was also performed in addition to transfection of an unrelated receptor, human transferrin receptor 1 (TFR1, encoded by *TFRC* gene) as a negative control. Similar to the untransfected parental HEK293 cells, only the RSPO2-WT fusion proteins with either α GFP- or α ASGR1- enhanced Wnt signaling in a Wnt dependent manner in cells transfected with *TFRC* (compare FIG. 2B

top panels to FIG. 3A, top panels). In contrast, in cells transfected with either *ASGR1* alone or co-transfected with both *ASGR1* and *ASGR2*, the fusion of α ASGR1 scFv partially rescued the loss of function RSPO2-RA mutant's ability to enhance Wnt signaling. The fusion of α ASGR1 also left shifted the dose response of RSPO2-WT protein, similar to what was observed in Huh-7 cells (compare FIG. 2B, lower panels, to FIG. 3A, middle and lower panels). The activities of the α ASGR1-RSPO fusion molecules were also completely dependent on the presence of Wnt ligands (FIG. 3A right panels).

[0256] The ASGR1-dependent activity was also confirmed in another ASGR1 negative cell line, A431, which is derived from human epidermoid carcinoma and doesn't express *ASGR* genes (FIG. 2A). Similar to HEK293 transfection studies, α ASGR1-RSPO2-RA only rescued RSPO2-RA activity in A431 cells expression ASGR1 but not in A431 cells expressing the negative control receptor, TFR1 (FIG. 3B). Furthermore, α ASGR1 scFv also left shifted RSPO2-WT dose response curve and all RSPO derivatives' activities were completely dependent on the presence of Wnt ligand (FIG. 3B, right panels). All the results together from FIG. 2 and 3 demonstrated that RSPO-mediated Wnt signal enhancing activity can be replaced by targeting to a different cell surface receptor, ASGR1, in place of LGR. The resulting RSPO mimetic molecule resembles WT RSPO in Wnt dependency and its action through E3 ligases, but differs in that its Wnt signaling enhancement is cell-type specific.

[0257] To further validate the mechanism of action of the RSPO derivative molecules, Frizzled (FZD) receptor levels on the cell surface were examined. To sensitize the system, ZNRF3 was over-expressed by transient transfection before treatment. A pan-Frizzled antibody 18R5 (cloned based on Patent EP2331136A4) was used to stain the cells, and found α GFP-RSPO2-WT clearly increased the signal (as expected) as compared to the untreated cells, and such a shift was not observed with α GFP-RSPO2-RA or α ASGR1-RSPO2-RA treatment (FIG. 3C, top). This is consistent with the lack of activity of these two RSPO-RA constructs in HEK293 cells. On the other hand, when the cells were co-transfected with both *ZNRF3* and *ASGR1*, α ASGR1-RSPO2-RA increased pan-FZD staining just like α GFP-RSPO2-WT, leaving α GFP-RSPO2-RA being similar to the untreated cells (FIG. 3C, bottom). This is consistent with the removal of the ZNRF3/RNF43 E3 ligases by RSPO or RSPO mimetics, which leads to the stabilization of Wnt receptors.

[0258] To validate the ability of the tissue-specific Wnt signal enhancing molecules to enhance Wnt signaling in additional cell-types, a second novel, bispecific construct targeting a different cell surface receptor, the transferrin receptor 1 (TFR1), was tested. TFR1 is encoded

by the *TFR1* gene, and is broadly expressed in many cell types. It has been reported to undergo continuous endocytosis. Fusion proteins containing an scFv binder to human TFR1, RSPO2-WT, RSPO2-RA, or RSPO2-5mut (SEQID NOS: 17-22) were constructed and characterized. The had a design similar to Fig. 1B, except that the anti-GFP or anti-ASGR1 component was replaced by an anti-TFR1 scFv. Similar to the anti-GFP or anti-ASGR1 fusion proteins, the α TFR1-RSPO2-RA protein lost the ability to interact with LGR5, and the α TFR1-RSPO2-5mut lost the ability to interact with both LGR5 and E3 ligases (FIGS. 4A-B). When tested in the HEK293 STF reporter assay in the presence of Wnt sources, the TFR1 targeted RSPO2-RA (α TFR1-RSPO2-RA) stimulated Wnt signaling and exhibited ~20-fold greater potency compared to wild-type RSPO (α GFP-RSPO2-WT). (FIG. 4C). The anti-TFR1 RSPO2-WT fusion, α TFR1-RSPO2-WT, further improved the EC₅₀ by another ~20-fold, for a nearly 400-fold improved potency compared to α GFP-RSPO2-WT. Similar results were obtained in the Huh-7 STF cells, consistent with the expression of the targeted receptor in both cell lines (FIG. 2A). Consistent with the mechanism of RSPO, no Wnt signaling was observed in the absence of Wnt ligand with anti-TFR1 RSPO mimetic molecules (FIG. 4C, right panels). The more potent activity observed with anti-TFR1 RSPO2 fusion proteins indicates that the particular combination of receptor and binder may play a role in the activity of tissue-specific Wnt signal enhancing molecules.

[0259] As was seen with α GFP-RSPO2-WT, α TFR1-RSPO2-RA, but not α ASGR1-RSPO2-RA, stimulated the phosphorylation of LRP6 and DVL2 in the presence of Wnt stimulation in HEK293 STF cells and increased total LRP6 protein levels (FIG. 4D). The effects of the RSPO mimetic molecule on FZD receptor levels on the cell surface was also examined by flow cytometry analysis. As shown in FIG. 4E, treatment of HEK293 cells with α GFP-RSPO2-WT, α TFR1-RSPO2-RA, but not α GFP-RSPO2-RA increased the FZD receptor levels on these cells measured by the pan-FZD antibody.

EXAMPLE 2

IN VIVO LIVER EFFECT USING A PROTOTYPE LIVER-SPECIFIC WNT SIGNALING ENHANCING MOLECULE

[0260] To demonstrate that α ASGR1-RSPO2-RA can activate the Wnt-signaling pathway in a tissue specific manner in vivo, mice were treated with α ASGR1-RSPO2-RA and control proteins. Since the molecular weight of scFv-RSPO2 fusion proteins are in the range of ~40kDa, to increase their plasma half-life, we switched the scFv of the binders to the IgG

format where the RSPO2 is fused to the N-terminus of the IgG heavy chain. α ASGR1-RSPO2-RA-IgG (SEQ ID NOs: 29-32) had similar potency as α GFP-RSPO2-RA-IgG (SEQ ID NOs: 25-28) in HEK293 cells, but was much more potent and efficacious than the latter in Huh-7 cells (FIG. 5A). In fact, the activity α ASGR1-RSPO2-RA-IgG at 100 pM is comparable to that of α GFP-RSPO2-RA-IgG at 10 nM (FIG. 5A bottom left), suggesting the strong targeting effect is preserved in the IgG format.

[0261] Expression of human *ASGR1* in mouse liver was induced by IV injection of ssAAV8-CAG-hASGR1, using 1×10^{11} genomic particles per mouse, a dose was shown to achieve transgene expression levels equivalent to the endogenous liver *Asgr1* mRNA, 7 days prior to treatment with recombinant proteins (data not shown).

[0262] In a first study (FIG. 5B), mice were injected i.p. with an equimolar dose of α GFP-IgG (SEQ ID NOs: 25-26 and 33-34) (1 mg/kg), Fc-RSPO2-WT (SEQ ID NOs: 23-24) (0.46 mg/kg), α GFP-RSPO2-RA-IgG (SEQ ID NOs: 25-28) (1 mg/kg), or α ASGR1-RSPO2-RA-IgG (SEQ ID NOs: 29-32) (1 mg/kg) recombinant proteins (with approximately matching molarity, n=8 mice per group). Liver and small intestine samples were collected 8 hrs later for expression analysis. Treatment with Fc-RSPO2-WT and α ASGR1-RSPO2-RA-IgG induced liver *Axin2* expression significantly when compared to liver *Axin2* expression in mice treated with either the α GFP or α GFP-RSPO2-RA-IgG negative controls (FIG. 5C). In contrast, treatment with Fc-RSPO2-WT, but not with α ASGR1-RSPO2-RA-IgG increased small intestine *Axin2* expression significantly (FIG. 5D). These results suggest that α ASGR1-RSPO2-RA-IgG can activate the Wnt pathway in a tissue-specific manner *in vivo*.

[0263]

[0264] In a second study (FIG. 6A), mice were injected i.p. with α GFP-IgG (1 mg/kg), α GFP-RSPO2-RA-IgG (1 mg/kg), or α ASGR1-RSPO2-RA-IgG (1 mg/kg) recombinant proteins (n=10 mice per group). Liver and small intestine samples were collected 48 hrs later for expression analysis and histoimmunochemistry. Treatment with α ASGR1-RSPO2-RA-IgG induced expression of the cellular proliferation marker gene *Mki67* (FIG. 6B), and increased the number of Ki-67-positive cells (FIGS. 6C-D) significantly in liver when compared to mice treated with either the α GFP-IgG or α GFP-RSPO2-RA-IgG negative controls. In contrast, this induction of *Mki67* expression by α ASGR1-RSPO2-RA-IgG was not observed in small intestine (FIG. 5E). These results suggest that α ASGR1-RSPO2-RA-IgG can stimulate proliferation in liver parenchymal cells in a tissue specific manner.

EXAMPLE 3

GENERATION OF ANTIBODIES

[0265] Antibodies directed against ASGR, ZNRF3 and RNF43 polypeptide sequences were identified. For the production of recombinant proteins for antibody screening and immunization, extracellular domains (ECDs) of the following proteins were cloned into a pcDNA eukaryotic expression vector with a His/Avi tag: human ASGR1 (hASGR1, NCBI reference sequence NP_001662.1, residues 62-291; SEQ ID NO:35-36 (polynucleotide and polypeptide, respectively)), human ASGR2 (hASGR2, NCBI reference sequence NP_550436.1, residues 66-292; SEQ ID NO:37-38 (polynucleotide and polypeptide, respectively)), cynomolgus ASGR1 (cynoASGR1, sequence ID XP_005582755.1, residues 62-291; SEQ ID NO:39-40 (polynucleotide and polypeptide, respectively)), cynomolgus ASGR2 (cynoASGR2, sequence cloned from cynomolgus liver cDNA sample from Fisher/Zyagen Labs; SEQ ID NO:41-42 (polynucleotide and polypeptide, respectively)), human RNF43 (hRNF43, NCBI reference sequence XP_011523257.1, residues 44-198; SEQ ID NO:43-44 (polynucleotide and polypeptide, respectively)), ZNRF3 (hZNRF3; NCBI reference sequence NP_001193927.1, residues 56-219; SEQ ID NO:45-46 (polynucleotide and polypeptide, respectively)). Constructs were expressed Expi293F cells (Thermo Fisher Scientific), purified by Ni-NTA resin followed by size exclusion chromatography. For phage display, the proteins were biotinylated according to published methods (Janda et al., Nature; 545: 234).

[0266] Biotinylated antigens were immobilized for panning against phage display libraries, and positive clones were sequenced. Further analysis was conducted, including expressing in Expi293F cells and characterization for antigen binding.

[0267] Non-biotinylated antigen was also used to immunize mice to generate hybridomas. Hybridoma lines were screened by ELISA against immunogen with a control protein containing the same purification tag as controls, and flow cytometry analysis (ASGR-expressing Huh-7 as the test line and ASGR non-expressing HEK293 as the control). Selected hybridoma lines were sequenced, and recombinant Fabs or IgGs were generated consequently for further binding characterization.

[0268] Binding characterization of recombinant Fabs or IgG's was carried out using Bio-Layer Interferometry (BLI) using the Octet Red 96 platform (PALL ForteBio, Fremont, CA) with streptavidin (SA) coated biosensors (PALL ForteBio.). Biotinylated-antigen was diluted to 50 nM for immobilization onto the sensors. Following immobilization, sensors were dipped into samples containing test molecules at seven concentrations. Values for K_D were determined

by fitting the resulting data with a 1:1 binding model. Table 2C provides the binding data for select clones.

[0269] FIG. 7 provides data showing binding of illustrative antibodies identified to hASGR1 (FIG. 7A and 7C) or hASGR2 (FIG. 7B).

EXAMPLE 4

IN VIVO DOSE-TITRATION AND TISSUE-SPECIFICITY OF ANTI-ASGR1-RSPO2-RA IN NAÏVE HEALTHY MICE

[0270] The activities of the ASGR1-targeted molecule and control molecules in IgG format were further examined in healthy naïve mice. The α ASGR1 antibody (e.g., RO-01) used in these studies had similar affinity to both the human and murine ASGR1 receptors (Fig. 9A).

[0271] In this study, six-week old C57Bl/6J male mice were injected intraperitoneally (i.p.) with α - β -Gal-IgG, Fc-RSPO2-WT, α GFP-RSPO2-RA or α ASGR1-RSPO2-RA at indicated doses (n=8 per group). 48 hours after protein dosing, mice were anesthetized with isoflurane and blood was removed by cardiac puncture. Portions of the left liver lobe and duodenum were collected and either snap-frozen for qPCR analysis or fixed in formalin for 24h, then transferred to 70% EtOH for immunohistochemistry analysis.

[0272] A dose response was performed for α ASGR1-RSPO2-RA-IgG (SEQ ID NOs: 29-32) as compared to α GFP-RSPO2-RA-IgG (SEQ ID NOs: 25-28) and other controls to examine induction of Wnt target gene *Axin2*. Mice received intraperitoneal (i.p.) injections of tested proteins at a range from 0.1 to 30 mg/kg. Liver and small intestine samples were collected 48 hours later for gene expression analyses. Fc-RSPO2-WT (SEQ ID NOs: 23-24) increased *Axin2* expression at 1 and 10 mg/kg treatment in both liver and small intestine (Fig. 9B). In contrast α ASGR1-RSPO2-RA-IgG at 10 and 30 mg/kg induced *Axin2* expression only in liver, but not in small intestine. Importantly, this specificity is dependent on α ASGR1 targeting module, because the untargeted molecule α GFP-RSPO2-RA-IgG showed no effect *in vivo* on *Axin2* expression in either tissue up to 30 mg/kg treatment (Fig. 9B). No effect was observed with control antibody anti- β -galactosidase (α - β -Gal-IgG, SEQ ID NOs: 155-158), at 0.01 and 10 mg/kg.

[0273] Similar tissue specificity of α ASGR1-RSPO2-RA-IgG and dependency on the targeting module was also observed in expression of a proliferation marker *Ki67* gene (Fig. 9C). To examine whether or not proliferation occurred in hepatocytes, we co-stained liver samples with antibodies specific for Ki67 protein and one of the mature hepatocyte markers

HNF4 α . Livers treated with α ASGR1-RSPO2-RA-IgG and Fc-RSPO2-WT appeared to have increased numbers of Ki67 positive nuclei that co-localized with HNF4 α , while livers treated with α GFP-RSPO2-RA-IgG or α - β -Gal-IgG appeared to have much less Ki67 stain (Fig. 9D). Taken together these results suggested that α ASGR1-RSPO2-RA-IgG can activate Wnt pathway in a liver-specific manner *in vivo*, and that hepatocytes are the primary cell population responsive to this stimulation.

EXAMPLE 5

EFFECT OF TISSUE-TARGETED RSPO MIMETICS ON LIVER FUNCTION IN A CHRONIC THIOACETAMIDE-INDUCED MOUSE MODEL OF LIVER FIBROSIS

[0274] Six-week old C57Bl/6J male mice were treated with thioacetamide (TAA). In Study #1 (*Wnt* and *Rspo* gene expression profiling), TAA was added to drinking water at a concentration of 200 mg/L for twenty-seven weeks to induce liver fibrosis. In addition, during the last four weeks of TAA conditioning, mice were administered with TAA i.p. 3 times weekly. In study #2 (liver and small intestine *Axin2* and *Ki67* expression at days 3 and 7), TAA was added to drinking water at a concentration of 200 mg/L for twenty weeks to induce liver fibrosis. In addition, during the last six weeks of TAA conditioning, mice were administered with TAA i.p. 3 times weekly. In study #3 (INR analysis at days 3, 7 and 14), TAA was added to drinking water for eighteen weeks. Mice were also administered with 200 mg/kg TAA i.p. 3 times weekly during the last nine weeks of TAA exposure. TAA treatment was discontinued 2 days prior to dosing with recombinant protein, and mice returned to purified, laboratory-grade acidified drinking water. Mice were injected intraperitoneally (i.p.) with recombinant α - β -gal-IgG (10 mpk) or Fc-RSPO2-WT (10 mpk) twice weekly, or α ASGR1-RSPO2-RA-IgG (10 mpk) daily. At times indicated, INR was measured using the Roche CoaguChek – XS Plus. At 3, 7 or 14 days after beginning dosing, mice were anesthetized with isoflurane and blood was removed by cardiac puncture. A portion of the left liver lobe and duodenum were collected for analysis. Formalin-fixed and paraffin-embedded liver samples were sectioned and stained with the anti-Ki-67 rabbit antibodies (Abcam, ab15580). The number of Ki-67 positive nuclei per randomly chosen field (100x magnification using 10x objective) were counted using Image J.

[0275] The activity and efficacy of α ASGR1-RSPO2-RA-IgG was examined in the chronic thioacetamide (TAA) model, in which extensive liver fibrosis was observed and liver function was impaired. In this model, Wnt signaling pathway components including genes encoding

many Wnt ligands were upregulated (Fig. 10A). In contrast, expression of the four R-spondins remained unchanged, or even decreased in the case of *Rspo2*. *Rspo4* was almost nondetectable in the mouse livers (Fig. 10A). Therefore administration of liver-specific RSPO mimetics may be beneficial (Fig. 10A).

[0276] The experimental design outlining the duration of TAA pre-treatment and subsequent protein treatment (α ASGR1-RSPO2-RA-IgG and control proteins SEQ ID NOs: 23-24, 29-32, 155-156, and 159-160) is outlined in Fig. 10B. Two studies of similar design were conducted. In one study, mice were terminated at 0, 3, and 7 days following initiation of protein treatment. In a second study, mice were terminated at 0 and 14 days after initiation of protein treatment (Fig. 10B). Liver and small intestine samples were collected and assessed for changes in gene expression. As expected, α ASGR1-RSPO2-RA-IgG led to a liver-specific increase of *Axin2* expression at days 3 and 7, while Fc-RSPO-WT induced *Axin2* in both liver and small intestine (Fig. 10C). No change was observed with the α - β -Gal-IgG control treatment. α ASGR1-RSPO2-RA-IgG also increased *Ki67* expression in a liver-specific manner (Fig. 10C).

[0277] To monitor liver function, blood samples were taken at indicated times during treatment and used to measure International Normalized Ratio (INR) of prothrombin time. The normal mice had an INR of approximately 0.9. TAA treatment increased INR to 1.1 due to serious liver damage (Fig. 10D). Upon TAA removal, mice are known to exhibit some natural resolution of liver damage, consistent with the INR drop observed in untreated animals from 1.1 at day 0 to <1.0 at day 14. However, α ASGR1-RSPO2-RA-IgG accelerated INR recovery, as 100% of α ASGR1-RSPO2-RA-IgG treated mice had an INR of 0.9 by day 3. Fc-RSPO2-WT treated mice had reduced INR compared to the α - β -Gal treated mice at day 7, and reached the same effect as α ASGR1-RSPO2-RA-IgG at day 14. Therefore, the liver-specific α ASGR1-RSPO2-RA-IgG molecule can improve liver synthetic function in chronic liver disease model.

EXAMPLE 6

EFFECT OF TISSUE-TARGETED RSPO MIMETICS ON LIVER FUNCTION IN A CHRONIC CCL₄-INDUCED MOUSE MODEL OF LIVER FIBROSIS

[0278] The activity and efficacy of α ASGR1-RSPO2-RA-IgG was examined in a second mouse model of liver fibrosis generated with CCl₄ plus allyl alcohol. Fifty-four 8-9 week-old C57BL/6 males (Jackson Laboratories) were intermittently treated with CCl₄ (0.5 mL/kg at Day 1,4,7,10) plus allyl alcohol (0.0125 mL/kg at Day 2,5,8) for 10 days, followed by 8 weeks of CCl₄ treatment (0.5 mL/kg, twice/week). The treatment protocol is illustrated in FIG 12.

Following CCl₄ treatment, mice were dosed with proteins for 2 weeks with discontinuous CCl₄ treatment. Treatment groups are as follows: 10 mg/kg α ASGR1-RSPO2-RA-IgG2, n=8 (daily dosing); 10 mg/kg α GFP-RSPO2-RA-IgG, n=8 (daily dosing); 4.6 mg/kg Fc-RSPO2-WT, n=7 (twice/week dosing); 10 mg/kg α - β -Gal-IgG, n=8 (twice/week dosing); no protein control, n=8. Additional control groups included no CCl₄ treatment (olive oil carrier (0.5 mL/kg), n=8; naïve control, n=7. Blood was drawn from mice on day 0, 3, 7 (first day of protein dosing denotes as Day 0) for INR (international normalised ratio) testing. All mice were terminated at Day 14.

[0279] Upon sacrifice, total body and liver weights were measured, blood, liver and small intestinal tissues were collected and preserved for testing. Liver weights showed an upward trend in groups treated with RSPO2 positive control as well as those treated with the RSPO2 mimetic, α ASGR1-RSPO2-RA-IgG2. When liver/body weight ratios were measured, only RSPO2 treated mice had an increase that was statistically significant.

[0280] As a measure of tissue repair and fibrosis, procollagen type III N-terminal peptide (P3NP) was measured in the mouse blood on day 0, 7, and 14 of protein treatment. A significant increase was observed in all groups treated with CCl₄ as compared with olive oil treated and naïve controls consistent with marked liver fibrosis. P3NP levels remained high in animals treated with the RSPO2 mimetic, α ASGR1-RSPO2-RA-IgG2, indicating ongoing tissue repair and extracellular matrix turnover, as compared with animals treated with α GFP-RSPO2-RA-IgG (lacking tissue targeting to the liver), where P3NP dropped back to the levels in naïve mice (data not shown).

[0281] After two weeks of protein treatment, the prothrombin time (PT) as a measure of blood clotting time indicated that no increase in time was seen, and the time actually significantly decreased in animal treated with the RSPO2 protein (data not shown).

[0282] At timepoints after one and two weeks of protein treatment, standard liver panel measurements were done in the serum. The mouse serum was collected from tail bleed at Day 7 and terminal bleed at Day 14. The sera were sent to IDEXX Laboratories (Fremont, CA) for liver panel serum chemistry measurement. Each group contained 6-8 mice and the data are presented in Table 4 and 5 as mean $\pm$ SEM.

Table 4. Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) levels measured in blood in animals one and two weeks after protein treatments.

Treatment group	ALT	AST	ALP

	U/L +/- SEM		U/L +/- SEM		U/L +/- SEM	
	wk 1	wk 2	wk 1	wk 2	wk 1	wk 2
Naïve	24.0+/- 1.9	32.0+/- 2.6	44.6+/- 2.4	41.5+/- 4.1	68.6+/- 4.1	55.5+/- 3.9
Oil control	22.8+/- 0.9	30.8+/- 4.2	43.0+/- 1.7	53.8+/- 9.7	78.1+/- 4.7	65.6+/- 3.1
No protein in CCl ₄ mice	33.2+/- 1.0	36.4+/- 2.5	53.6+/- 3.9	54.8+/- 4.0	108.6+/- 3.5	87.8+/- 4.1
α - β -Gal-IgG in CCl ₄ mice	28.7 +/- 1.7	33.9 +/- 3.3	48.3 +/- 3.5	68.9+/- 17.5	113.3+/- 7.1	102.9+/- 4.3
Fc-RSPO2-WT in CCl ₄ mice	51.7+/- 14.4	42.1 +/- 5.1	83.0+/- 14.0	74.4 +/- 9.8	83.0 +/- 8.5	28.4 +/- 5.2
α -GFP-RSPO2-RA-IgG in CCl ₄ mice	27.9 +/- 1.2	36.4 +/- 5.7	52.9 +/- 4.6	69.0+/- 13.3	117.9+/- 9.4	70.3 +/- 2.5
α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	59.4+/- 27.7	57.9+/- 18.7	85.6+/- 33.0	98.1+/- 20.2	*411.4+/- 63.9	**164.9+/- 24.0

* Statistically different from α - β -Gal-IgG and α GFP-RSPO2-RA-IgG treated groups, $p < 0.0001$; ** Statistically different from α - β -Gal-IgG ($p = 0.0012$) and α GFP-RSPO2-RA-IgG ($p < 0.0001$) treated groups; One-way ANOVA.

As shown in Table 4, ALT and AST values were not statistically different with any of the protein treatments and controls. ALP, however, was statically higher at both one-week and two-week timepoints, consistent with the upregulation of the alkaline phosphatase protein levels due to the elimination of ASGR receptor as described in an ASGR1 KO mouse model (see, e.g., *Cell Host Microbe*. 2018 Oct 10;24(4):500-513).

Table 5. Albumin, and billirubin levels measured in the blood of animals one and two weeks after protein treatments.

Treatment group	Albumin		Billirubin	
	g/dL +/- SEM		mg/dL +/- SEM	
	wk 1	wk 2	wk 1	wk 2
Naïve	3.1+/-0.2	2.9+/-0.0	0.2+/-0.0	0.1+/-0.0
Oil control	3.2+/-0.1	2.8+/-0.0	0.2+/-0.0	0.2+/-0.0
no protein in CCl ₄ mice	3.5+/-0.1	2.8+/-0.0	0.2+/-0.0	0.2+/-0.0
α - β -Gal-IgG in CCl ₄ mice	3.2+/-0.2	2.8+/-0.0	0.2+/-0.0	0.2+/-0.0
Fc-RSPO2-WT in CCl ₄ mice	2.6+/-0.1	*1.6+/-0.1	0.2+/-0.0	0.1+/-0.0
α -GFP-RSPO2-RA-IgG in CCl ₄ mice	3.0+/-0.1	2.5+/-0.0	0.2+/-0.0	0.2+/-0.0

α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	2.5+/-0.1	*2.2+/-0.1	0.2+/-0.0	0.2+/-0.0

* Statistically different from α - β -Gal-IgG treated groups, p<0.0001 for Fc-RSPO2-WT and p=0.0009 for α ASGR1-RSPO2-RA-IgG2; ** Statistically different from α - β -Gal-IgG (p<0.0001) and α -GFP-RSPO2_RA-IgG (p<0.0009) treated groups; One-way ANOVA.

[0283] While there was no significant effect on albumin, bilirubin, levels one week after treatment, significantly less albumin in blood was observed after two weeks of protein treatment in both the RSPO2 postive control and RSPO mimetic (α ASGR1-RSPO2-RA-IgG2) treatment groups as compared with α - β -Gal-IgG and α -GFP-RSPO2_RA-IgG protein controls. This result suggests an expected temporary shut down in function of periportal hepatocytes due to increased pericentral hepatocyte expansion, induced by increased Wnt signaling.

[0284] Semi-quantitative PCR was used to measure changes in gene expression in liver and small intestine with protein treatments (Table 6).

Table 6. Changes in expression of Wnt-inducible genes and proliferation marker genes in liver and small intestine as measured by qPCR

Treatment group	Liver				Small intestine		
	<i>Axin2</i>	<i>Hal</i>	<i>Ki67</i>	<i>Cyclin D1</i>	<i>Axin2</i>	<i>Ki67</i>	<i>Cyclin D1</i>
Naïve	1.0+/- 0.1	1.0+/- 0.00	1.0+/- 0.1	1.0+/- 0.1	1.0+/- 0.1	1.0+/- 0.1	1.0+/- 0.2
Oil control	0.7+/- 0.1	0.8+/- 0.0	0.6+/- 0.1	1.1+/- 0.1	0.7+/- 0.0	0.7+/- 0.1	0.7+/- 0.1
no protein in CCl ₄ mice	1.0+/- 0.1	1.0+/- 0.1	2.3+/- 0.4	2.0+/- 0.3	0.8+/- 0.1	0.9+/- 0.1	0.6+/- 0.1
α - β Gal-IgG in CCl ₄ mice	2.2+/- 0.2	1.0+/- 0.1	2.8+/- 0.4	2.8+/- 0.4	1.0+/- 0.1	0.6+/- 0.1	1.4+/- 0.3
Fc-RSPO2-WT in CCl ₄ mice	3.3+/- 0.8	0.4+/- 0.2	13.8+/- 3.3	14.1+/- 4.4	1.8+/- 0.7	0.5+/- 0.2	0.6+/- 0.2
α GFP-RSPO2-RA-IgG in CCl ₄ mice	1.8+/- 0.2	1.0+/- 0.1	7.2+/- 0.9	3.6+/- 0.5	0.6+/- 0.1	0.7+/- 0.0	0.4+/- 0.1
α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	4.2+/- 1.0	0.4+/- 0.1	11.4+/- 3.2	6.3+/- 1.8	0.6+/- 0.1	0.6+/- 0.0	0.8+/- 0.2

* Statistically different changes shown in bold. *Axin2*: α ASGR1-RSPO2-RA-IgG2 vs α -GFP-RSPO2-RA-IgG, p=0.0092. *Hal*: Fc-RSPO2-WT vs. α - β Gal-IgG, p=0.0259; α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p=0.0042; α ASGR1-RSPO2-RA-IgG2 vs α -GFP-RSPO2-RA-IgG, p=0.0018. *Ki67*: Fc-RSPO2-WT vs. α - β Gal-IgG, p=0.0010; α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p=0.0135. *Cyclin D1*: Fc-RSPO2-WT vs. α - β Gal-IgG, p=0.0004. Calculated by one-way ANOVA.

[0285] Treatment of mice with Fc-RSPO2-WT positive control protein or RPSO mimetic protein, α ASGR1-RSPO2-RA-IgG2, both lead to increased expression of the Wnt-inducible *Axin2* gene and decreased expression of the Wnt-repressable *Hal* gene in liver. Measured changes that were statistically significant are shown in bold in Table 6. There was no significant change in *Axin2* expression in small intestine. These data indicate that Wnt signaling was induced in a tissue-specific manner.

[0286] Treatment with Fc-RPSO2-WT and α ASGR1-RSPO2-RA-IgG2 also revealed increases in *Ki67* and *Cyclin D1* proliferation markers in the liver but not in small intestine. Changes that reached statistical significance are shown in bold. No significant changes were seen in small intestine with any treatment (Table 6). These data show that proliferation was induced in a tissue-specific manner

[0287] Additional qPCR analysis was done to measure changes in specific liver cell types, including hepatocytes, cholangiocytes, immature hepatocytes, and oval cells (Table 7).

Table 7. Changes in expression of genes used as markers for liver cell types with protein treatment as measured by qPCR

Treatment group	hepatocytes	Cholangiocytes	Immature hepatocytes	Cholangiocytes/Oval cells
	<i>CK8</i>	<i>CK19</i>	<i>Afp</i>	<i>Sox9</i>
Naïve	1.0+/-0.1	1.0+/-0.1	1.0+/-0.1	1.0+/-0.1
Oil control	0.8+/-0.0	0.9+/-0.1	1.1+/-0.1	0.8+/-0.1
no protein in CCl ₄ mice	0.9+/-0.1	1.4+/-0.1	1.3+/-0.2	1.2+/-0.1
α - β Gal-IgG in CCl ₄ mice	0.7+/-0.1	1.0+/-0.1	1.3+/-0.1	1.5+/-0.1
Fc-RSPO2-WT in CCl ₄ mice	*1.4+/-0.3	0.7+/-0.1	*3.5+/-0.3	1.3+/-0.1
α GFP-RSPO2-RA-IgG in CCl ₄ mice	0.6+/-0.0	1.0+/-0.1	1.6+/-0.1	1.2+/-0.1
α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	*1.8+/-0.2	1.5+/-0.2	*3.7+/-0.7	1.0+/-0.1

* Statistically different changes shown in bold. CK8: α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p=0.0001; α ASGR1-RSPO2-RA-IgG2 vs α -GFP-RSPO2-RA-IgG, p<0.0001. Afp: Fc-RSPO2-WT vs. α - β Gal-IgG, p=0.0002; α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p<0.0001; α ASGR1-RSPO2-RA-IgG2 vs α -GFP-RSPO2-RA-IgG, p=0.0001. Calculated by one-way ANOVA.

[0288] Assessment of statistically significant changes in the hepatocyte marker, CK8 but not cholangiocyte marker, CK19 indicates that proliferative response in the liver is confined to hepatocytes. Moreover, a statistically significant increase in Afp reveals a surge of immature hepatocytes (Table 7). There was no significant change in oval cells.

Table 8. Changes in expression of genes related to function of hepatocytes and periportal hepatocytes with protein treatment as measured by semi-quantitative PCR

Treatment group	Hepatocyte function	Pericentral hepatocyte function	Pericentral hepatocyte function	Periportal hepatocyte function
	<i>Factor X</i>	<i>Cyp1a2</i>	<i>Cyp2e1</i>	<i>Cyp2f2</i>
Naïve	1.0+/-0.1	1.0+/-0.1	1.0+/-0.1	1.0+/-0.2
Oil control	0.9+/-0.1	0.9+/-0.1	0.9+/-1.2	0.8+/-0.1
no protein in CCl ₄ mice	1.1+/-0.1	0.6+/-0.0	1.0+/-0.1	1.2+/-0.1
α - β Gal-IgG in CCl ₄ mice	1.2+/-0.1	0.8+/-0.1	1.0+/-0.1	0.8+/-0.1
Fc-RSPO2-WT in CCl ₄ mice	*1.9+/-0.3	0.7+/-0.3	1.2+/-0.2	*0.1+/-0.0
α GFP-RSPO2-RA-IgG in CCl ₄ mice	1.0+/-0.2	0.5+/-0.1	0.8+/-0.1	0.8+/-0.0
α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	1.2+/-0.1	*2.0+/-0.4	*2.7+/-0.5	*0.1+/-0.0

*Statistically different changes shown in bold. Factor X: Fc-RSPO2-WT vs. α - β -Gal-IgG, p=0.0463. Cyp1a2: α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p=0.0044; α ASGR1-RSPO2-RA-IgG2 vs α GFP-RSPO2-RA-IgG, p=0.0001. Cyp2e1: α ASGR1-RSPO2-RA-IgG2 vs α - β -Gal-IgG, p<0.0001; α ASGR1-RSPO2-RA-IgG2 vs α GFP-RSPO2-RA-IgG, p<0.0001. Cyp2f2: Fc RSPO2-WT vs α - β Gal-IgG, p<0.0001; α ASGR1-RSPO2-RA-IgG2 vs α - β Gal-IgG, p<0.0001; α ASGR1-RSPO2-RA-IgG2 vs α GFP-RSPO2-RA-IgG, p<0.0001. Calculated by one-way ANOVA.

[0289] Wnt signaling controls the expression of two CypP450 enzymes, Cyp2e1 and Cyp1a2 predominantly in pericentral hepatocytes (ref). Treatment of mice with the RSPO mimetic significantly increased the expression of the genes for these two enzymes (Table xx). In addition, significantly lower Cyp2f2 indicates a temporary reduction in periportal hepatocyte function due to temporary expansion of pericentral zone.

[0290] After two weeks of protein treatment, mouse livers were stained with Sirius red to measure the levels of the Sirius red staining collagen content in all the mice (FIG. 13 and Table 9). Mice were anesthetized by isoflurane inhalation, cardiac bleed and followed by cervical dislocation. The livers were freshly harvested and immediately immersed into 10% neutral buffered formalin for

overnight incubation. Next day, the livers were transferred to 70% ethanol and prepared for paraffin embedding. The liver tissues were cut into 5 μ m thickness, de-wax and hydrated by alcohol gradient. The slides were stained with Picro-sirius red solution (Sigma- Aldrich) and wash with acidified water. Dehydrate in three changes of 100% ethanol, clear in xylene, air dry and mount with cover slip. The Sirius red stained area was quantitated by Image J (NIH) and normalized with liver from anti- β gal control treated CCl₄ mice (set as 100%). Each group contained 7-8 mice and the data are presented as mean $\pm$ SD.

Table 9. Quantification of Sirius Red staining of liver tissue normalized to anti- β Gal treated CCl₄ mice

Treatment group	Percent Sirius Red (relative to β Gal)
no protein in CCl ₄ mice	93.0 $\pm$ 4.8
α - β -Gal-IgG in CCl ₄ mice	100 $\pm$ 5.4
Fc-RSPO2-WT in CCl ₄ mice	*60.0$\pm$2.9
α GFP-RSPO2-RA-IgG in CCl ₄ mice	87.0 $\pm$ 7.1
α ASGR1-RSPO2-RA-IgG2 in CCl ₄ mice	*66.3$\pm$3.2

*Statistically different changes shown in bold. Fc-RSPO2-WT vs. α - β -Gal-IgG, $p < 0.0001$; Fc-RSPO2-WT vs α GFP-RSPO2-RA-IgG, $p = 0.0059$; α -ASGR1-RSPO2-RA-IgG2 vs α - β -Gal-IgG, $p = 0.0003$; α -ASGR1-RSPO2-RA-IgG2 vs α GFP-RSPO2-RA-IgG, $p = 0.0410$; Calculated by one-way ANOVA.

[0291] After treatment, Sirius red staining was used to quantify the amount of liver fibrosis in all mice in this study. For this method, the mouse was anesthetized by isoflurane inhalation, cardiac bleed and followed by cervical dislocation. The livers were freshly harvested and immediately immersed into 10% neutral buffered formalin for overnight incubation. Next day, the livers were transferred to 70% ethanol and prepared for paraffin embedding. The liver tissues were cut into 5 μ m thickness, de-wax and hydrated by alcohol gradient. The slides were stained with Picro-sirius red solution (Sigma- Aldrich) and wash with acidified water. Dehydrate in three changes of 100% ethanol, clear in xylene, air dry and mount with cover slip. The Sirius red stained area was quantitated by Image J (NIH) and normalized with liver from α - β -Gal-IgG control treated CCl₄ mice (set as 100%). Each group contained 7-8 mice and the data are presented as mean $\pm$ SD.

[0292] After two weeks of treatment with Fc-RSPO2-WT or RPSO mimetic, α ASGR1-RSPO2-RA-IgG2, CCl₄-treated mice had a ~40% reduction in Sirius Red staining than that seen in mice treated with control proteins, indicating that liver fibrosis was resolving in these mice faster than in mice treated with control proteins (FIG 13 and Table 9)

[0293] Additional experiments were done with immunohistochemistry, staining for HNF4 α and Ki67 on paraffin fixed liver tissue from all animals in this study. In both Fc-RSPO2-WT and α ASGR1-RSPO2-RA-IgG2 treated mice, significant colocalization of the HNF4 α hepatocyte marker and the Ki67 proliferation marker was seen throughout the liver (data not shown). In contrast, far fewer double stained cells were seen in α - β -Gal-IgG treated control mice. These results confirmed that Fc-RSPO2-WT and α ASGR1-RSPO2-RA-IgG2 can induce hepatocyte proliferation in these mice.

[0294] Together these data suggest that the RSPO mimetic, α ASGR1-RSPO2-RA-IgG2, has a significant impact on the rate at which mice in this model of fibrotic liver disease can resolve fibrosis and regenerate functional hepatocytes.

EXAMPLE 7

CONSTRUCTION OF LIVER-TARGETED RSPO MIMETIC MOLECULES USING NOVEL ASGR1 BINDERS

[0295] Novel binders to human ASGR1 were developed as hybridomas which were raised against human ASGR1 and selected based on cross-reactivity to recombinant human and cynomolgus ASGR1 ECD domains. The hybridomas were further ranked for specific staining of Huh-7 cells (using HEK293 as controls) by flow cytometry. Selected hits were subcloned and sequenced to deduce their VH and VL sequences (SEQ ID NOs: 274-305). To make liver-specific RSPO mimetics, fusion proteins were made, with ASGR1 binders expressed as human IgG2 or human IgG1 containing the effectorless mutation N297G, while the mutant RSPO module was fused to the N- or C-terminus of the heavy chain via a linker (SEQ ID NOs: 190-271). Recombinant proteins were expressed in Expi293 cells by transient transfection and purified by Protein A resin followed by size exclusion chromatography. Hepatocyte specific Wnt signal enhancement were analyzed in luciferase assay comparing the activity in Huh-7 and HEK293 STF reporter cell lines in the presence of a recombinant WNT surrogate R2M3-26 (see, e.g., WO2019/126398). Figure 12 demonstrates specific activity of 16 novel ASGR1 targeted RSPO-mimetic molecules in Huh-7 cells, as IgG1 or IgG2 fusions.

EXAMPLE 8

PHARMACODYNAMIC (PD) ANALYSIS OF TISSUE-TARGETED RSPO MIMETICS IN MOUSE LIVER

[0296] In order to measure the *in vivo* activity of liver-targeted RSPO mimetics, 5-6 wks old C57BL/6 males JAX (56 mice total) were humanized for human *ASGR* gene expression. Mice were injected (IV) mice with AAV8 vectors expressing *hASGR1* and *hASGR2* genes (1×10^{11} genome copies/mouse).

[0297] After 6 days, multiple ASGR1-targeted RSPO mimetics, together with controls, were administered to mice via i.p. injection at 5 mg/kg dosage (Fig 15A).

[0298] After 24 hours, mice were euthanized; livers were dissected out and snap frozen for RNA isolation. mRNA analysis was done to determine the relative expression of *Axin2*. Semi-quantitative PCR was used to measure the relative gene expression in liver tissue from treated mice. Values were normalized to expression of constitutive *Actin B* gene expression (Fig 15B).

[0299] As compared with α - β -Gal-IgG, α ASGR1- IgG (RO-01) did not induce *Axin2* expression, suggesting this binder has no effect by itself on Wnt signaling. Similarly, α GFP-RSPO2-RA-IgG did not induce *Axin2*, confirming that the mutant RSPO2 module by itself has no activity either. In contrast, α ASGR1-RSPO2-RA-IgG (the prototypical liver-targeted RSPO mimetic constructed with binder RO-01), demonstrated potent *Axin2* inductin in liver, consistent with the requirement of the targeting module.

[0300] All the additional ASGR1-targeted RSPO mimetic molecules (constructed with in-house rased binders) showed either a trend or significant induction of *Axin2* expression. 7B13, 8M24, 2I13, and 9M16-based RSPO mimetic molecules showed statistically significant increase in stimulating *Axin2* expression as compared to α - β -Gal-IgG control by one-way ANOVA, while 3A24, 2I22, 1P13, 1N15, 3E20 showed a trend in stimulating *Axin2* expression (Fig 15B).

[0301] The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent application, foreign patents, foreign patent application and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, application and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of

equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

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Claims:

1. A tissue-specific Wnt (“Wingless-related integration site” or “Wingless and Int-1” or “Wingless-Int”) signal enhancing molecule, or a pharmaceutically acceptable salt thereof, comprising a first domain that specifically binds one or more transmembrane E3 ubiquitin ligases selected from Zinc and Ring Finger 3 (ZNRF3) and Ring Finger Protein 43 (RNF43), and a second domain that specifically binds asialoglycoprotein receptor 1 (ASGR1) and/or asialoglycoprotein receptor 2 (ASGR2), wherein:

(a) the first domain comprises an antibody or antigen-binding fragment thereof comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A,

or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences; and/or

(b) the second domain comprises an antibody or antigen-binding fragment thereof comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A,

or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

2. The molecule of claim 1, wherein the molecule is a liver-specific Wnt signal enhancing molecule, and the second domain comprises an antibody or antigen-binding fragment thereof comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies

of Table 3A,

or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences

3. The molecule of claim 1, wherein the first domain comprises an antibody or antigen-binding fragment thereof comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A,

or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

4. The molecule of claim 1 or claim 2, wherein the first domain comprises an R-spondin polypeptide sequence or a fragment or variant thereof, wherein the R-spondin is optionally R-spondin-1, R-spondin-2, R-spondin-3, or R-spondin-4.

5. The molecule of claim 4, wherein the first domain comprises an R-spondin Furin domain 1 sequence and, optionally a wild-type or mutated Furin domain 2 or a fragment or variant thereof, wherein the first polypeptide sequence optionally has reduced binding to Leucine-rich repeat-containing G-protein coupled receptors 4-6 (LGR4-6) as compared to a full length R-spondin.

6. The molecule of claim 4 or claim 5, wherein the R-spondin Furin domain 1 has at least 90% identity to any of the Furin 1 domains present in SEQ ID NOs:1-4.

7. The molecule of any of claims 1-6, wherein the molecule is a fusion protein, wherein the first domain and the second domain are polypeptides, optionally linked via a linker moiety.

8. The molecule of claim 7, wherein the linker moiety is a peptidyl linker sequence.

9. The molecule of claim 8, wherein the linker sequence comprises one or more amino acids selected from the group consisting of: Glycine, Asparagine, Serine, Threonine and Alanine.
10. A nucleic acid sequence encoding for at least the first domain or second domain of the molecule of any of claims 1-9.
11. The nucleic acid sequence of claim 10, wherein the nucleic acid sequence is DNA or mRNA.
12. A vector comprising the nucleic acid sequence of claim 11.
13. The vector of claim 12, wherein the vector is an expression vector comprising a promoter sequence operatively linked to the nucleic acid sequence.
14. The vector of claim 13, wherein the vector is a virus comprising a promoter sequence operatively linked to the nucleic acid sequence.
15. A host cell comprising the vector of claim 14.
16. A process for producing the fusion polypeptide of any of claims 7-9, comprising culturing the host cell of claim 15 under conditions wherein the fusion polypeptide is expressed by the expression vector.
17. The process of claim 16, further comprising the step of isolating the fusion polypeptide produced.
18. A pharmaceutical composition comprising:
 - a) an effective amount of the molecule of any of claims 1-9, the nucleic acid sequence of any of claims 10-11, the vector of any of claims 12-14, or the host cell of claim 15; and
 - b) a pharmaceutically acceptable diluent, adjuvant or carrier.
19. The pharmaceutical composition of claim 18, comprising the effective amount of the

molecule of any of claims 1-9 and an effective amount of a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule.

20. The pharmaceutical composition of claim 18, comprising the effective amount of the nucleic acid sequence of any of claims 10-11 and an effective amount of a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule is optionally DNA or mRNA.

21. The pharmaceutical composition of claim 20, wherein the nucleic acid sequence of any of claims 13-14 and/or the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule are modified mRNAs.

22. The pharmaceutical composition of claim 18, comprising the effective amount of the vector of any of claims 12-14 and an effective amount of a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein the vector comprising the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule is optionally an expression vector.

23. The pharmaceutical composition of any of claims 19-22, wherein the Wnt polypeptide is a mammalian Wnt polypeptide selected from: Wnt1, Wnt2, Wnt2B, Wnt3, Wnt3A, Wnt4, Wnt5A, Wnt5B, Wnt6, Wnt7A, Wnt7B, Wnt8A, Wnt8B, Wnt9A, Wnt9B, Wnt10A, Wnt10B, Wnt11, and Wnt 16, and functional variants and fragments of any of the foregoing.

24. The pharmaceutical composition of any of claims 19-22, wherein the Norrin polypeptide is a mammalian Norrin polypeptide or a functional variant or fragment thereof.

25. The pharmaceutical composition of any of claims 19-22, wherein the Wnt signaling agonist molecule is a water soluble Wnt signaling agonist that dimerizes a Frizzled (Fz) receptor with Lrp5/6.

26. The pharmaceutical composition of claim 25, wherein the Wnt signaling agonist molecule comprises a polypeptide.

27. The pharmaceutical composition of claim 26, wherein the polypeptide comprises a binding domain having affinity for one or more Fzd proteins and a binding domain having affinity to Lrp5/Lrp6 protein, and wherein the binding domains are optionally directly joined or joined through a linker.

28. A method for increasing Wnt (“Wingless-related integration site” or “Wingless and Int-1” or “Wingless-Int”) signaling in a target tissue, comprising contacting the target tissue with:

a) the molecule of any of claims 1-9; the nucleic acid of any of claims 10-11; the vector of any of claims 12-14; or the host cell of claim 15, wherein the second domain specifically binds a cell-specific surface molecule on the target tissue, and wherein the molecule of any one of claims 1-12 binds the target tissue and sequesters or increases endocytosis of one or more transmembrane E3 ubiquitin ligases selected from Zinc and Ring Finger 3 (ZNRF3) and Ring Finger Protein 43 (RNF43) in the target tissue; and/or

b) a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule; a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule; a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule; or a host cell comprising an expression vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule; wherein the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule is optionally DNA or mRNA, optionally a modified mRNA.

29. The method of claim 28, comprising contacting the target tissue with the molecule of any of claims 1-9.

30. The method of claim 28, comprising contacting the target tissue with the nucleic acid of any of claims 10-11.

31. The method of claim 28, comprising contacting the target tissue with the vector of any of claims 12-14.

32. The method of claim 28, comprising contacting the target tissue with the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule.

33. A method for treating or preventing a liver disease or liver condition in a subject in need thereof, wherein the liver disease or liver disorder is associated with reduced Wnt (“Wingless-related integration site” or “Wingless and Int-1” or “Wingless-Int”) signaling or would benefit from increased Wnt signaling, comprising providing to the subject an effective amount of the pharmaceutical composition of any of claims 18-27, optionally wherein the molecule is the molecule of claim 2.

34. The method of claim 33, further comprising providing to the subject a pharmaceutical composition comprising a pharmaceutically acceptable diluent, adjuvant or carrier, and an effective amount of:

a) a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule;
 b) a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule is optionally DNA or mRNA;

c) a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein the vector comprising the nucleic acid sequence that encodes the Wnt polypeptide, the Norrin polypeptide, or the Wnt signaling agonist molecule is optionally an expression vector; or

d) a host cell comprising an expression vector comprising a nucleic acid that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule.

35. The method of claim 34, comprising providing to the subject a pharmaceutical composition comprising an effective amount of a molecule of any of claims 1-9 and a pharmaceutical composition comprising an effective amount of a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule.

36. The method of claim 34, comprising providing to the subject a pharmaceutical composition comprising an effective amount of a nucleic acid sequence of any of claims 10-

11 and a pharmaceutical composition comprising an effective amount of a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein one or both of the nucleic acid sequences are optionally DNA or mRNA, optionally modified mRNAs.

37. The method of claim 34, comprising providing to the subject a pharmaceutical composition comprising an effective amount of a vector of any of claims 12-14 and a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide, a Norrin polypeptide, or a Wnt signaling agonist molecule, wherein one or both of the vectors are optionally expression vectors or viral vectors.

38. The method of any of claims 34-37, wherein the Wnt polypeptide is a mammalian Wnt polypeptide selected from: Wnt1, Wnt2, Wnt2B, Wnt3, Wnt3A, Wnt4, Wnt5A, Wnt5B, Wnt6, Wnt7A, Wnt7B, Wnt8A, Wnt8B, Wnt9A, Wnt9B, Wnt10A, Wnt10B, Wnt11, and Wnt 16, and functional variants and fragments of any of the foregoing.

39. The method of any of claims 34-37, wherein the Norrin polypeptide is a mammalian Norrin polypeptide or a functional variant or fragment thereof.

40. The method of any of claims 34-37, wherein the Wnt signaling agonist molecule is a water soluble Wnt signaling agonist that dimerizes a Frizzled (Fzd) receptor with Lrp5/6.

41. The method of claim 40, wherein the Wnt signaling agonist molecule comprises a polypeptide.

42. The method of claim 41, wherein the polypeptide comprises a binding domain having affinity for one or more Fzd proteins and a binding domain having affinity to Lrp5/Lrp6 protein, and wherein the binding domains are optionally directly joined or joined through a linker.

43. The method of any of claims 33-42, wherein the liver disease or liver condition is selected from the group consisting of: acute liver failure of all causes, acute liver failure drug-induced,

alcoholic liver diseases, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, end stage liver disease (ESLD), nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, liver surgery, liver injury, liver transplantation, “small for size” syndrome in liver surgery and transplantation, congenital liver disease and disorders, any other liver disorder or defect resulting from genetic diseases, degeneration, aging, drugs, or injuries.

44. The method of any of claims 33-43, wherein the pharmaceutical composition is provided parenterally, orally, intramuscularly, or locally to the liver.

45. The method of any one of claims 33-44, wherein the subject is a mammal, optionally a human.

46. An isolated antibody, or an antigen-binding fragment thereof, that binds to a RNF43 or a ZNRF3 polypeptide, comprising a sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

47. The antibody or antigen-binding fragment thereof of claim 46, comprising a heavy chain variable region and/or a light chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 2B or SEQ ID NOs: 78-150 or 165-170.

48. The antibody, or antigen-binding fragment thereof of claim 47, comprising a heavy chain variable region and/or a light chain variable region comprising an amino acid sequence set forth in Table 2B or SEQ ID NOs: 78-150 or 165-170.

49. An isolated antibody, or an antigen-binding fragment thereof, that binds to an ASGR1 or ASGR2 polypeptide, comprising a sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 3A; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 3A, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

50. The antibody or antigen-binding fragment thereof of claim 49, comprising a heavy chain variable region and/or a light chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 3B or SEQ ID NOs:47-77, 151-154, 171-179, or 274-305.

51. The antibody, or antigen-binding fragment thereof of claim 50, comprising a heavy chain variable region and/or a light chain variable region comprising an amino acid sequence set forth in Table 3B or SEQ ID NOs:47-77, 151-154, 171-179, or 274-305.

52. An antibody comprising a heavy chain variable region or a light chain variable region comprising an amino acid sequence having at least 90% identity to an amino acid sequence set forth in Table 3C or SEQ ID NOs:180-185, or a fragment or variant thereof.

53. An antibody, or antigen-binding fragment thereof, that competes for binding with the antibody or antigen binding fragment thereof of any of claims 46-52.

54. A pharmaceutical composition comprising the antibody of any of claims 46-53.

55. A method for increasing liver to body weight ratio, promoting liver regeneration, increasing liver cell proliferation or mitosis, decreasing liver fibrosis, optionally following a chronic liver injury, increasing hepatocyte function, or decreasing coagulation time in liver, comprising providing to a subject an effective amount of the pharmaceutical composition of claim 53, wherein the antibody or antigen-binding fragment thereof, that binds to an ASGR1 or ASGR2 polypeptide.

Rspo1	MRLGLC--VVALVLSWTHLTISSRGIKGRQRRISAEGSQACAKGCELCSEVNGCLKCSFK	59	
Rspo2	MQFRLFSFALIILNCMDYSHCQGNR--WRRSKR--ASYVSNEFICKGCLSCSKDNOCSRQCK	58	
Rspo3	MHLRLISWLFIIILNFMEYIGSQNASRGRQRRMHFNVSSQGCQGGCATCSDYNGCLSKPR	60	
Rspo4	MRAPLCLLLL--VAHAVDMLA-----LNRKKQVGTGLGGNCTGCIICSEENGCSSTCQQR	53	
	*: * : . . * :: ** ** . *** * . :		
Rspo1	LEFILLERNDIRQVGVCLPSCPFGYFDARNFDMKCIKCKLERCEACTSHMTCTCKEEL	119	
Rspo2	LFFFLRREGMROYGECLHSCPSGGYGHRAFDMMRCARIEKCDSCFERNPCTCKVGFY	118	
Rspo3	LFFALERIGKQIGVCLSSCPSGYYGTRYPDINKCTKESA--DQDTCPNEMFCTCKVGFY	119	
Rspo4	LELFIRREGIRQYVKCLHDCFPGYFGIRQGEVNRCKKGA--TCESCFQDPCIRCKRQFY	112	
	** : . * : * * * . * * * : * : * : * * * * * * * *		
Rspo1	LHNSRCYFACPEGSEAMETHCESSPAQCEMSEWSPWGPCSKKQQLCGFRGSEERTRRV	179	
Rspo2	LHNGRCFDECFDGFAPLEETHCEVE--GCEVGHWSEWGTCSSNNRTCGFKWGLETRTRQI	176	
Rspo3	LHLGKCLDNCFEGLEAMHTECVSIVHCEVSEWNFWSPCTKKGKTCGFKGTETRVREI	179	
Rspo4	LYHCKCLPTCFPGTLAHQNTRECEH--ECELGPWGGWSPCTHNGKTCGSAWGLESRVREA	170	
	* . * * * * * . * * * * * * * * * * * * * * * *		
Rspo1	LHAPVGDHAACSDTKETRRTVRRVPCPEGQKR--RKGGQGRRENANRNLARKESKE----	234	
Rspo2	VKKPVKDTILCPTIAESRRCKMTMRHCPGGKRT--PKAKEKRNNKKKKRKLIERAQEQHSV	234	
Rspo3	IQHPSAKGNLCPTNETRKCTVQKKCKQGERG--KKGREKRKKKPNKGESKEAIPDSKS	237	
Rspo4	GRAGHEEAATCQVLSERKCP IQR--PCPGERSPGQKKGRKDRRPRKDRKLDRLDVR----	226	
	: . * * : * : * : * . * . : . . : . .		
Rspo1	--AGAGS--RRRKGGQQQQ--QGGTVGPLTSAGPA	263 (SEQ ID NO:1)	Fu1
Rspo2	FLA-----TDRANQ-----	243 (SEQ ID NO:2)	
Rspo3	LESSKEIPEQRENKQQQKKRKVQDKQKSVSVTVH----	272 (SEQ ID NO:3)	Fu2
Rspo4	-----PRQFGLQP-----	234 (SEQ ID NO:4)	
	: .		

FIG. 1A

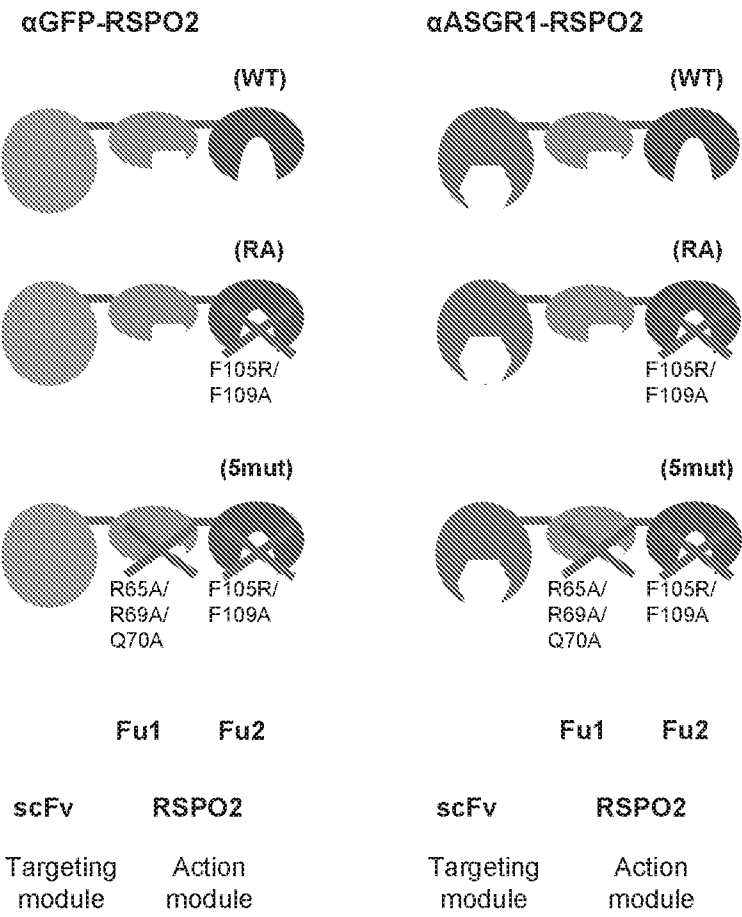


FIG. 1B

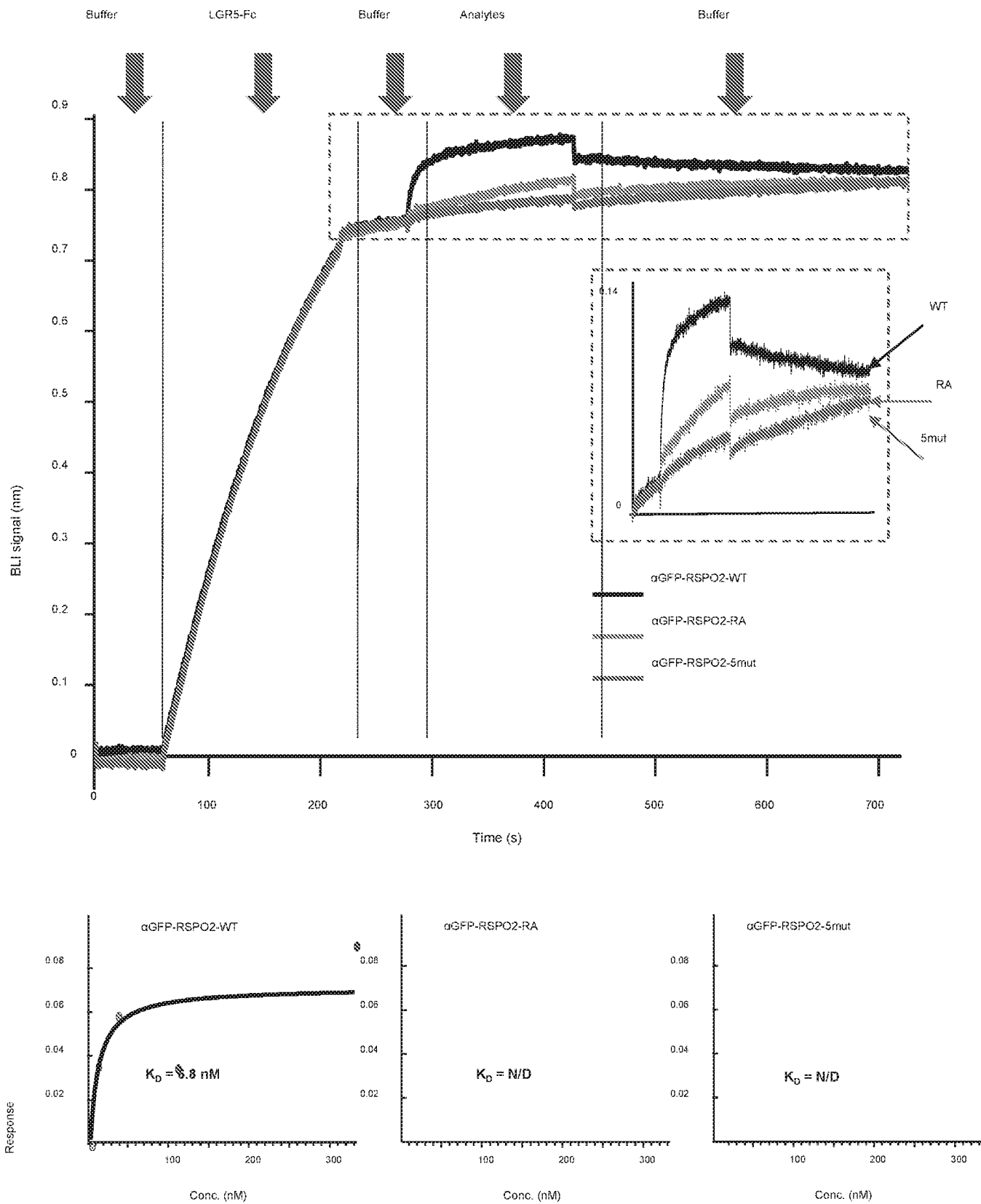


FIG. 1C

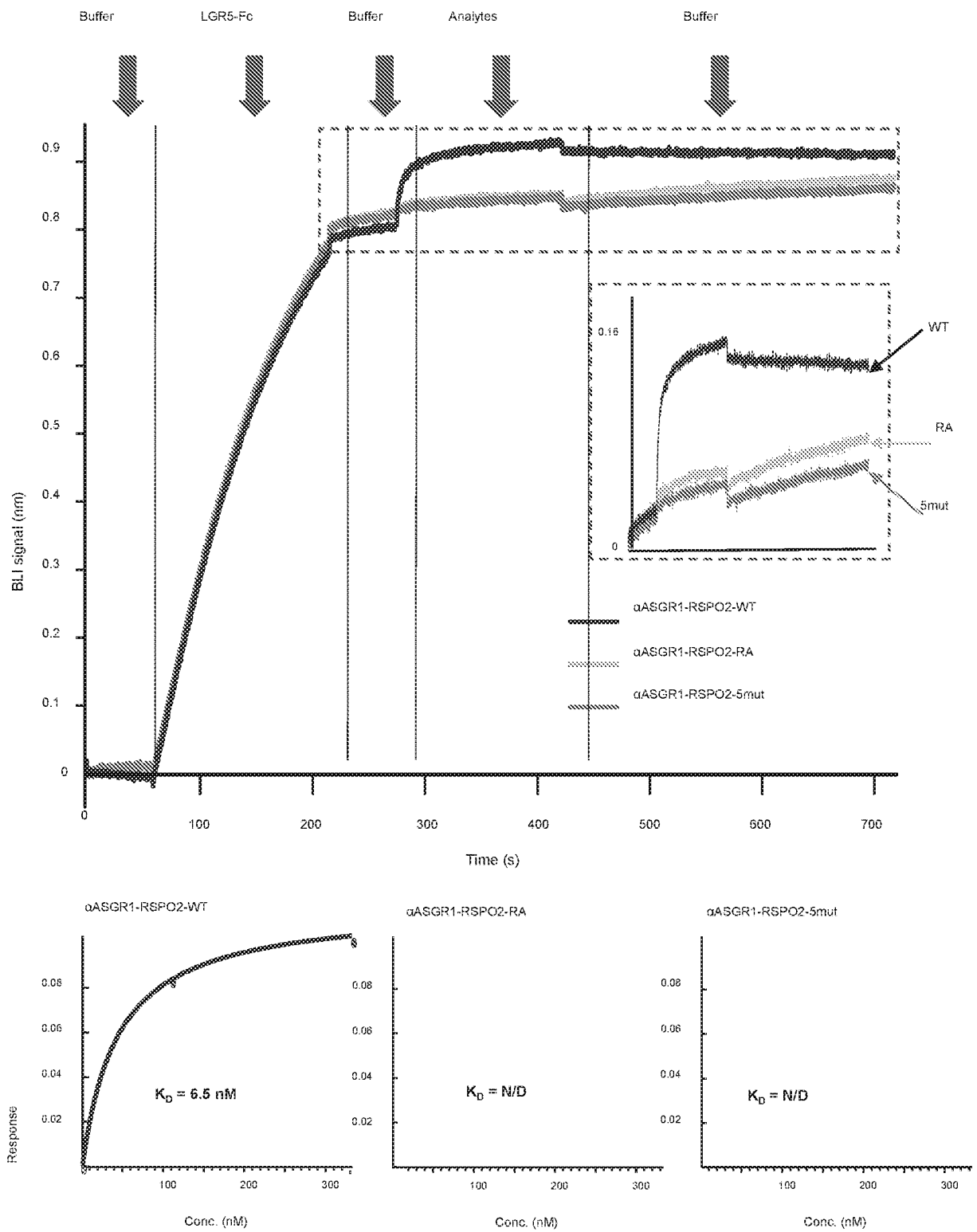


FIG. 1C (cont.)

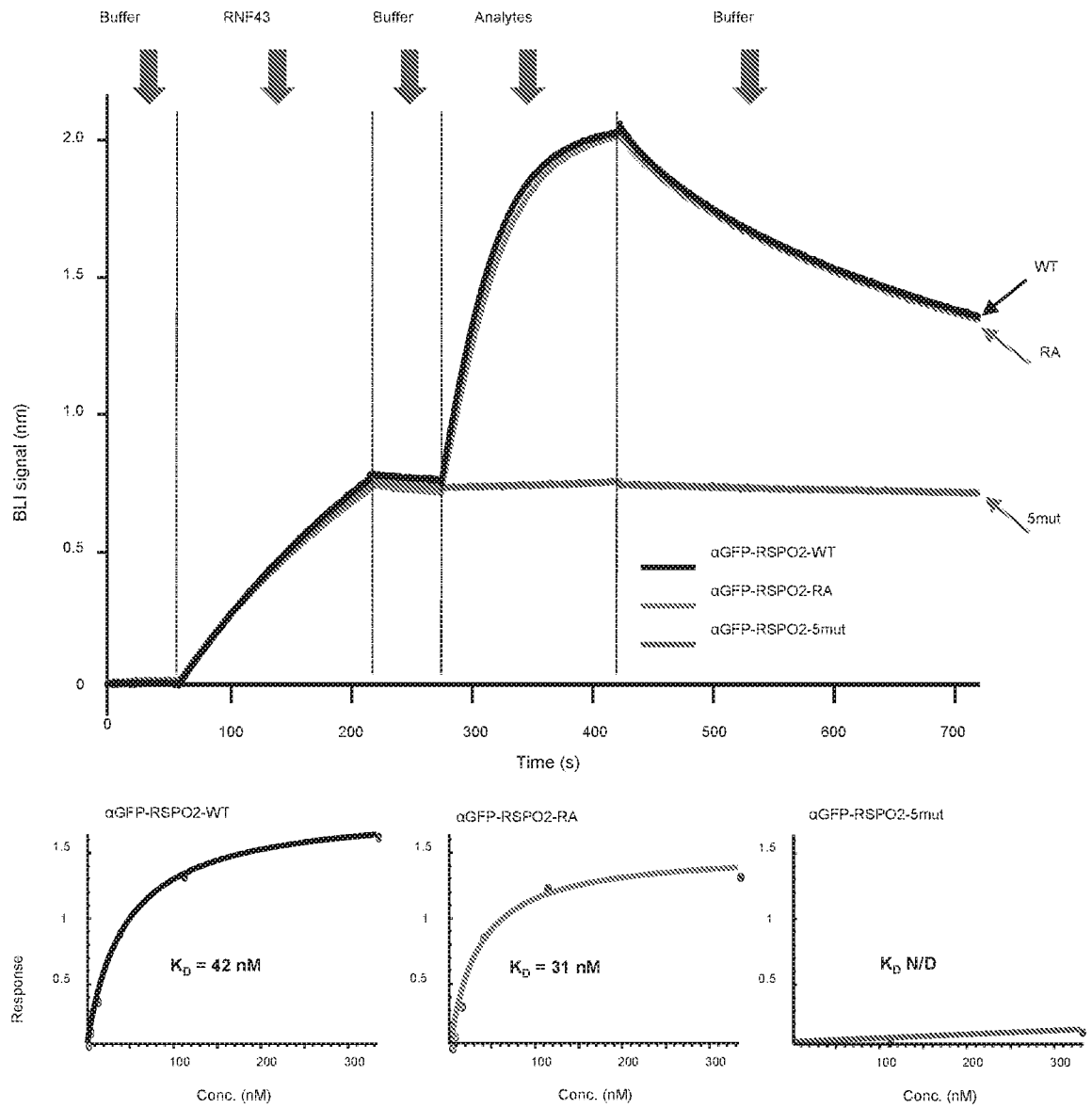


FIG. 1D

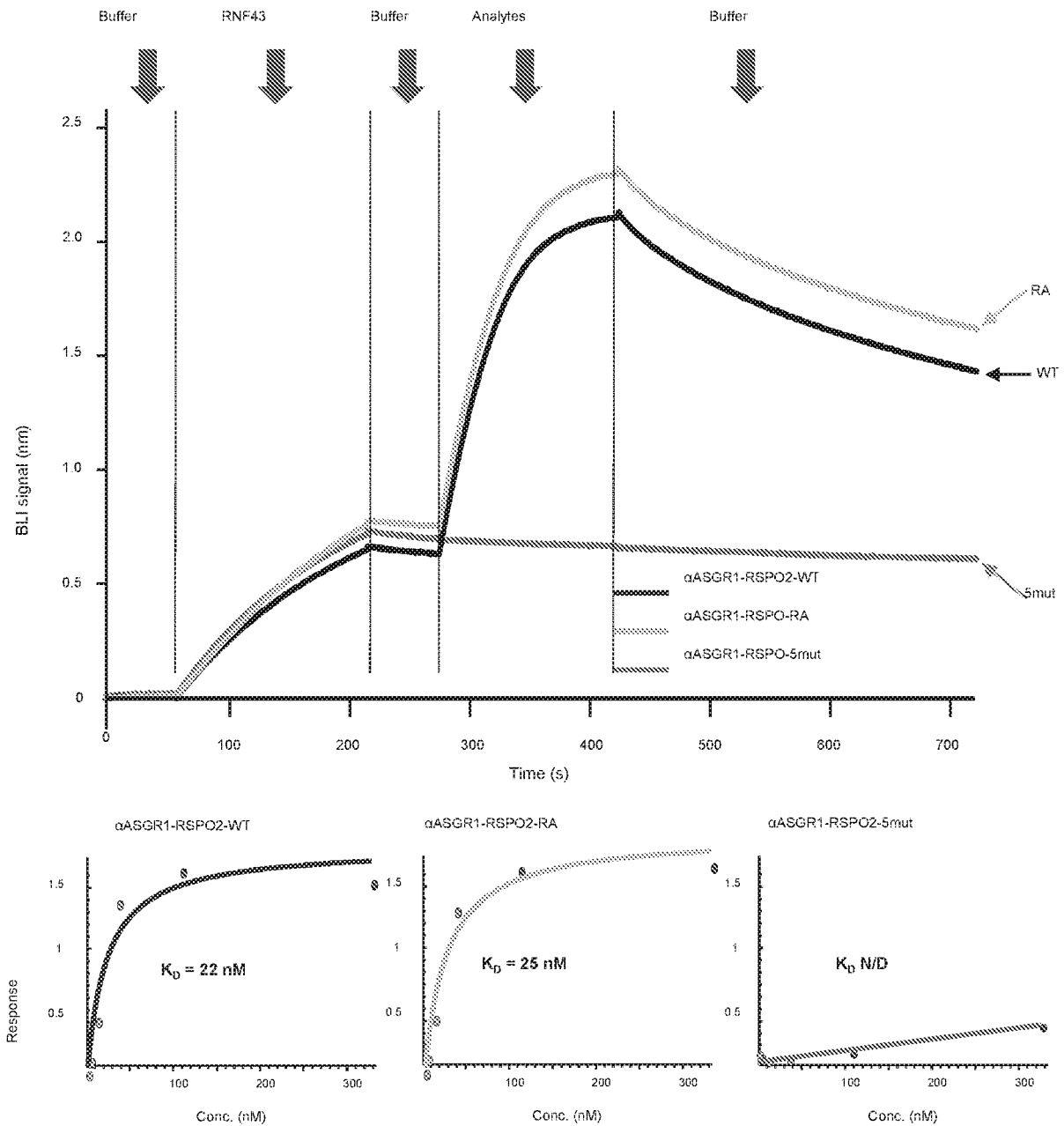


FIG. 1D (cont.)

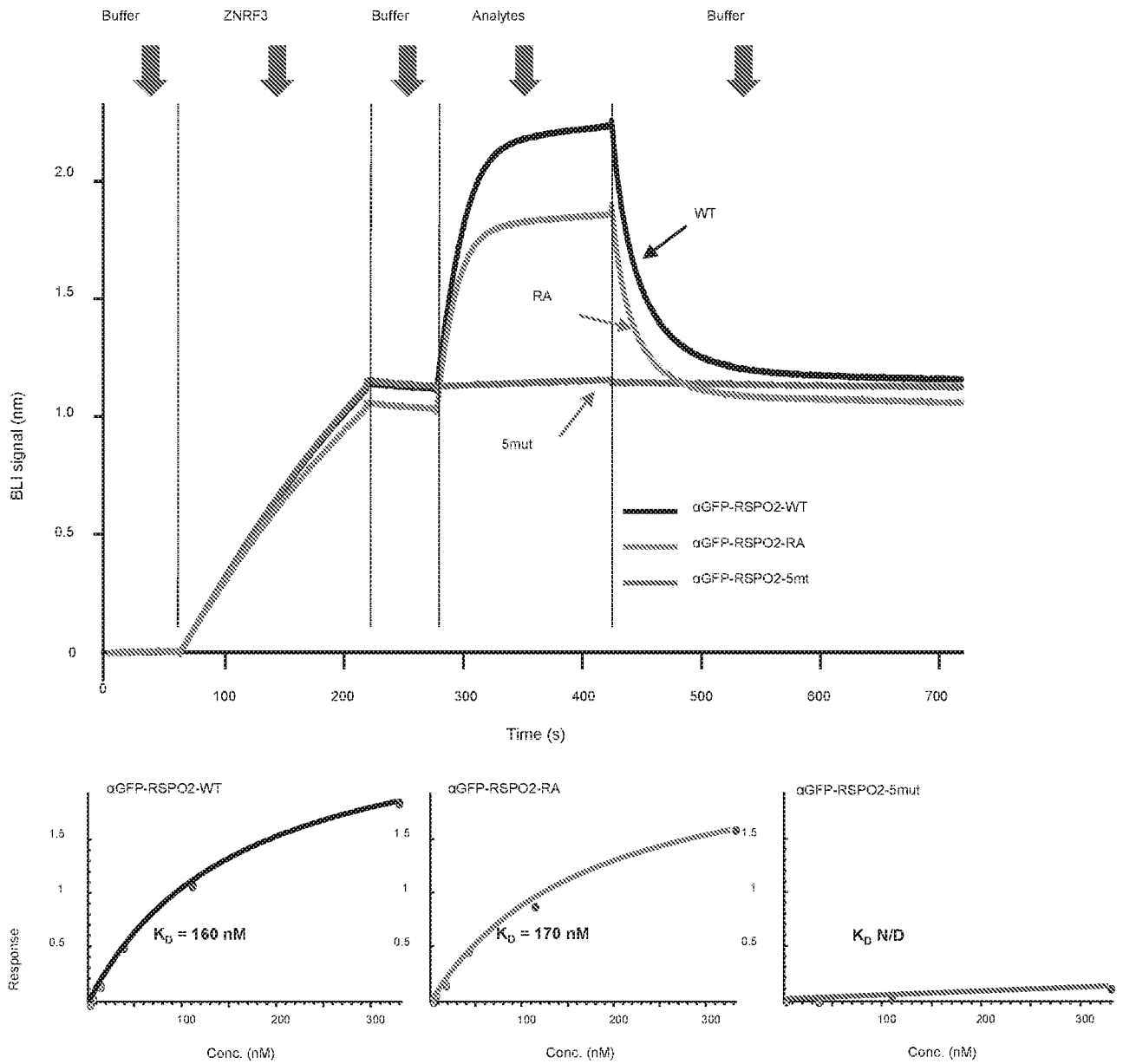


FIG. 1D (cont.)

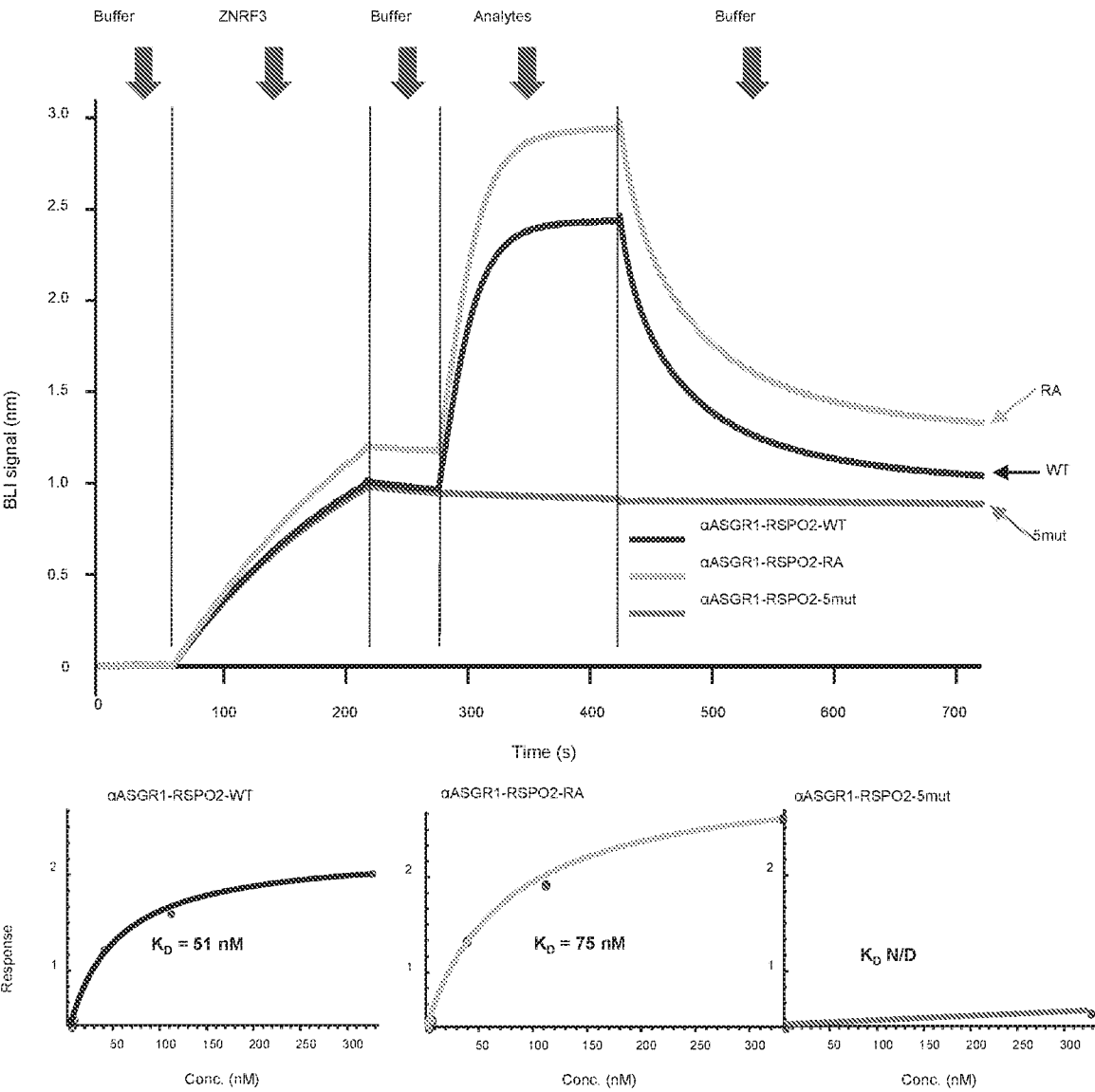


FIG. 1D (cont.)

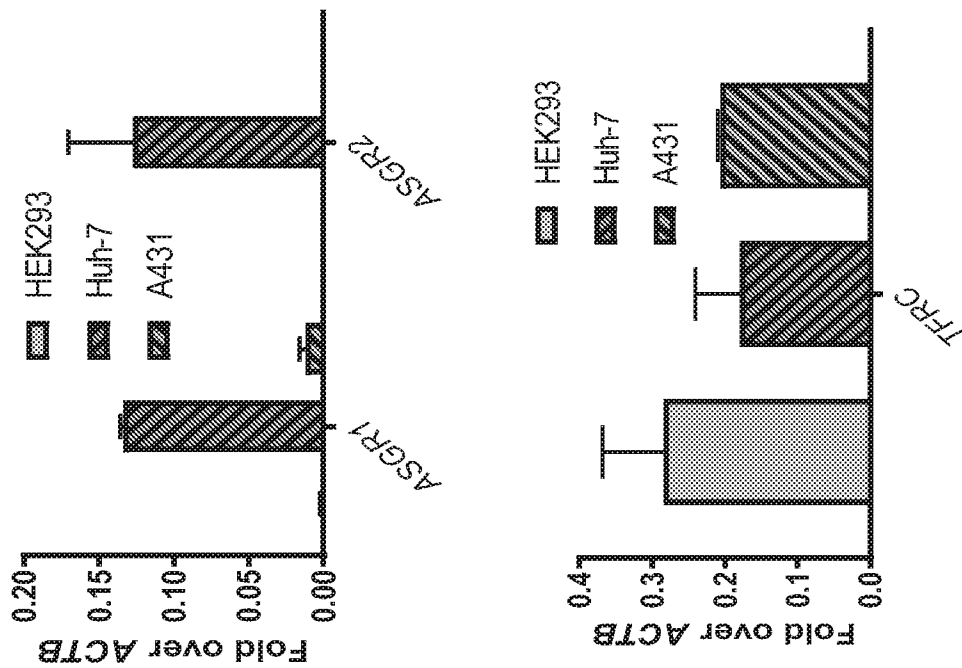


FIG. 2A

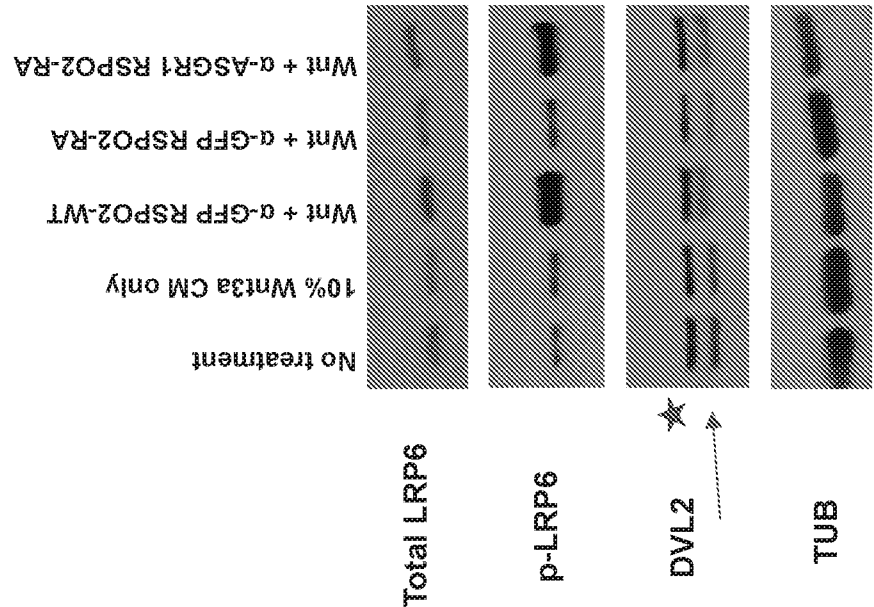


FIG. 2C

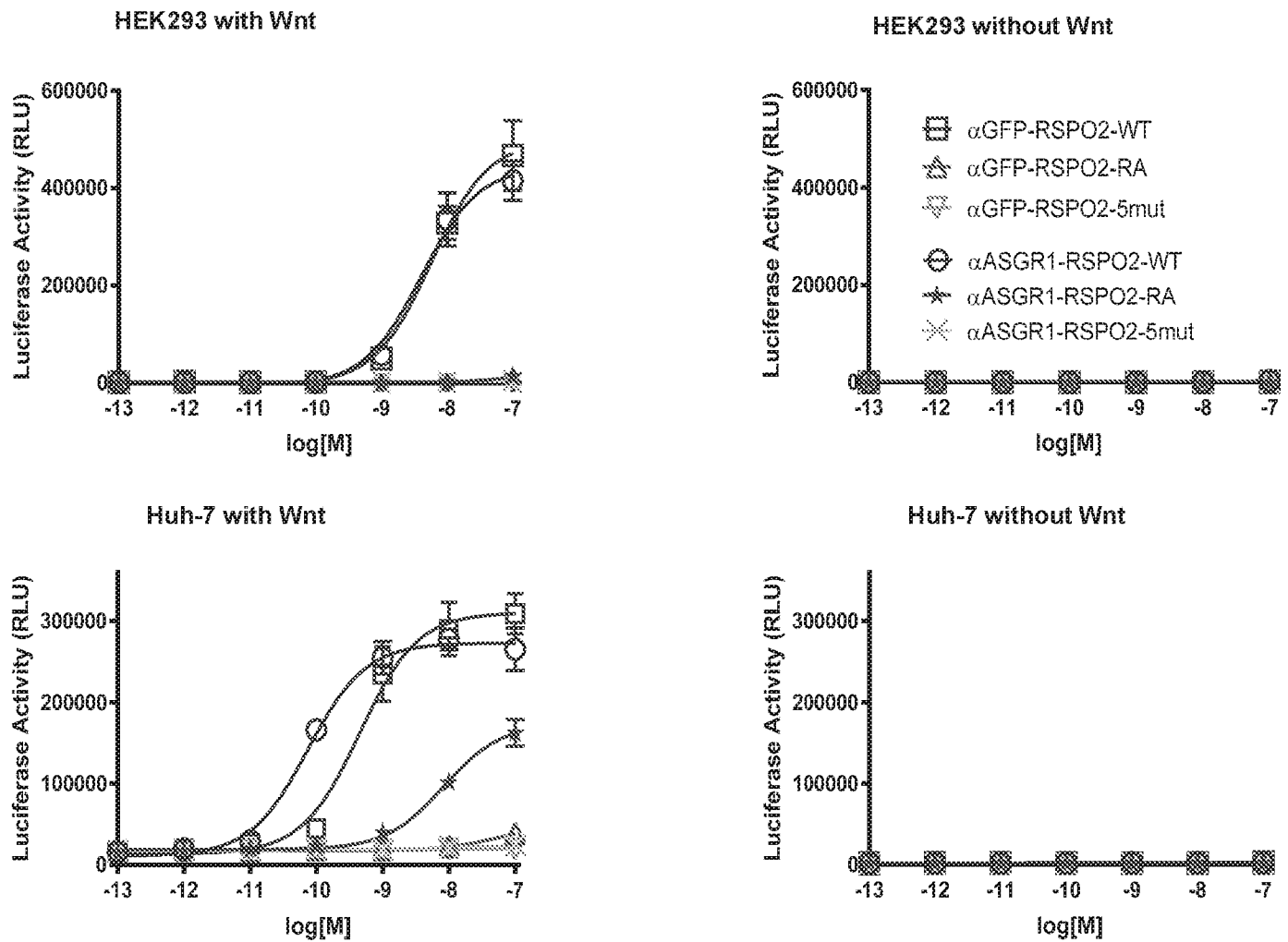


FIG. 2B

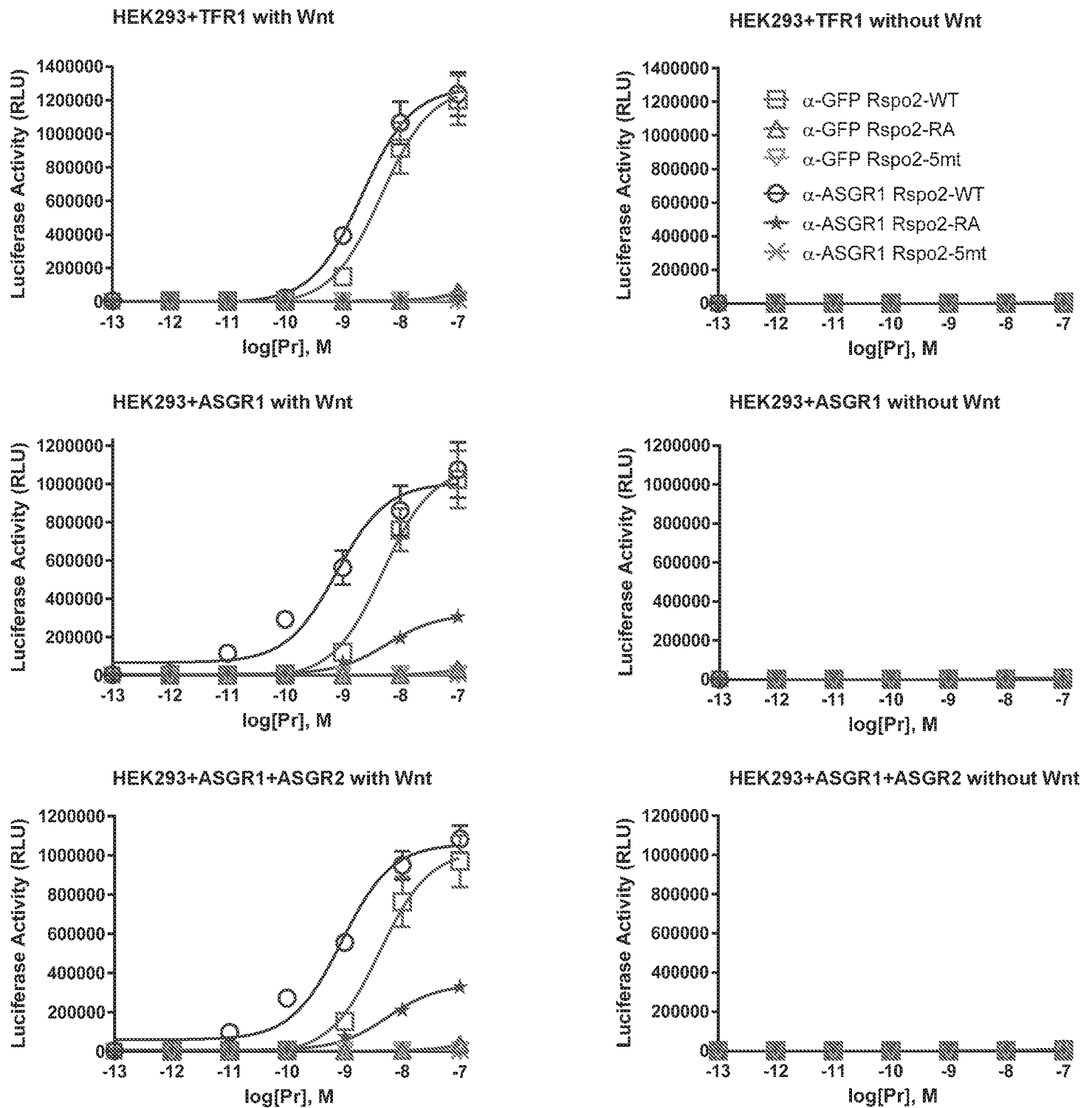


FIG. 3A

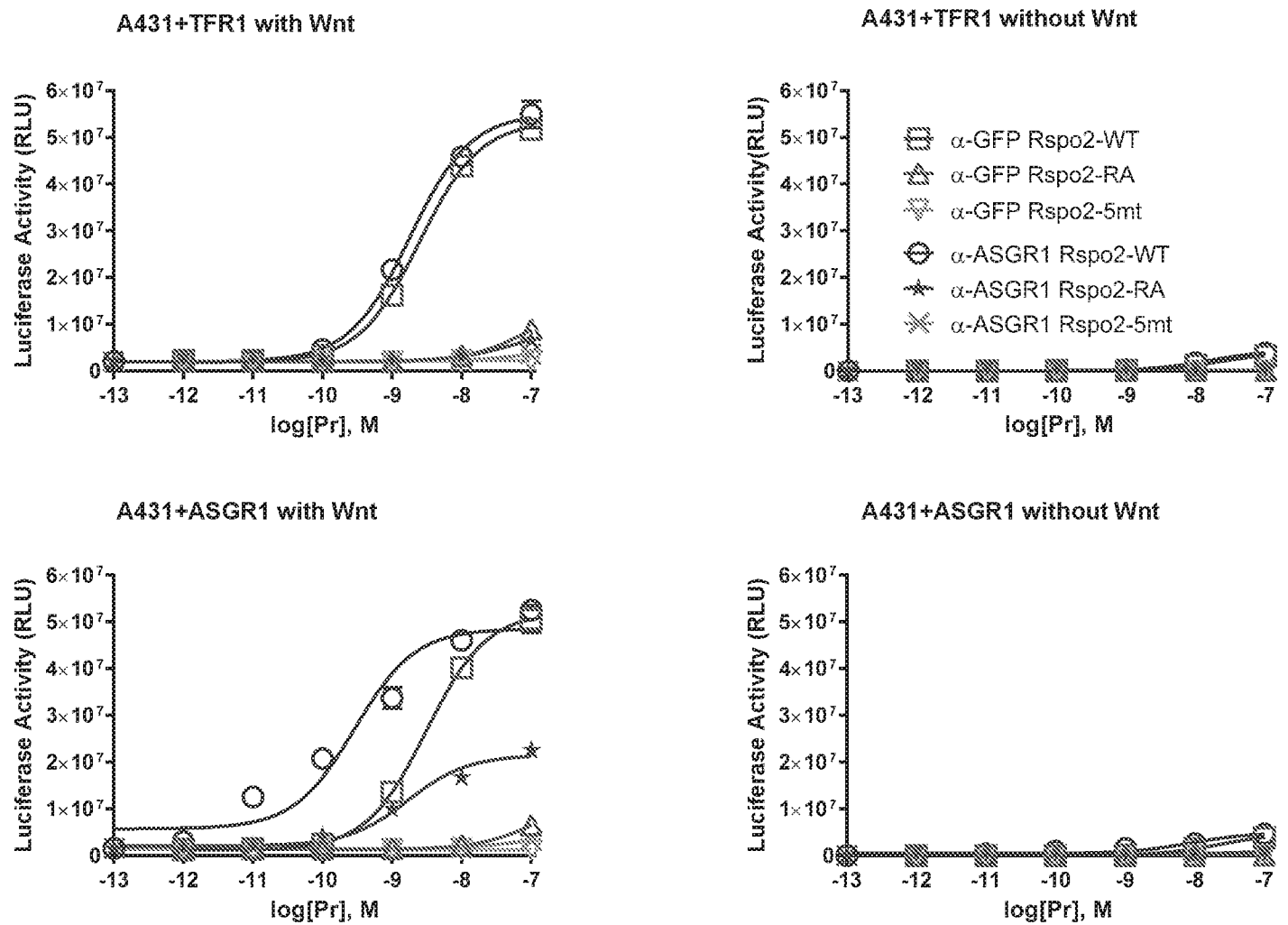


FIG. 3B

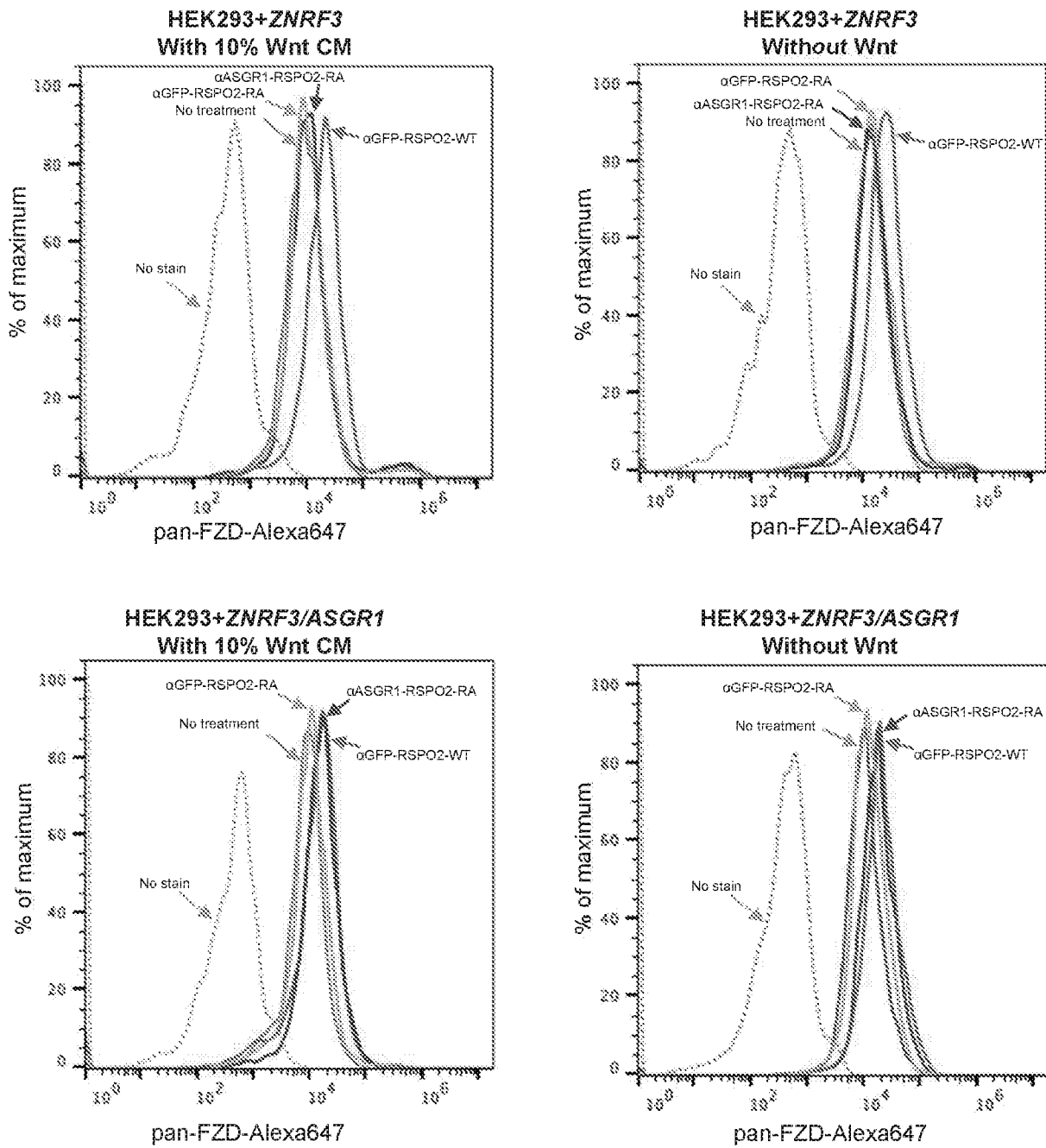


FIG. 3C

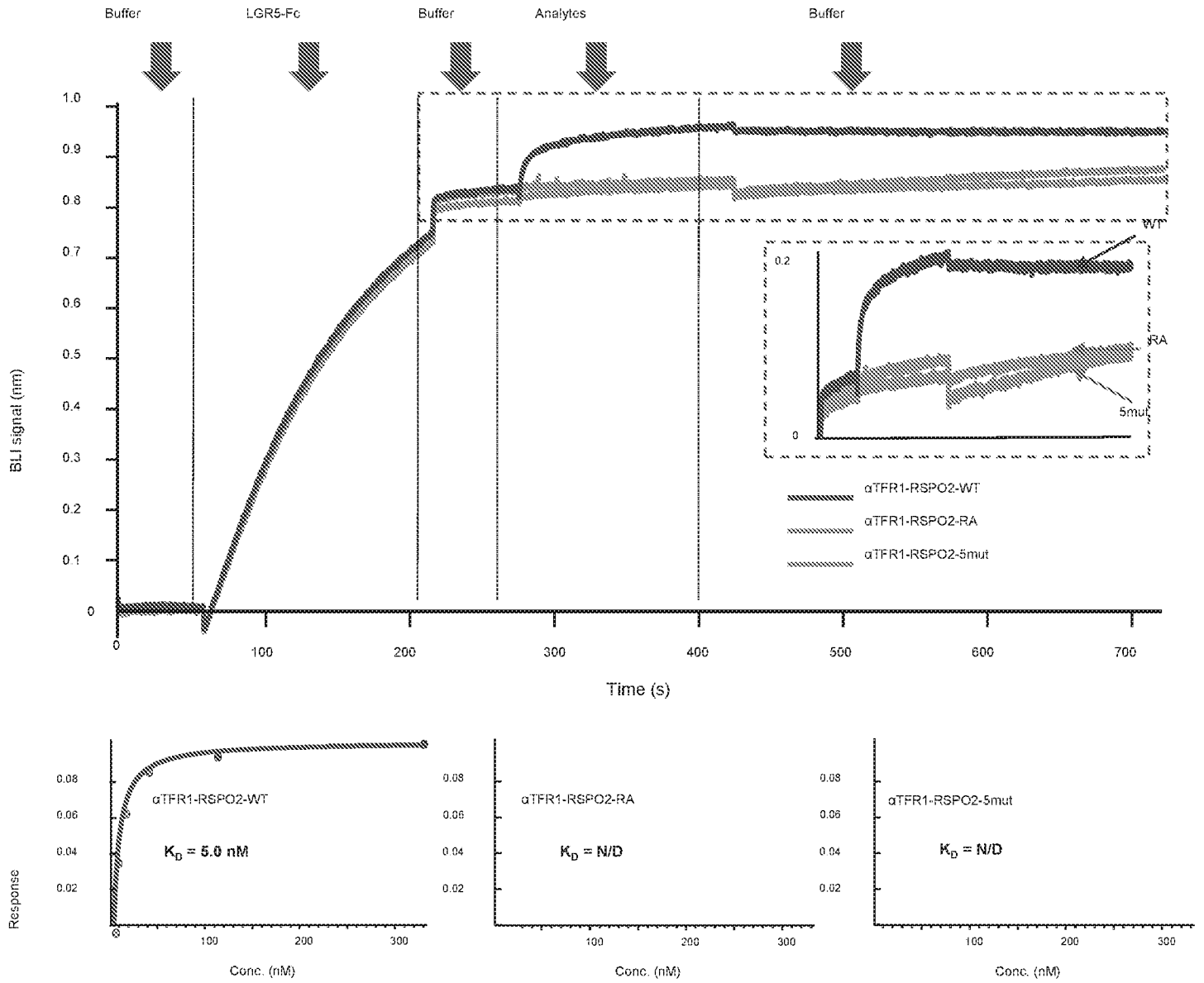
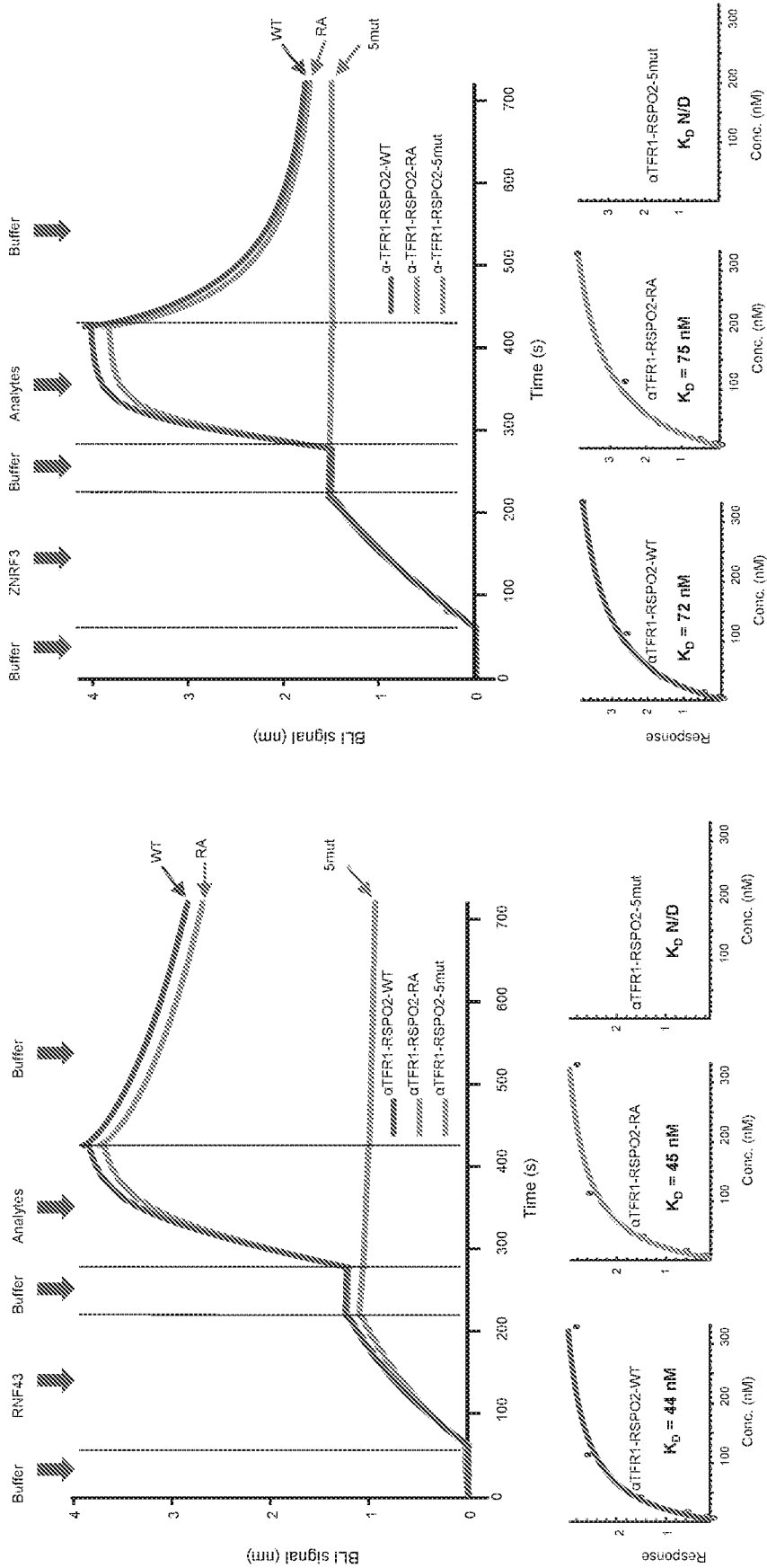


FIG. 4A

FIG. 4B



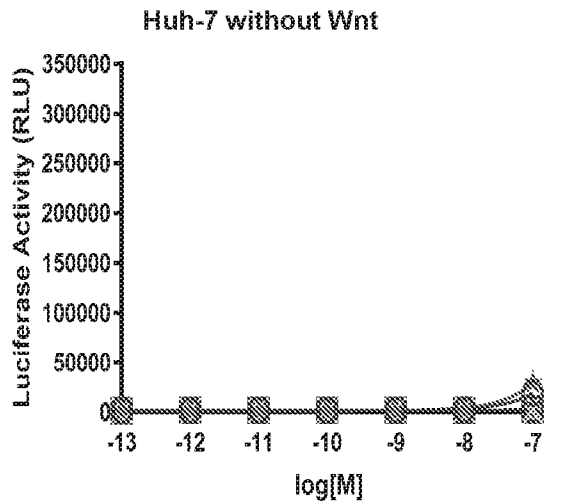
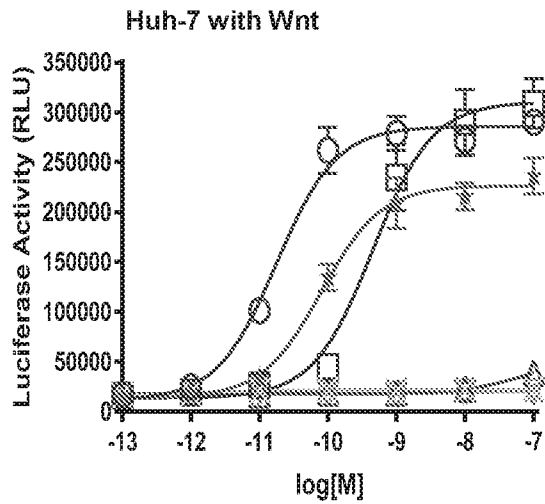
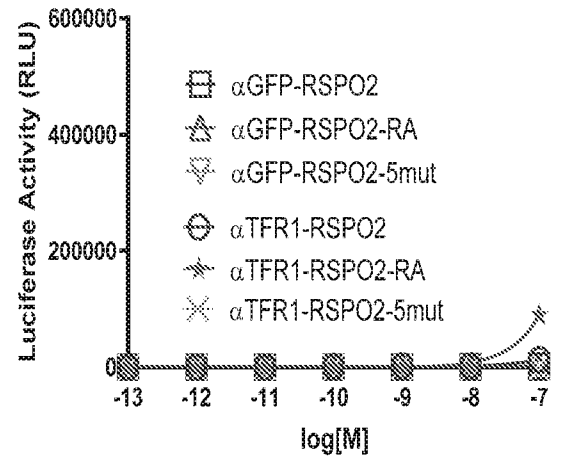
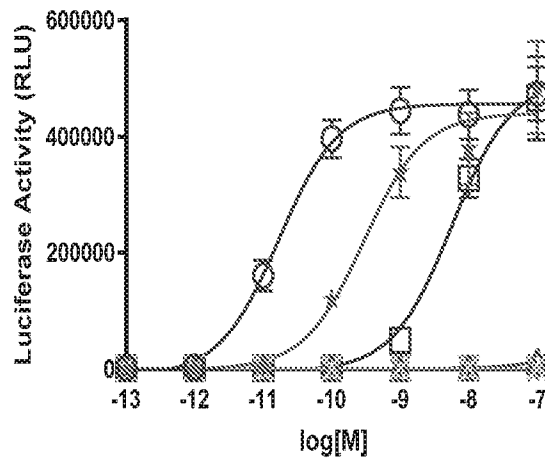


FIG. 4C

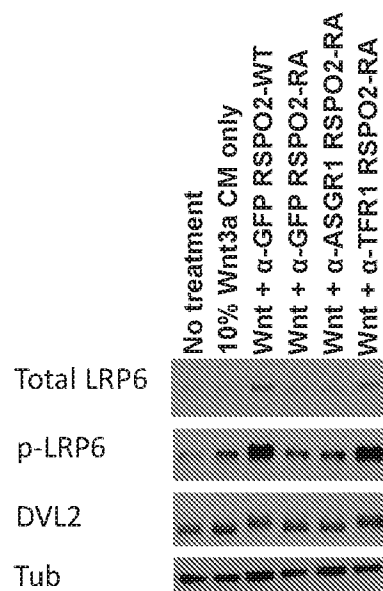
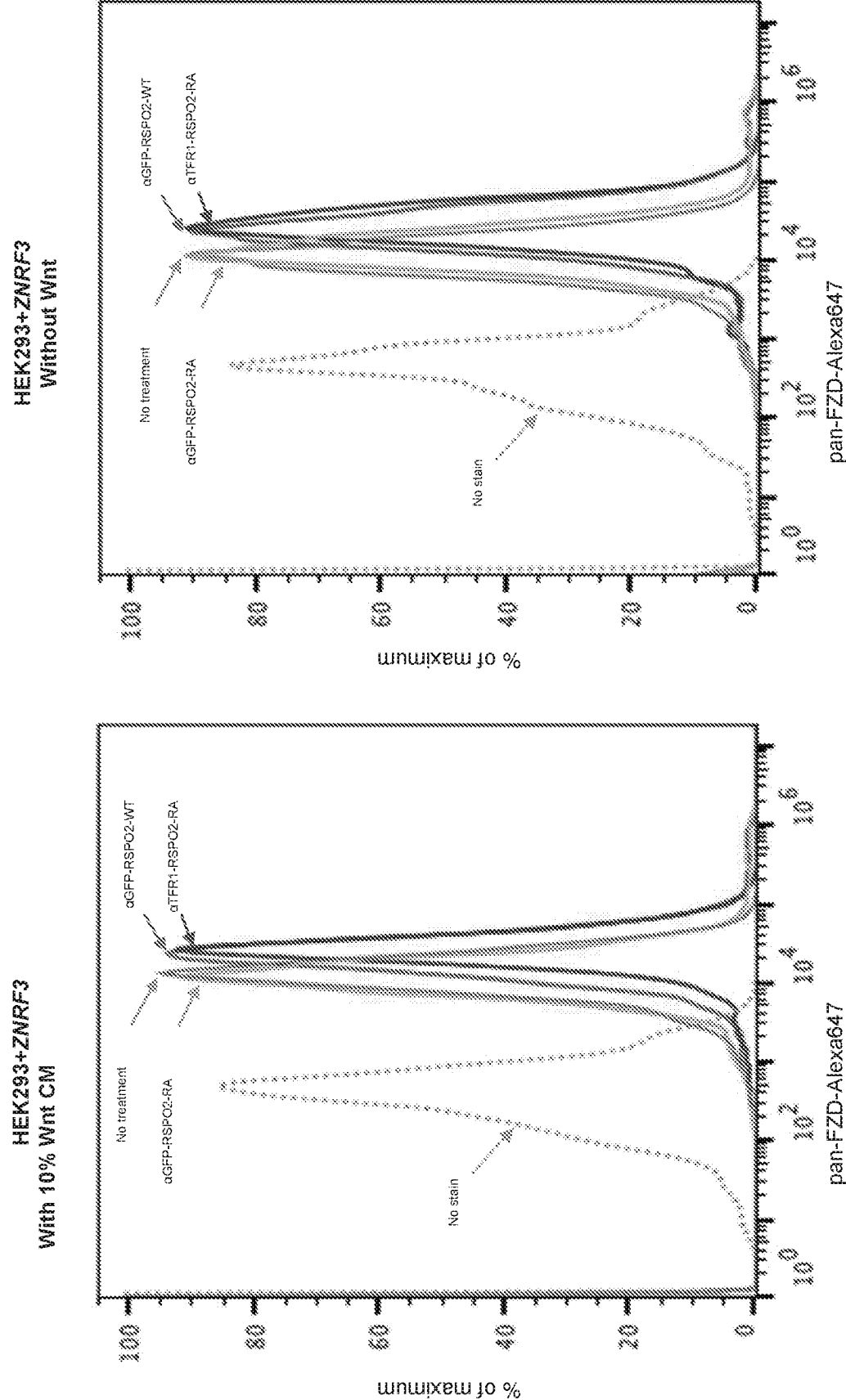


FIG. 4D

FIG. 4E



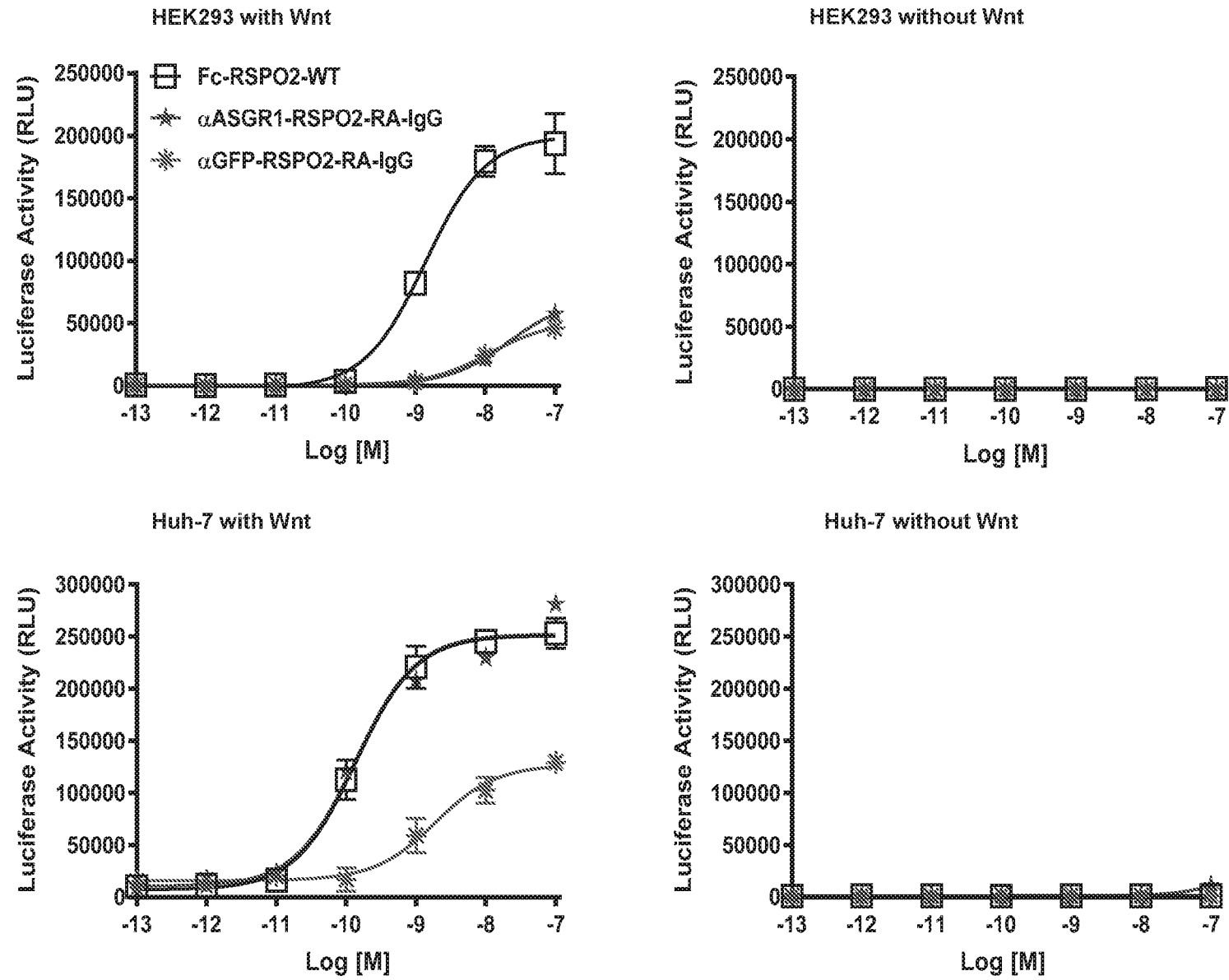


FIG. 5A

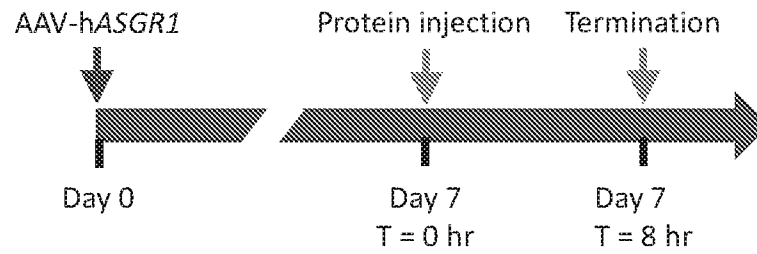


FIG. 5B

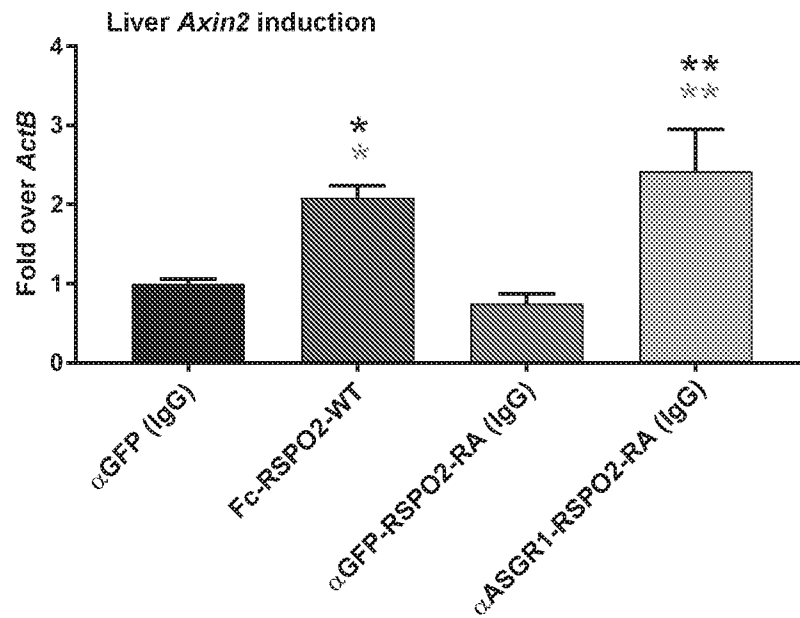


FIG. 5C

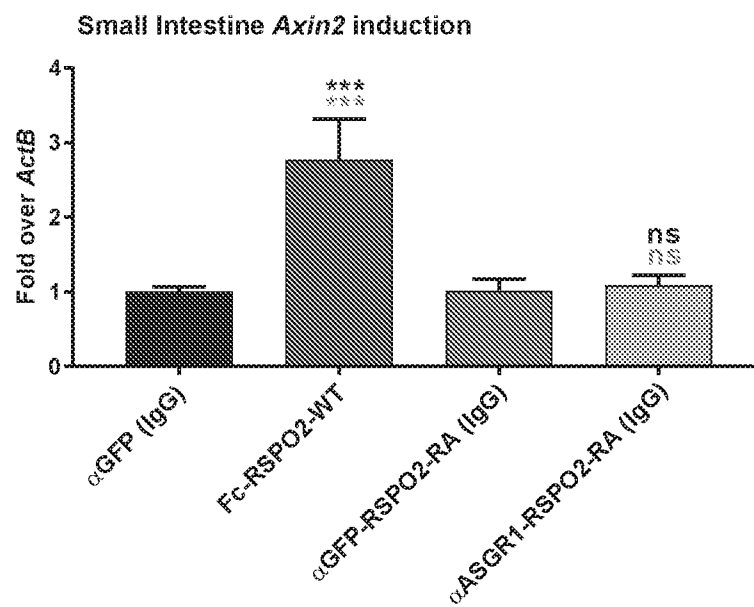


FIG. 5D

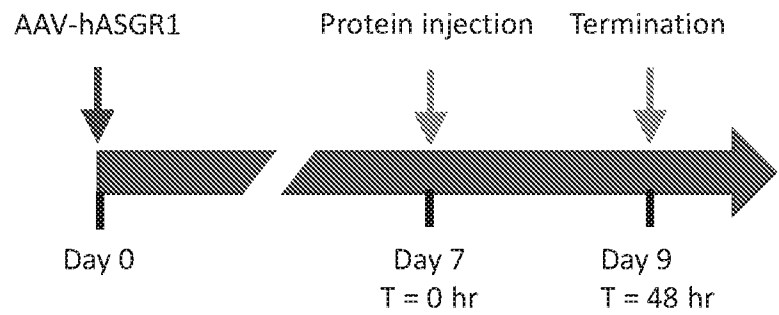


FIG. 6A

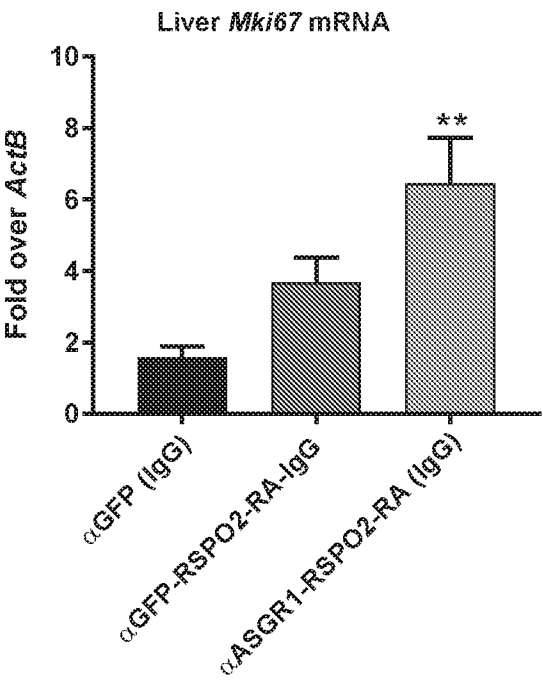


FIG. 6B

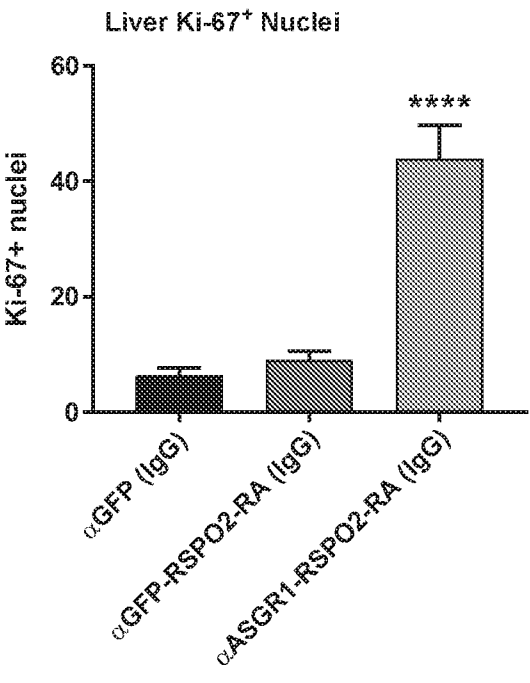


FIG. 6C

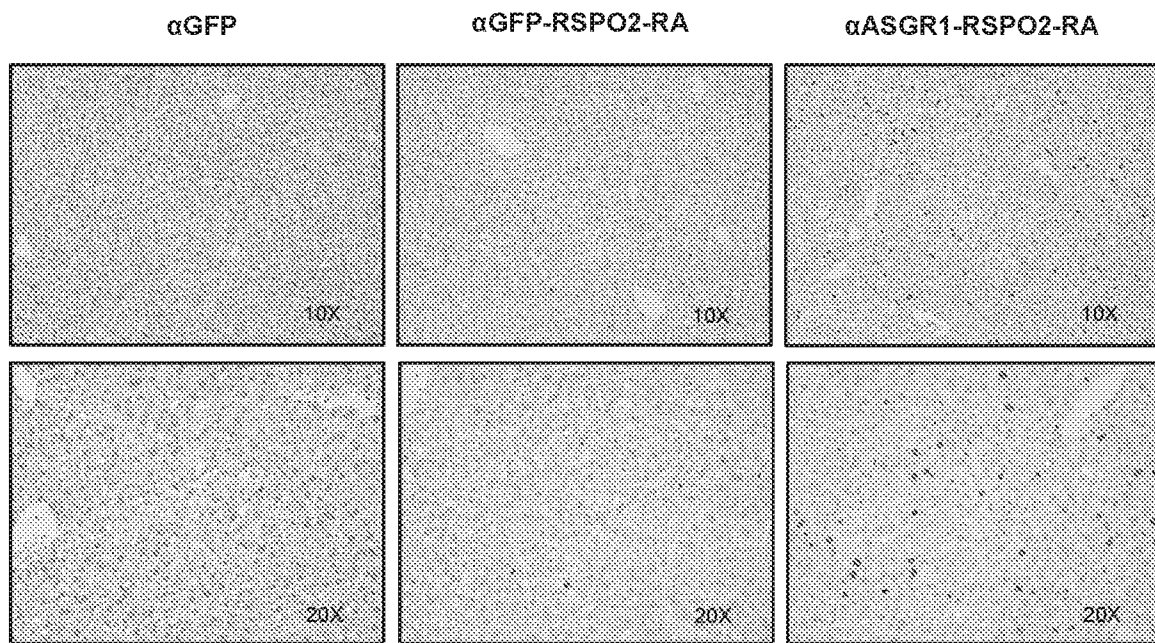


FIG. 6D

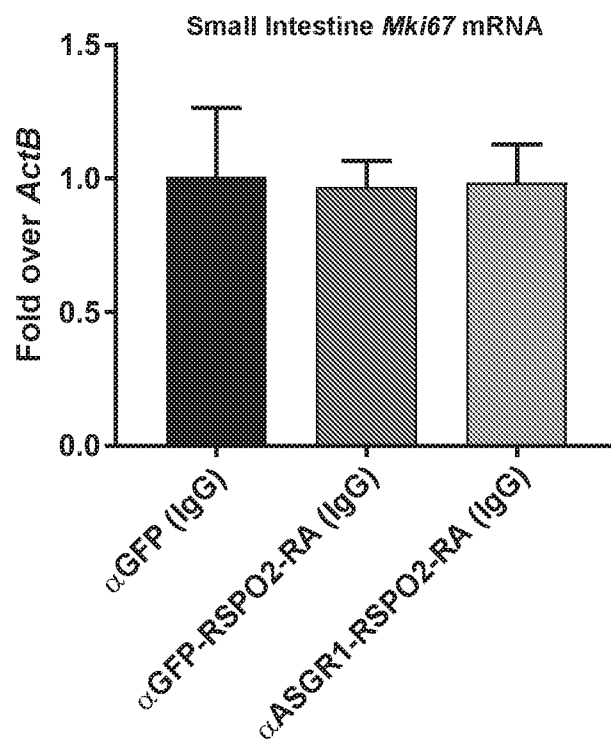


FIG. 6E

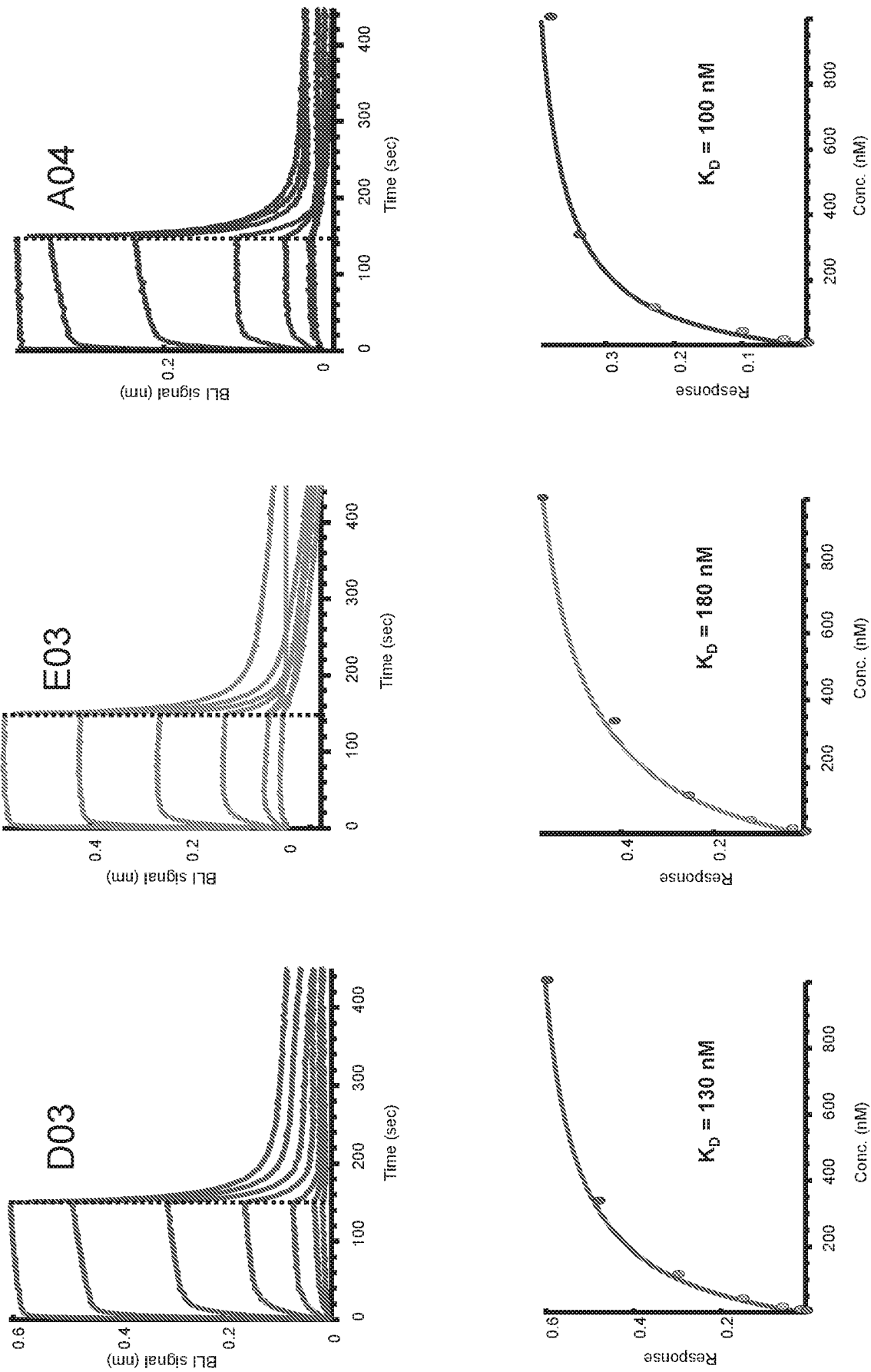


FIG. 7A

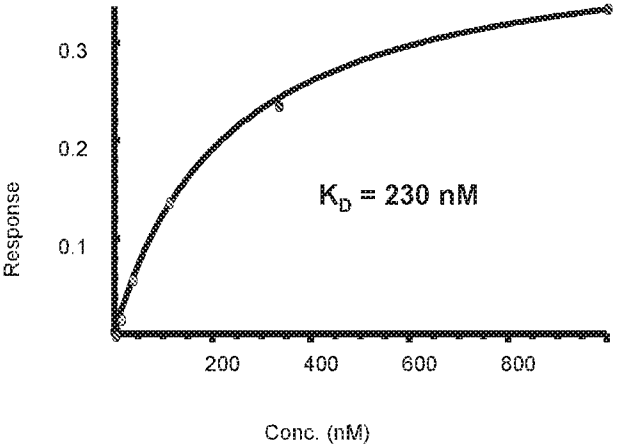
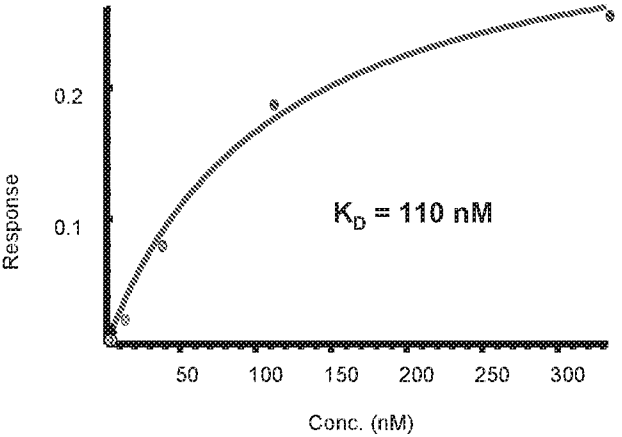
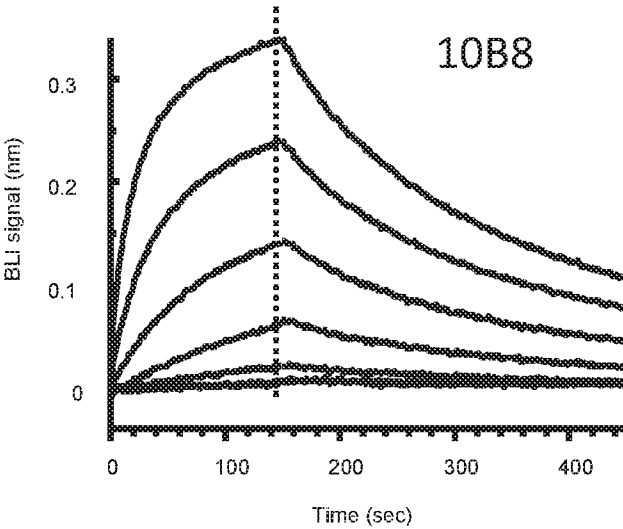
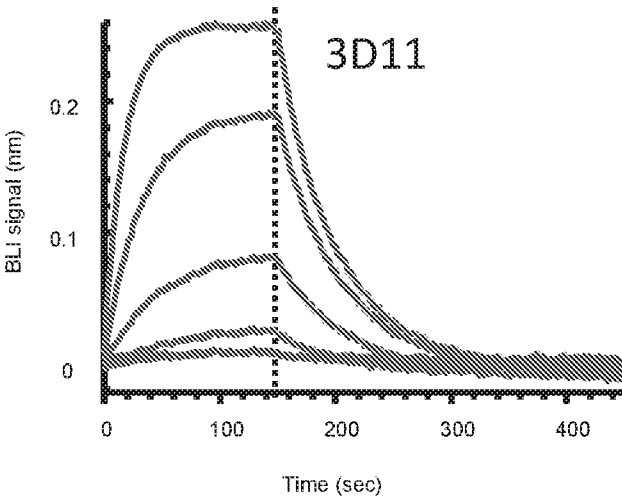


FIG. 7B

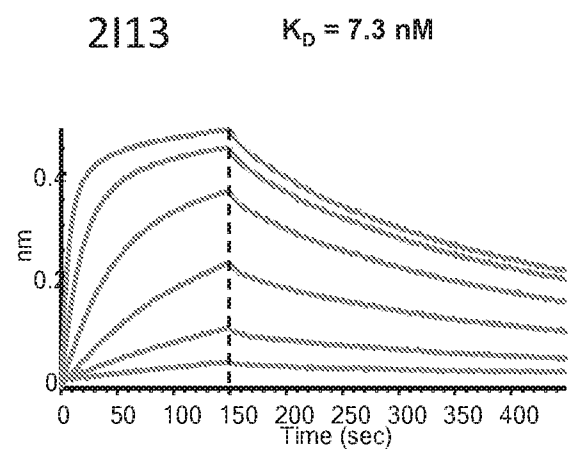
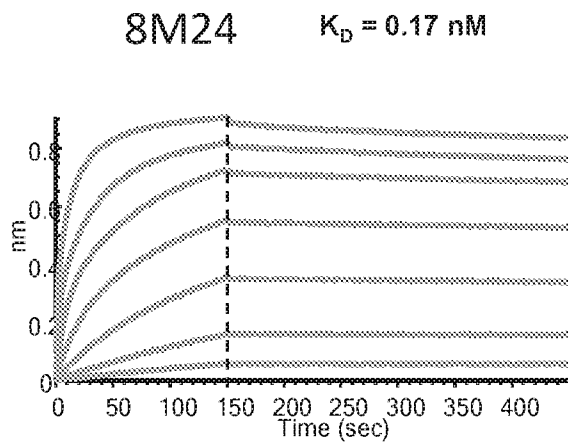


FIG. 7C

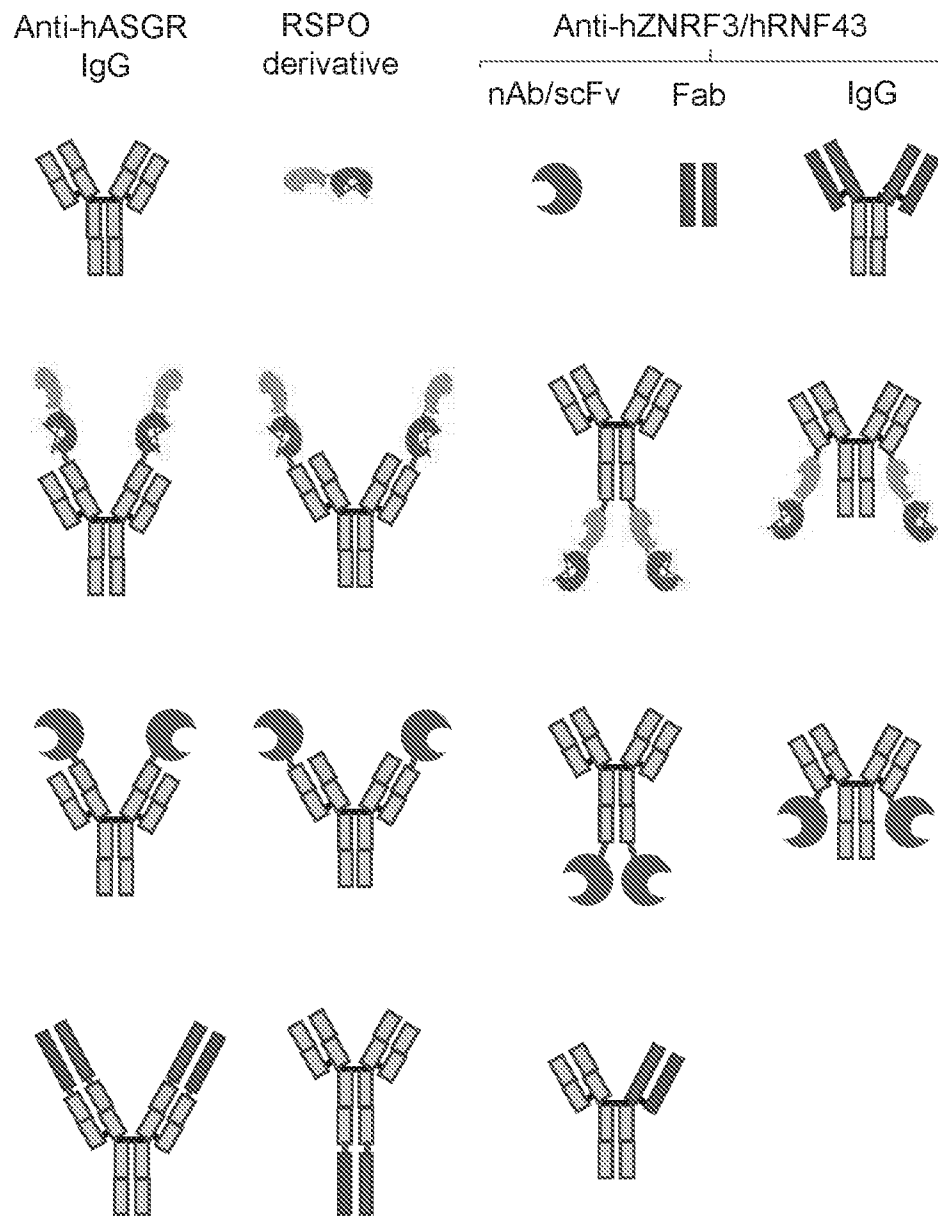


FIG. 8

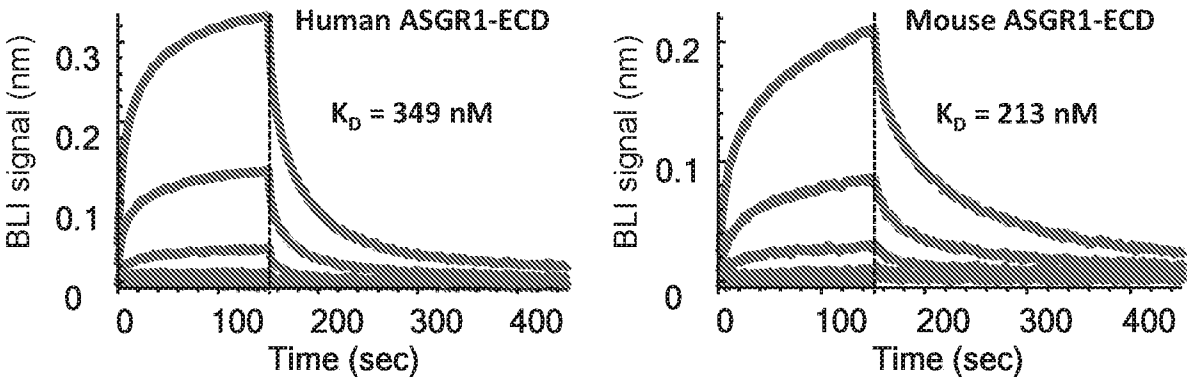


FIG. 9A

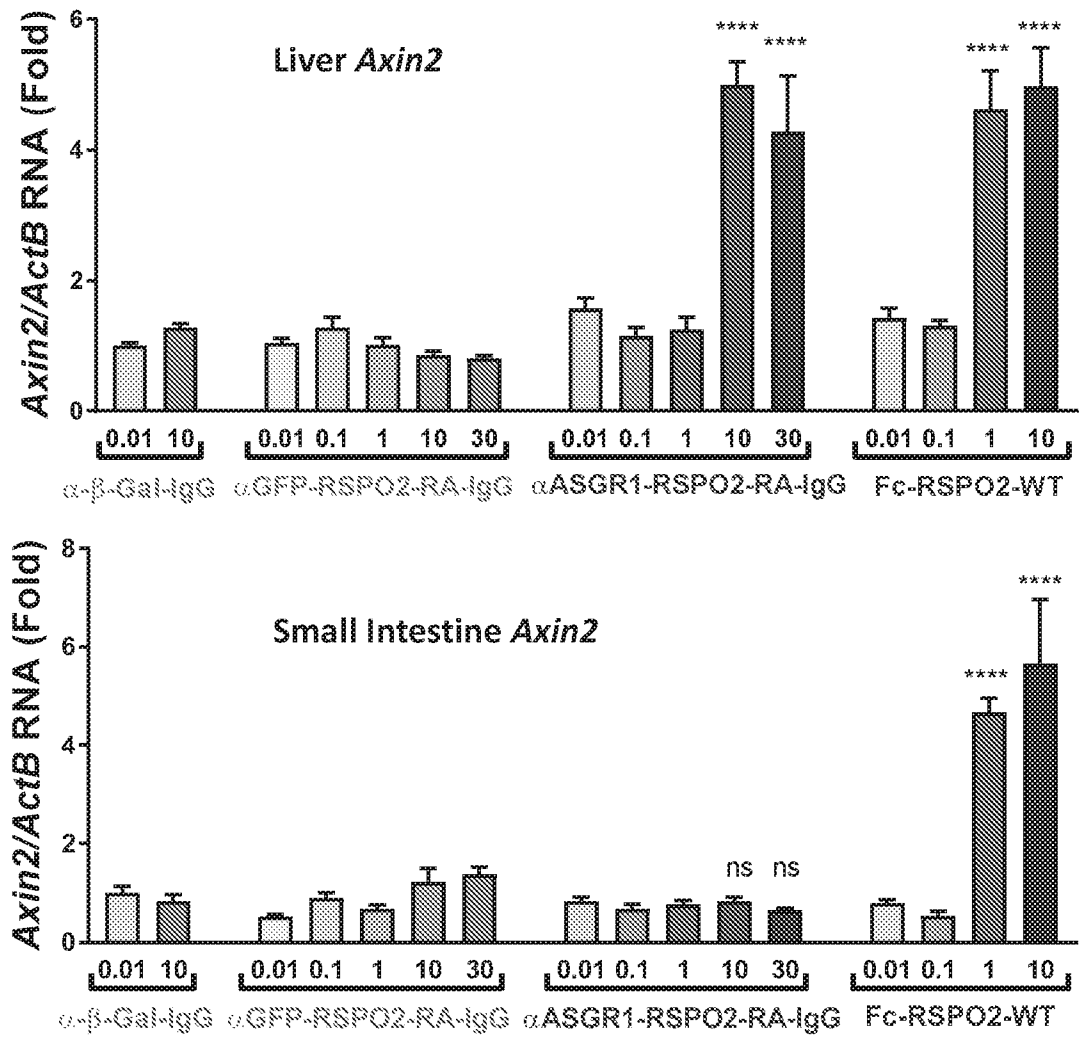


FIG. 9B

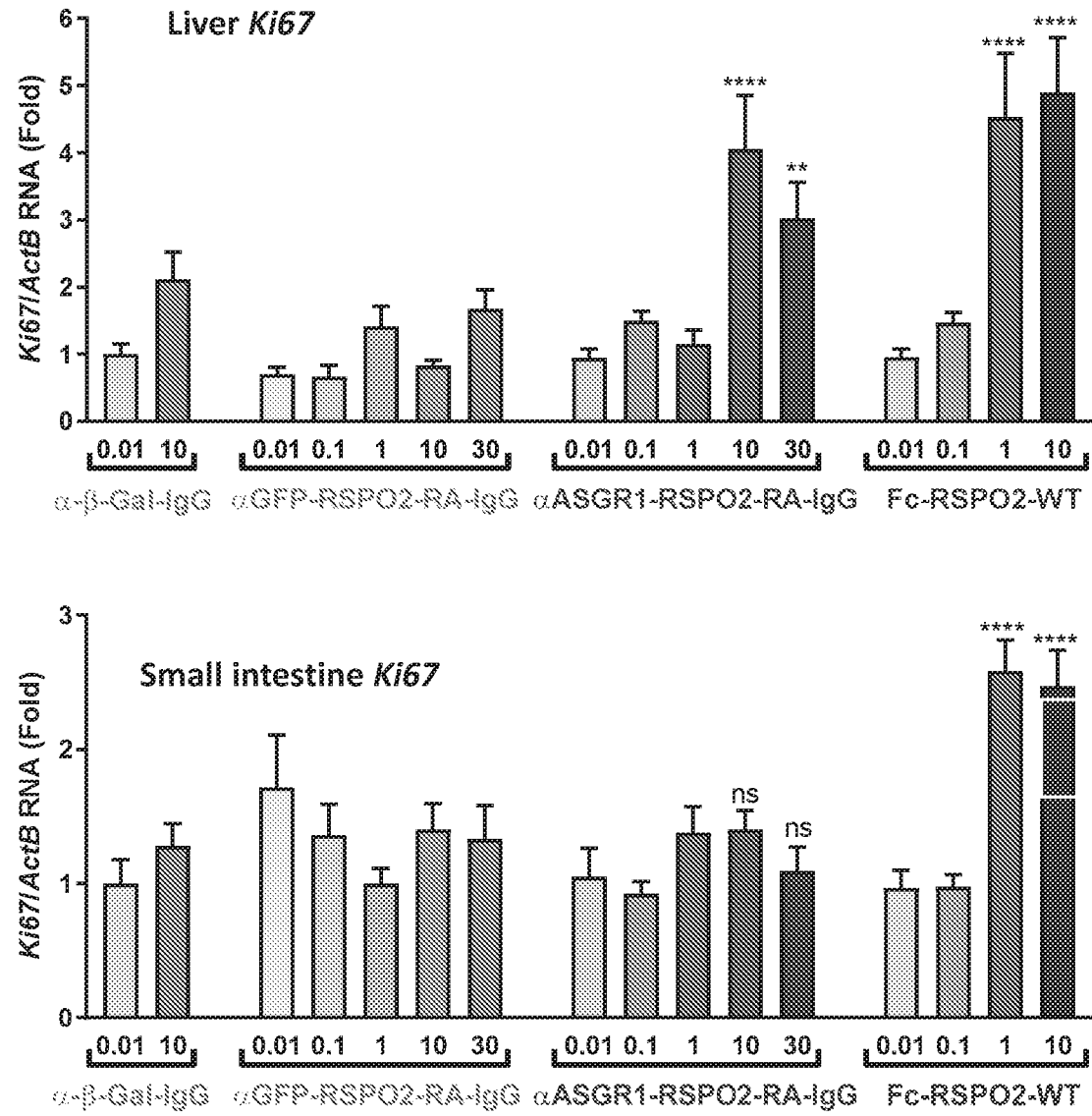


FIG. 9C

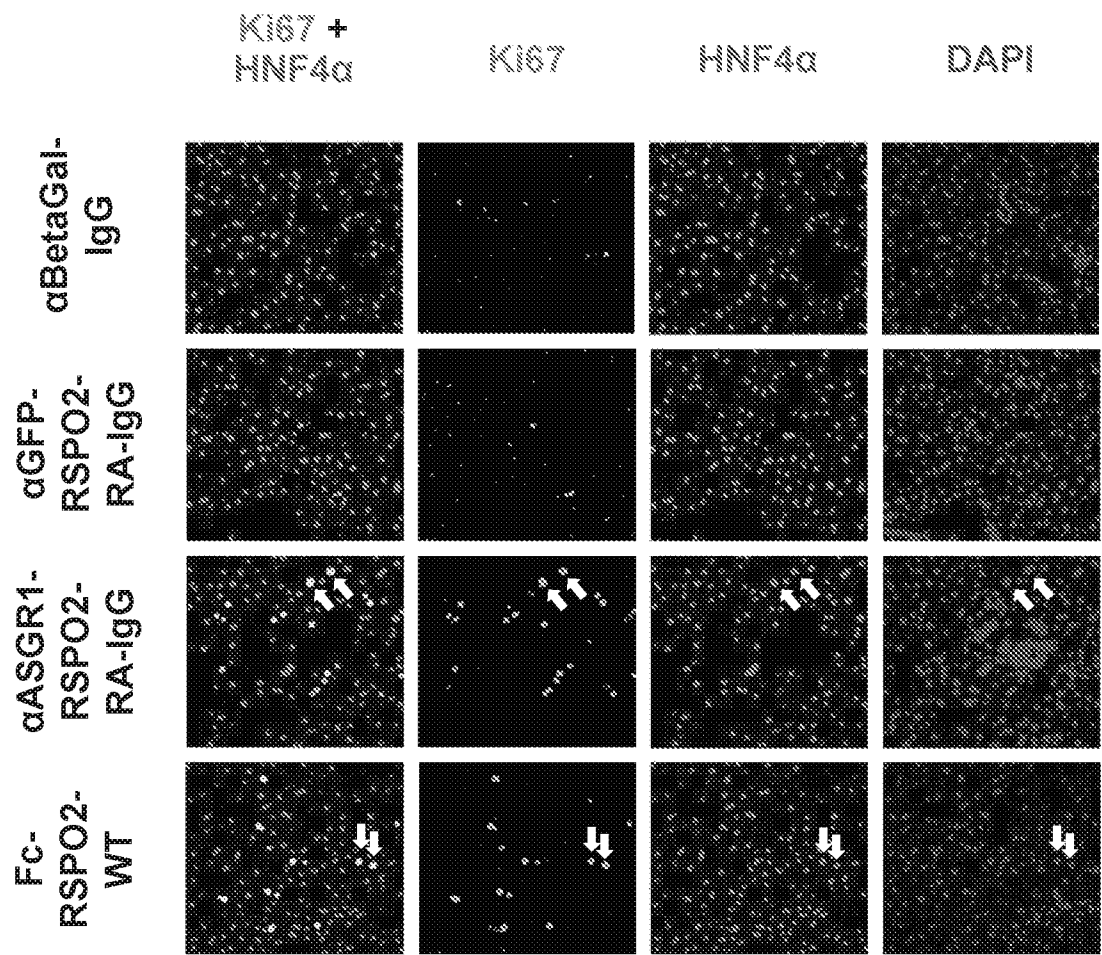


FIG. 9D

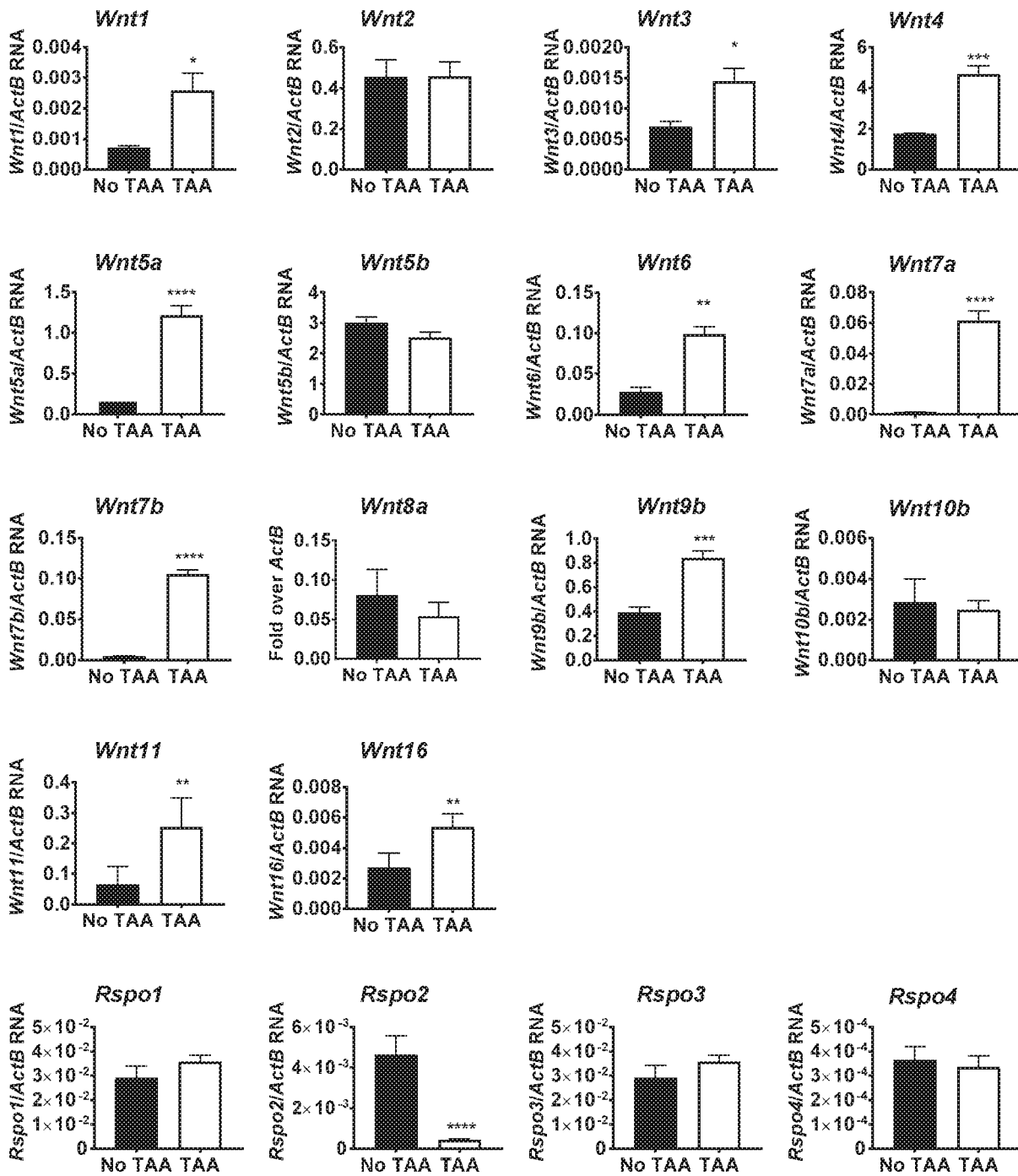


FIG. 10A

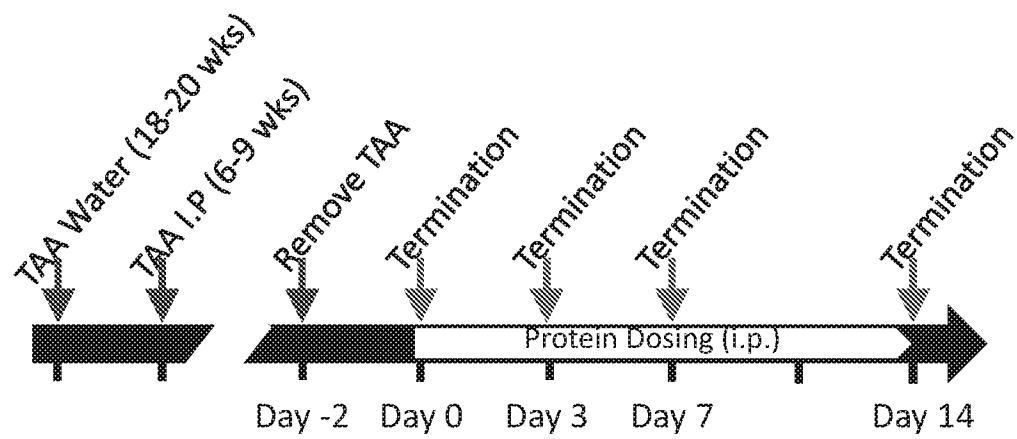


FIG. 10B

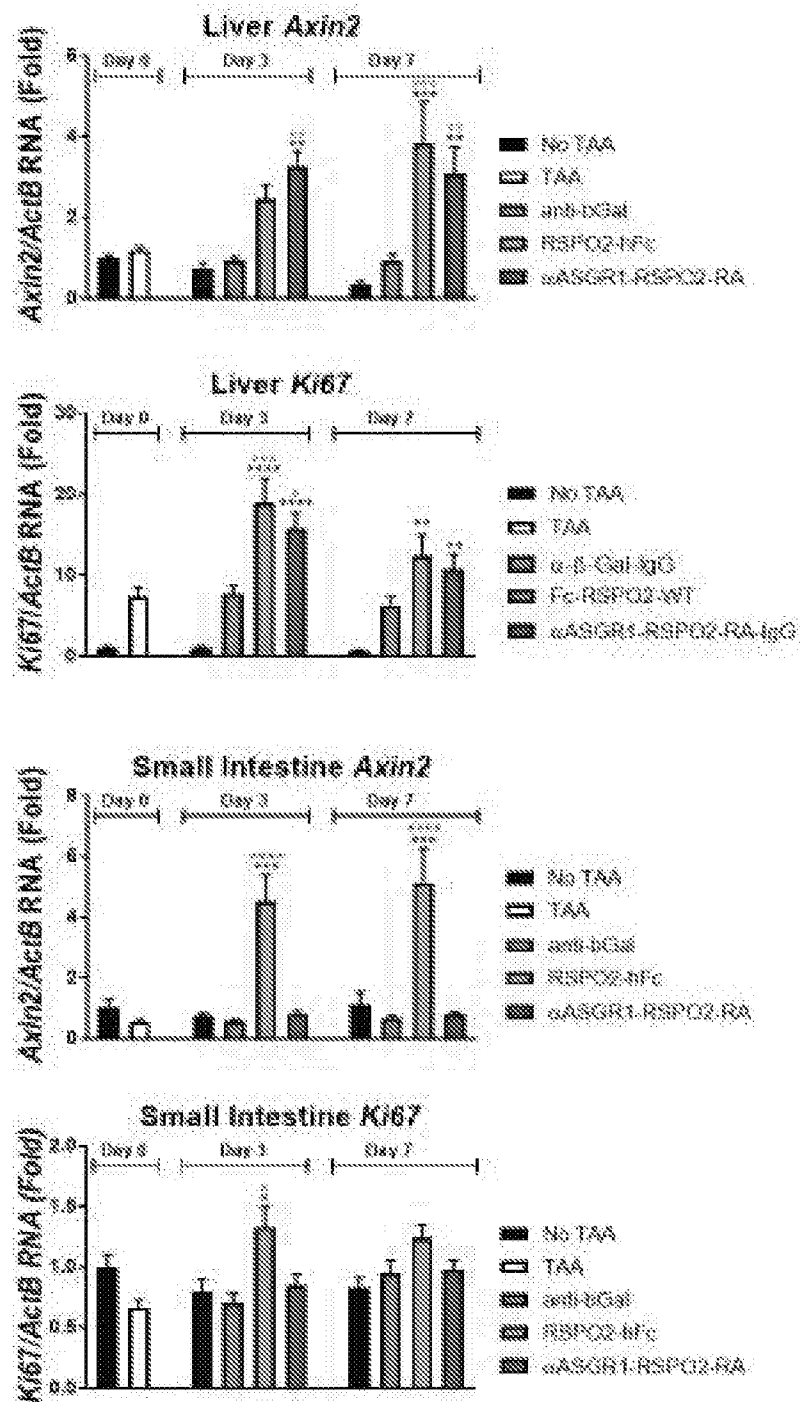


FIG. 10C

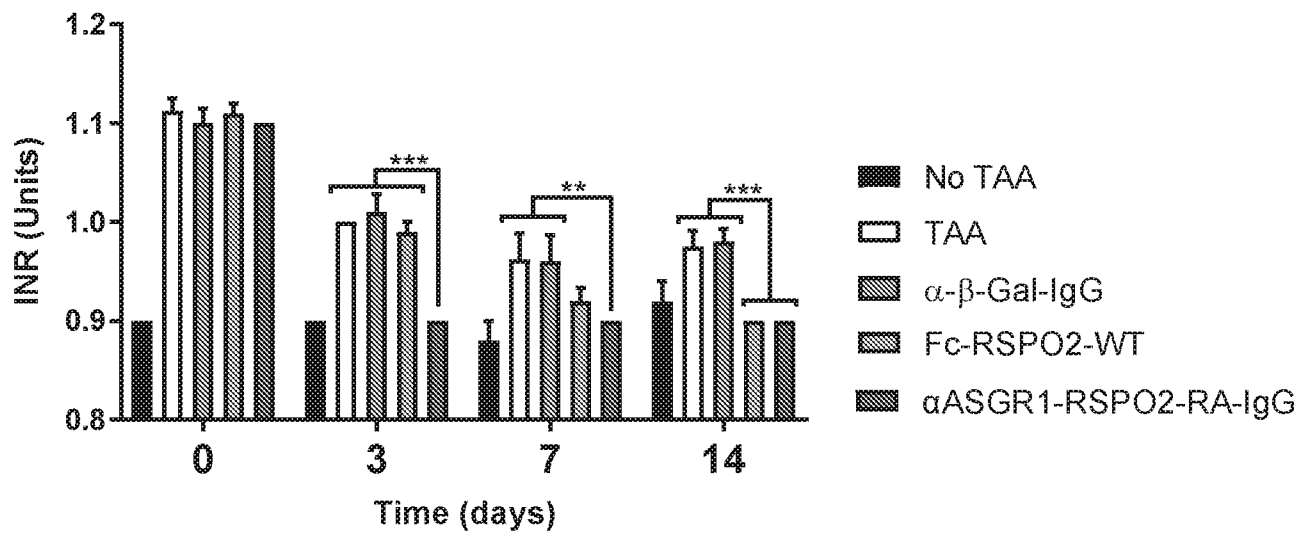


FIG. 10D

WNT SIGNAL ENHANCER SEQUENCES

Anti-GFP, RSPO2 wild type – polynucleotide (SEQ ID NO: 5)

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAGGACTCGAATGGGTGTCGGGCATTTCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACAACCTCTGTACTTGCAAATGAACTCCCTGCGGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTTCATCCGGTGGTGGAGGATCCGGAGGGCGGAGGAAG
CGGAGGAGGGGGTTTCAGACATCGAACTCACCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCTGCTCCGGCGACAACCTGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACCTCCGGG
AATACTGCCACCCTTACCATTTCGGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTGTTTGGAGGCGGTACTAA
GCTGACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTACGGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTGCAAAGTCGGCTTCT
ACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGA
GGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAGG
GCTCCCACCATCACCACCATCATCACCCTAG

Anti-GFP, RSPO2 wild type – polypeptide (SEQ ID NO: 6)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LTVVSSGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGEC
LHSCPSGYYGHRAPDMNRCARCRIENCDSFCKDFCTKCKVGFYLRGRCFDECPD
GFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11A

Anti-GFP, RSPO2 (F105R/F109A) – polynucleotide (SEQ ID NO: 7)

CAGGTCCAGTTGGTGGAAATCCGGAGGGGGTGGTCCAGCCTGGTGGAAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAGGAAAGGACTCGAATGGGTGTCGGGCATTTCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACAACACTCTGTACTTGCAAATGAACTCCCTGCGGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTTCATCCGGTGGTGGAGGATCCGGAGGCGGAGGAAG
CGGAGGAGGGGGTTCAGACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCTGCTCCGGCGACAACCTGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACCTCCGGG
AATACTGCCACCCTTACCATTTCGGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTGGAGGCGGTACTAA
GCTGACCGTGTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTC
TACCTTCACCGGGGCGAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGG
AGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAG
GGCTCCCACCATCACCACCATCATCACCCTAG

Anti-GFP, RSPO2 (F105R/F109A) – polypeptide (SEQ ID NO: 8)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LTVTVSSGGGGSGGGSGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRQKQLFFFLRREGMRQYGE
LHSCPSGYYGHRAPDMNRCARCRIENCDSCRSDACTKCKVGFYLRGRCFDECPD
GFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11B

Anti-GFP, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polynucleotide (SEQ ID NO: 9)

CAGGTCCAGTTGGTGGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACAACACTCTGTACTTGCAAATGAACTCCCTGCGGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTTCATCCGGTGGTGGAGGATCCGGAGGCGGAGGAAG
CGGAGGAGGGGGTTTCAGACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCCTGCTCCGGCGACAACCTGGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGG
AATACTGCCACCCTTACCATTTCGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACTAA
GCTGACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTACGGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTCCTGCCCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTC
TACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGG
AGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAG
GGCTCCCACCATCACCACCATCATCACCCTAG

Anti-GFP, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polypeptide (SEQ ID NO: 10)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRQKQLFFFLRAEGMAAYGE
CLHSCPSGYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECP
DGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHHH

FIGURE 11C

Anti-ASGR1, RSPO2 wild type – polynucleotide (SEQ ID NO: 11)

GAAGTGCAGCTGCTGGAATCCGGGGGGCGGACTGGTGTCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCCTGGAAAAGGCCTCGAATGGGTGTGCGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCCTTGTCACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCTGGTTCATCTACG
GAAAGAACAACCGCCCCGTCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTTACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCT
CGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCAACCATCATCACTACTAG

Anti-ASGR1, RSPO2 wild type – polypeptide (SEQ ID NO: 12)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGSGGGGSELTDPAVSVALGQTVRITCQGD SLRSYYASW
YQKPGQAPV LVIYGKNNRPSGIPDRFSGSSS GNTASLTITGAQAEDEADY YCNSLER
IGYLSYVFGGG TKLTVLGSGG SNPICKGCLSCSKDNGCSRCQQKLFFF LRREGMRQY
GECLHSCPSGY YGHRAPDMNRCARCRIENCDS CF SKDFCTKCKVGFYLHRGRCFDE
CPDGFAPLEETMEC VEGGDYKDDDDKGSHHHHHHHH

FIGURE 11D

Anti-ASGR1, RSPO2 (F105R/F109A) – polynucleotide (SEQ ID NO: 13)

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCCTGGAAAAGGCCTCGAATGGGTGTGCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCCTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCCTTGTCACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCTGGTTCATCTACG
GAAAGAACAACCGCCCGTCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCGGATTGGATACTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTTACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCT
CGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCAACCATCATCACTACTAG

Anti-ASGR1, RSPO2 (F105R/F109A) – polypeptide (SEQ ID NO: 14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGGSGGGGSELTQDPAVSVALGQTVRITCQGDSLRSYYASW
YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSLER
IGYLSYVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQKQLFFFLRREGMRQY
GECLHSCPSGYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRGRGCFDE
CPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11E

Anti-ASGR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polynucleotide (SEQ ID NO: 15)

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCCTGGAAAAGGCCTCGAATGGGTGTGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCCTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCCTTGTACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCCCTGGTCACTACG
GAAAGAACAACCGCCCGTCCGGAATTCCAGACAGGTTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCGGATTGGATACTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTCCTGCCCCCT
CGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCAACCATCATCACCCTAG

Anti-ASGR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polypeptide (SEQ ID NO: 16)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGGG
STYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGGSGGGGSELTDPAVSVVALGQTVRITCQGDSLRSYYASW
YQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSLER
IGYLSYVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQKQLFFFLRAEGMAAY
GECLHSCPSGYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDE
CPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11F

Anti-TFR1, RSPO2 wild type – polynucleotide (SEQ ID NO: 17)

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCTCTGGCGGAGGCGGGTCCGGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCTCTGCCGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACTACCTTCG
GAGGTGGCACTAAATTGGAAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTTACGGGTGCCAGCAAAAGC
TGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTC
CTGCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCCTAG

Anti-TFR1, RSPO2 wild type – polypeptide (SEQ ID NO: 18)

QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLSEGPARGFSGSGSRIDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRGSGGSPICKGCLSCSKDNGCSRCQQKLFFFLRREGMR
QYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSFCKDFCTKCKVGFYLRGRCF
DECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11G

Anti-TFR1, RSPO2 (F105R/F109A) – polynucleotide (SEQ ID NO: 19)

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCTCTGGCGGAGGCGGGTCCGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCTCTGCCGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACTACCTTCG
GAGGTGGCACTAAATTGGAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTACGGGTGCCAGCAAAAGC
TGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTC
CTGCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCCTAG

Anti-TFR1, RSPO2 (F105R/F109A) – polypeptide (SEQ ID NO: 20)

QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLESGIPARFSGSGSRITDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRGSGGSPICKGCLSCSKDNGCSRCQQKLFFFLRREGMR
QYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRGRCF
DECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11H

Anti-TFR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polynucleotide (SEQ ID NO: 21)

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCTCTGGCGGAGGCGGGTCCGGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCTGCGGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACTACCTTCCG
GAGGTGGCACTAAATTGGAAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGC
TGTTTTTCTTCTCCGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTC
CTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCCTAG

Anti-TFR1, RSPO2 (R65A/R69A/Q70A/F105A/F109A) – polypeptide (SEQ ID NO: 22)

QVQLQQSGPELVPRGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLSEGPARGFSGSGSRIDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRAEGM
AAYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRGR
CFDECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

FIGURE 11I

Fc-RSPO2 – polynucleotide (SEQ ID NO: 23)

GACAAAACCTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGGACCG
TCAGTCTTCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
TCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG
AGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCG
GAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCGTGTCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGAGGAGG
AGGCTCCGTGGCGGTGGCAGC_{ta}AATCCCATTTGCAAGGGTTGTTTGTCTTGTTT
AAAGGACAATGGGTGTAGCCGATGTCAACAGAAGTTGTTCTTCTTCCTTCGAAGA
GAAGGGATGCGCCAGTATGGAGAGTGCCTGCATTCCCTGCCCATCCGGGTACTAT
GGACACCGAGCCCCAGATATGAACAGATGTGCAAGATGCAGAATAGAAAACGTG
GATTCTTGCTTTAGCAAAGACTTTTGTACCAAGTGCAAAGTAGGCTTTTATTTGCA
TAGAGGCCGTTGCTTTGATGAATGTCCAGATGGTTTTGCACCATTAGAAGAAACC
ATGGAATGTGTGGAATGA

Fc-RSPO2 – polypeptide (SEQ ID NO: 24)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSP
GKGGGSGGGGSGGGGSSNPICKGCLSCSKDNGCSRQKQLFFFLRREGMRQYGEC
LHSCPSGYYGHRAPDMNRCARCRIENCDSFCKDFCTKCKVGFYLHRGRCFDECPD
GFAPLEETMECVE

FIGURE 11J

Anti-GFP light chain – polynucleotide (SEQ ID NO: 25)

GACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGCCCCCTGGACAGACTGCGC
GCATCTCCTGCTCCGGCGACAACCTGGGGAAGAAATACGTGTACTGGTACCAGC
AGAAGCCAGGTCAAGCCCCCTGTGCTGGTTCATCTACGGCGACGACGAAAGGCCGT
CAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGGAATACTGCCACCCTTAC
CATTTCCGGAACCCAGGCCGAGGATGAAGCGGATTACTATTGCGCGAGCTACGA
TAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACCAAGCTTACCGTCCTAGGT
CAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTC
AAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCG
TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACC
ACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGC
CTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA

Anti-GFP light chain – polypeptide (SEQ ID NO: 26)

DIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWYQQKPGQAPVLVIYGDDERPSGI
PERFSGSNSGNTATLTISGTQAEDEADYYCASYDSSHILIVFGGGTKLTVLGQPKAAP
SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN
KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 11K

RSPO2 (F105R/F109A), anti-GFP Heavy chain IgG2 – polynucleotide (SEQ ID NO: 27)

AACCCAATTTGCAAGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGAGGAGGAGGCTCCGGTGGCGGTGGCAGCCAGGTCCAGTTGGT
GGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAAGCCTGCGCCTCTCATGCGC
CGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGGTGAGACAGGCACCC
GGAAGGAGCTCGAATGGGTGTCGGGCATTTCTCGATCGGGTCAAACACCTAT
TACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGGATAACAGCAAGAAC
ACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACACCGCCGTGTACTACT
GTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACAGGGTACCCTCGTGA
CCGTGTCGAGTGCTAGCACCAAGGGGCCATCGGTCTTCCCCCTGGCGCCCTGCTC
CAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT
CCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGCGGCGTGCA
CACCTTCCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTG
ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACA
AGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGT
GCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTTCCCCC
AAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGT
GGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCA
CGTTCGGTGTGGTTCAGCGTCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCGAGAAAAC
CATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
CTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2 (F105R/F109A), anti-GFP Heavy chain IgG2 – polypeptide (SEQ ID NO: 28)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECEVEGGGS
GGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGL
EWVSGISSIGSNTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWYK
TYIDVWGQGLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTV
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE
KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPG
K

FIGURE 11L

Anti-ASGR1 light chain – polynucleotide (SEQ ID NO: 29)

GACATCGAGCTCACCCAGGACCCCGCTGTGTCCGTGGCCTTGGGACAGACCGTG
CGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATTACGCCTCGTGGTACCAG
CAGAAGCCTGGTCAAGCGCCGGTCCTGGTCATCTACGGAAAGAACAACCGCCCG
TCCGGAATTCCAGACAGGTTTCAGCGGATCCAGCTCGGGGAACACCGCCTCACTG
ACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACTACTACTGCAACTCCCTG
GAGCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGGTACCAAGCTTACCGTCC
TAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA
GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA
GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGA
GACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCT
GAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC
GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA

Anti-ASGR1 light chain – polypeptide (SEQ ID NO: 30)

DIELTQDPAVSVALGQTVRITCQGDLSRSYYASWYQQKPGQAPVLVIYGKNNRPSGI
PDRFSGSSSGNTASLTITGAQAEDEADYYCNSLERIGYLSYVFGGGTKLTVLGQPKA
APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSN
NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 11M

RSPO2 (F105R/F109A), anti-ASGR1 Heavy chain IgG2 – polynucleotide (SEQ ID NO: 31)

AACCCAATTTGCAAGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGAGGAGGAGGCTCCGGTGGCGGTGGCAGCGAAGTGCAGCTGCT
GGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTCAGACTGTCCTGTGC
CGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGTGAGACAGGCCCT
GGAAGAGGCTCGAATGGGTGTGCGCTATCTCCGGATCGGGGGGATCTACTTAC
TACGCCGACTCCGTGAAGGGCCGGTTCCTATCTCGAGGGACAACCTCCAAGAAT
ACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACCGCGGTGTATTACT
GCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACTGGGGACAGGGAA
CCCTTGTCACCGTGTCGAGTGCTAGCACCAAGGGGCCCATCGGTCTTCCCCCTGGC
GCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAA
GGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAG
CGGCGTGACACCTTCCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
GTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT
TGTGTCGAGTGCCACCGTGCCACGACCACTGTGGCAGGACCGTCAGTCTTCC
TCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGT
TCAACAGCACGTTCCGTGTGGTCAGCGTCTCACCCTTGTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACACAGGTGTACAC
CCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT
GGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTT
CTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT
CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGC
CTCTCCCTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), anti-ASGR1 Heavy chain IgG2 – polypeptide (SEQ ID NO: 32)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLRHGRCFDECPDGFAPLEETMECEVEGGGGS
GGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE
WVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDFSS
RRWYLEYWGGQTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDK
TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF
N WYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QDWLNGKEYKCKVSNKGLP
APIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPMLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSL
SPGK*

FIGURE 11N

Anti-GFP Heavy chain IgG1 – polynucleotide (SEQ ID NO: 33)

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAGGACTCGAATGGGTGTCGGGCATTTCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTGAGTGTAGCACCAAGGGCCCATCGGTCTTCCCC
CTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACCTCACACATGCCACCCGTGCCAGCACCTGAACTCCTGGG
GGGACCGTCAGTCTTCTCTTCCCCCCTCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG
GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

Anti-GFP Heavy chain IgG1 – polypeptide (SEQ ID NO: 34)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDS DGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK*

FIGURE 110

Human ASGR1 Extracellular Domain – polynucleotide (SEQ ID NO: 35)

CAGAACAGCCAGCTCCAGGAAGAACTGAGGGGCTCCGCGAAACCTTCTCCAAC
TTCACGGCTTCGACCGAAGCTCAAGTCAAGGGGTTGTCCACACAAGGCGGCAAC
GTCGGACGCAAGATGAAGTCGCTGGAGTCCCAGCTGGAAAAGCAGCAGAAGGA
TCTCTCCGAGGATCACAGCTCACTGCTGTTGCACGTGAAGCAGTTCGTGTCGGAC
CTGAGGTCCCTGAGCTGTCAGATGGCGGCACTGCAGGGAAACGGTTCCGAAAGA
ACTTGCTGCCCTGTGAATTGGGTGGAGCACGAGAGAAGCTGCTACTGGTTCTCGC
GGTCCGGCAAAGCCTGGGCGGACGCCGACAACCTATTGTCCGGCTGGAGGATGCGC
ACCTGGTGGTCGTGACCTCCTGGGAGGAACAGAAGTTTGTGCAGCACCATATCG
GTCCCGTGAACACTTGGATGGGGCTGCACGACCAAAACGGACCGTGGAAATGGG
TGGATGGGACTGATTACGAAACCGGATTCAAGAACTGGCGCCCAGAGCAGCCCG
ACGATTGGTACGGACATGGACTGGGGGGCGGAGAGGACTGCGCCCACTTCACCG
ACGACGGCCGGTGGAAACGACGACGTGTGCCAGCGGCCGTACCGCTGGGTCTGCG
AAACCGAGCTGGACAAGGCCAGCCAGGAGCCACCTCTCCTTTGA

Human ASGR1 Extracellular Domain – polypeptide (SEQ ID NO: 36)

QNSQLQEELRGLRETFSNFTASTEAVKGLSTQGGNVGRKMKSLESQLEKQQKDLS
EDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERTCCPVNWVEHERSCYWFSRSGK
AWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTWMGLHDQNGPWKWVDG
TDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDDGRWNDDVCQRPYRWVCETE
LDKASQEPPLL

FIGURE 11P

Human ASGR2 Extracellular Domain – polynucleotide (SEQ ID NO: 37)

AGGGGCGCACAGCTGCAAGCCGAGCTGCGGTCCCTGAAGGAAGCTTTCTCAAAC
TTCTCGAGCTCGACCCTCACC GAAGTGCAGGCCATTAGCACCCACGGGGGTCCG
TGGGGGACAAGATCACCTCGCTGGGAGCGAAGCTGGAGAAGCAGCAGCAAGAC
CTCAAGGCCGACCACGACGCGCTGCTGTTCCACTTGAAGCACTTCCCAGTGGACT
TGCGGTTCGTGGCGTGCCAGATGGAGCTGCTGCACTCCAATGGGAGCCAGAGAA
CTTGTTGCCCTGTGAAC TGGGTGGAACACCAGGGATCCTGCTACTGGTTT AGCCA
CTCCGGAAAGGCCTGGGCGGAAGCCGAGAAGTACTGCCAGCTTGAGAACGCGCA
CCTGGTCGTGATCAACTCCTGGGAAGAACAGAAAGTTCATTGTGCAACACACTAA
CCCGTTCAACACCTGGATCGGCCTGACCGACTCCGACGGCTCATGGAAATGGGT
GGACGGAACCGATTACCGGCATAACTATAAGA ACTGGGCCGTGACTCAGCCGGA
TAATTGGCACGGACACGAGCTGGGTGGATCCGAGGACTGCGTCGAAGTGCAGCC
CGACGGCAGATGGAACGATGACTTCTGTCTGCAAGTGTACCGCTGGGTCTGCGA
GAAGCGCCGCAACGCCACTGGCGAAGTGGCTTGA

Human ASGR2 Extracellular Domain – polypeptide (SEQ ID NO: 38)

RGAQLQAELRSLKEAFSNFSSSTLTEVQAISTHGGSVGDKITSLGAKLEKQQQDLKA
DHDALLFHLKHFPVDLRFVACQMELLHSNGSQRTCCPVNWVEHQGSCYWFSHSGK
AWAEAEKYCQLENAHLVVINSWEEQKFIVQHTNPFNTWIGLTDSDGSWKWVDGTD
YRHNYKNWAVTQPDNWHGHELGGSEDCVEVQPDGRWNDDFCLQVYRWVCEKRR
NATGEVA

FIGURE 11Q

Cynomologous ASGR1 Extracellular Domain – polynucleotide (SEQ ID NO: 39)

CAAAACGCCCAGCTGCAGCGGGAGCTGCGGGGCCTGAGAGAGACGCTCAGCAA
CTTCACAGCGAGCACCGAGGCCCAGGTCAAGGGCTTGAGCACCCAGGGAGGCAA
TGTGGGAAGAAAGATGAAGTCGCTGGAGTCCCAGCTGGAGAAACAGCAGAAGG
ACTTGAGTGAAGATCACTCCAGCCTGCTGCTCCACGTGAAGCAGTTTCGTGTCTGA
CCTGCGGAGCCTGAGCTGTCAGATGGCGGGCGCTCCAGGGCAATGGCTCGGAAAG
GGCCTGCTGCCCAGTCAACTGGGTGGAGCACGAGCGCAGCTGCTACTGGTTCTCT
CGCTCCGGGAAGGCCTGGGCCGACGCCGACAATACTGCCGGCTGGAGGACGCG
CACCTGGTGGTGGTCACGTCCTGGGAGGAGCAGAAATTTGTCCAGCACACATA
GGTCCTGTGAACACCTGGATGGGCCTCCACGACCAAAACGGGCCCTGGAAGTGG
GTGGACGGGACGGACTACGAGACGGGCTTCAAGAACTGGAGACCGGAGCAGCC
GGACGACTGGTACGGCCACGGGCTCGGGGGAGGGGAGGACTGTGCCCACTTCAC
CGACGACGGCCGCTGGAACGACGACGTCTGCCAGAGGCCCTACCGCTGGGTCTG
CGAGACAGAGCTGGACAAGGCCAGTCAGGAGCCACCTCTCCTT

Cynomologous ASGR1 Extracellular Domain – polypeptide (SEQ ID NO: 40)

QNAQLQRELRLRETLNFTASTEAVKGLSTQGGNVGRKMKSLQLEKQQKDL
EDHSSLLLHVKQFVSDLRLSLCQMAALQNGSERACCPVNWVEHERSCYWFSRSGK
AWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTWMGLHDQNGPWKWVDG
TDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDDGRWNDDVCQRPYRWVCETE
LDKASQEPPLL

FIGURE 11R

Cynomologous ASGR2 Extracellular Domain – polynucleotide (SEQ ID NO: 41)

CAAAGTGCACAGCTGCAAGCAGAGaTGcGGAGCCTGAAGGAAGCTTTCAGCAAC
TTCTCCTCGAGCACGCTGgTGGAGGTCCATGCTCTCGGCACCCACGGAGGCAGCG
TGGGTGACAAGATCACATCCCTAGGAGACAAGTTGGAGAAACAGCAGCAcGACC
TGAAAGCAGATCATGACATCCTGCTCCTCCATCTGAAGCACTTCCCCGTGGACCT
GCGCTTCGTGGCCTGCCAGATGGAGCTCCTCCACAGCAACGGCTCCCAAAGGAC
CTGCTGCCCTGTCAACTGGGTGGAGCACCAAGGCAGCTGCTACTGGTTCTCTCGC
TCCGGGAAGGCCTGGGCCGAGGCGGAGAAGTACTGCCAGCTGGAGAACTCACAC
CTGGTGGTTCATCAACTCCTGGGAGGAGCAGAAATTCATTGTACAACACACGAAC
CCCTTCAATACCTGGATAGGTCTCACGGACAGTGATGGCTCCTGGAAATGGGTGG
ACGGCACAGACTATAGGCACAACACTACAAGAACTGGGCTGTCACTCAGCCAGATG
ATTGGCACGGGCATGAGCTGGGCGGAAGTGAAGACTGTGTTGAAGTCCGGCCGG
ATGGCCGCTGGAACGATGATTTCTGCCTGCAGGTGCACCGCTGGGTGTGTGAGA
AGAGGCGGAATGCCACCGGCGAGGCAGCCTGA

Cynomologous ASGR2 Extracellular Domain – polypeptide (SEQ ID NO: 42)

QSAQLQAEMRSLKEAFSNFSSSTLVEVHALGTHGGSVGDKITSLGDKLEKQQHDLK
ADHDILLHLKHFPVDLRFVACQMELLHSNGSQRTCCPVNWVEHQGSCYWFSRSGK
AWAEAEKYCQLENSHLVVINSWEEQKFIVQHTNPENTWIGLTDSDGSWKWVDGTD
YRHNYKNWAVTQPDDWHGHELGGSEDCVEVRPDGRWNDDFCLQVHRWVCEKRR
NATGEAA

FIGURE 11S

Human RNF43 Extracellular Domain – polynucleotide (SEQ ID NO: 43)

CAGAAAGCTATTATCAGAGTGATCCCCTTGAAAATGGACCCACAGGAAAACCTG
AATCTCACTTTGGAAGGTGTGTTTGCTGGTGTGCTGAAATAACTCCAGCAGAAG
GAAAATTAATGCAGTCCCACCCGCTGTACCTGTGCAATGCCAGTGATGACGACA
ATCTGGAGCCTGGATTTCATCAGCATCGTCAAGCTGGAGAGTCCTCGACGGGCCCC
CCGCCCCCTGCCTGTCACTGGCTAGCAAGGCTCGGATGGCGGGTGAGCGAGGAGC
CAGTGCTGTCCTCTTTGACATCACTGAGGATCGAGCTGCTGCTGAGCAGCTGCAG
CAGCCGCTGGGGCTGACCTGGCCAGTGGTGTGATCTGGGGTAATGACGCTGAG
AAGCTGATGGAGTTTGTGTACAAGAACCAAAAGGCCCATGTGAGGATTGAGCTG
AAGGAGCCCCCGGCCTGGCCAGATTATGATTGA

Human RNF43 Extracellular Domain – polypeptide (SEQ ID NO: 44)

QKAHIVIPKMDPTGKLNLLEGVFAGVAEITPAEGKLMQSHPLYLCNASDDDNLEP
GFISIVKLESPRRAPRPCLSLASKARMAGERGASAVLFDITEDRAAAEQLQQPLGLTW
PVVLIWGNDAEKLMEFVYKNQKAHVRIELKEPPAWPDYD

FIGURE 11T

Human ZNRF3 Extracellular Domain – polynucleotide (SEQ ID NO: 45)

AAGGAGACGGCGTTTCGTGGAGGTGGTGCTGTTCGAGTCGAGCCCAAGCGGCGAT
TACACCACCTACACCACCGGCCTCACGGGGCCGCTTCTCGCGGGCCGGGGCCACG
CTCAGCGCCGAGGGCGAGATCGTGCAGATGCACCCACTGGGCCTATGTAATAAC
AATGACGAAGAGGACTTGTATGAATATGGCTGGGTAGGAGTGGTGAAGCTGGAA
CAGCCAGAATTGGACCCGAAACCATGCCTCACTGTCCTAGGCAAGGCCAAGCGA
GCAGTACAGCGGGGAGCTACTGCAGTCATCTTTGATGTGTCTGAAAACCCAGAA
GCTATTGATCAGCTGAACCAGGGCTCTGAAGACCCGCTCAAGAGGCCGGTGGTG
TATGTGAAGGGTGCAGATGCCATTAAGCTGATGAACATCGTCAACAAGCAGAAA
GTGGCTCGAGCAAGGATCCAGCACCGCCCTCCTCGACAACCCACTGAATACTTTG
ACATGTGA

Human ZNRF3 Extracellular Domain – polypeptide (SEQ ID NO: 46)

KETAFVEVVLFESSPSGDYTTYTTGLTGRFSRAGATLSAEGEIVQMHPGLGLCNNNDE
EDLYEYGWVG VVKLEQPELDPKPCLTVLGKAKRAVQRGATAVIFDVSENPEAIDQL
NQGS EDPLKRPVVYVKGADAIKLMNIVNKQKVARARIQHRPPRQPTEYFDM

FIGURE 11U

Anti- β -Gal light chain – polynucleotide (SEQ ID NO: 155)

CAGAGCGTGTTAACCCAGCCCGCCAGCGTGAGCGGCAGCCCCGGCCAGAGCATC
ACCATCAGCTGCGCCGGCACCAGCAGCGACGTGGGCGGCTACAACTACGTGAGC
TGGTACCAGCAGCACCCCGGCAAGGCCCCCAAGCTGATGATCTACGAGGACAGC
AAGAGACCCAGCGGCGTGAGCAACAGATTCAGCGGCAGCAAGAGCGGCAACAC
CGCCAGCCTGACCATCAGCGGCCTGCAGGCCGAGGACGAGGCCGACTACTACTG
CAGCAGCTACACCACCAGAAGCACCCAGAGTGTTTCGGCGGCGGCACCAAGCTGGC
CGTGCTGGGTTCAGCCCAAGGCTGCCCCCTCGGTCACCTCTGTTCCCGCCCTCCTCT
GAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACC
CGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA
GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGC
TATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG
GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA

Anti- β -Gal light chain – polypeptide (SEQ ID NO: 156)

QSVLTQPASVSGSPGQSITISCAGTSSDVGGYNYVSWYQQHPGKAPKLMYEDSKRP
SGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLAVLGQPK
AAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS
NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 11V

Anti- β -Gal Heavy chain IgG1-LALAPG – polynucleotide (SEQ ID NO: 157)

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAA
CTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGACCCC
AGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGA
AAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGCCCACCGTGCCAGCAC
CTGAAGCCGCGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACA
CCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA
GGTCTCCAACAAAGCCCTCGGAGCCCCCATCGAGAAAACCATCTCCAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGAT
GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCA
CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGT
GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Anti- β -Gal Heavy chain IgG1-LALAPG – polypeptide (SEQ ID NO: 158)

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFDVKGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
VLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

FIGURE 11W

Anti- β -Gal Heavy chain IgG2 – polynucleotide (SEQ ID NO: 159)

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTCACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAA
CTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCC
AGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
CAGTTGAGCGCAAATGTTGTGTCGAGTGCCCCACCGTGCCCAGCACCACTGTGGC
AGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCATGCTGGA
CTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Anti- β -Gal Heavy chain IgG2 – polypeptide (SEQ ID NO: 160)

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFDVKGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVERKCCVECPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDS
DGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*

FIGURE 11X

Anti-ASGR1 VH-CH1 – polynucleotide (SEQ ID NO: 161)

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCCTACTATCTCGAGGGAC
AACTCCAAGAATAACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCCTTGTCACCGTGTCCAGCGCTAGCACCAAGGGGCCCATCGG
TCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA
GCCCCAAATCTTGTGGATCCGGCTCCGGACATCATCATCACCATCAC

Anti-ASGR1 VH-CH1 – polynpeptide (SEQ ID NO: 162)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGS
GSGHHHHHH

FIGURE 11Y

Murine ASGR1 Extracellular Domain – polynucleotide (SEQ ID NO: 163)

CAAAATTCCCAACTCCGGGAAGATCTGCTGGCTCTAAGGCAGAATTTTCAGCAAC
CTCACTGTGAGCACTGAGGACCAGGTCAAGGCCCTGAGCACCCAGGGAAGTAGT
GTGGGAAGAAAGATGAAGTTAGTGGAGTCGAAGCTGGAAAAACAGCAGAAGGA
TCTGACTGAAGATCACTCCAGTTTGCTACTGCACGTGAAGCAGTTAGTGTCTGAC
GTGCGAAGCTTGAGCTGCCAGATGGCTGCATTTTCGGGGCAATGGCTCTGAAAGG
ACCTGCTGCCCCATCAACTGGGTGGAGTATGAAGGCAGCTGCTACTGGTTCTCCA
GCTCTGTGAGGCCTTGGAAGCTGACAAGTACTGCCAGCTGGAAAATGCCC
ATCTGGTGGTGGTGACCTCCAGGGATGAGCAGAACTTCCTCCAGCGCCACATGG
GCCCCTTAAACACTTGGAATTGGCCTAACTGACCAGAACGGGCCCTGGAAATGGG
TGGATGGAACAGACTACGAGACAGGCTTCCAGAATTGGAGACCAGAGCAGCCAG
ATAACTGGTACGGACATGGGCTTGGAAGGAGGCGAGGACTGTGCCCACTTCACGA
CGGATGGCCGCTGGAATGACGACGTCTGCAGGAGGCCCTACCGCTGGGTCTGTG
AGACAAAGTTGGATAAGGCTAATTCGGCTCCGGAGGTCTTAATGATATTTTCGA
GGCTCAGAAGATTGAGTGGCATGAAGGATCCGGCTCCCACCACCATCATCACCA
CCACCAC

Murine ASGR1 Extracellular Domain – polypeptide (SEQ ID NO: 164)

QNSQLREDLLALRQNFSNLTVSTEDQVKALSTQGSSVGRKMKLVESKLEKQQKDLT
EDHSSLLLHVKQLVSDVRSLSQMAAFRGNGSERTCCPINWVEYEGSCYWFSSSVRP
WTEADKYCQLEN AHLVVVTSRDEQNFLQRHMGPLNTWIGLTDQNGPWKWVDGTD
YETGFQNRPEQPDNWYGHGLGGGEDCAHFTTDGRWNDDVCRRPYRWVCETKLD
KANSGSGGLNDIFEAQKIEWHEGSGSHHHHHHHH

FIGURE 11Z

Anti- β -Gal Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SID NO: 186)

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG
CCCTGGGCTGCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAA
CTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCC
AGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
CAGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCCAGCACCACTGTGGC
AGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCATGCTGGA
CTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGAT
CCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCT
GTAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCG
GCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTA
TTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAA
CTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTA
CCTTACCCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAG
GAGACTATGGAATGCGTGGAG

Anti- β -Gal Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 187)

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFKVGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDS
DGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGSGG
SGGGGSPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHR
APDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECV
E

FIGURE 11AA

Anti-GFP Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 188)

CAGGTCCAGTTGGTGGAAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAGGAAAGGACTCGAATGGGTGTCGGGCATTTCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACAACACTCTGTACTTGCAAATGAACTCCCTGCGGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCTAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCC
CTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACCTCACACATGCCACCCGTGCCAGCACCTGAACTCCTGGG
GGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCCTCATGATCTCC
CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGA
GAACACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG
GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGA
TCCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGC
TGTAAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCC
GGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGT
ATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGA
ACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCT
ACCTTACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGA
GGAGACTATGGAATGCGTGGAG

Anti-GFP Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 189)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LTVVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
VLDSGDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKLSLSLSPGKGGGGS
GSGSGGGGSGNPICKGCLSCSKDNGCSRQKLFFFLRREGMRQYGECLHSCPSGY
GHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRGRCFDECPDGFAPLEETM
ECVE

FIGURE 11AB

LP1-1F8 light chain polynucleotide (SEQ ID NO: 190)

GACATTGTGATGTCACAGTCTCCATCCTCCCCTGGCTGTGTCAGCAGGAGAGAAGG
TCACTATGAGCTGCAAGTCCAGTCAGAGTCTGTTCAACAGTAGAACCCGAAAGA
ACTACTTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTGCTGATCTA
CTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTT
ATTACTGCAAGCAATCTTATTATCTGCTCACGTTCCGGTGCTGGGACCAAGCTGGA
GCTGAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-1F8 light chain polypeptide (SEQ ID NO: 191)

DIVMSQSPSSLAVSAGEKVTMSCKSSQSLFNSRTRKNYLAWYQQKPGQSPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISVQAEDLAVYYCKQSYLLTFGAGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 11AC

LP1-1F8 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 192)

GAAGTGAAACTGGTGGAGTCTGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCTG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTACCTATAACCATGTCTTGGGT
TCGCCAGACTCCGGCGAAGAGGCTGGAGTGGGTCGCAACCATTAGTAGTATTGG
TGTTAACACCTACTATCCAGACAGTGTGAAGGGCCGATTCACCATCTCCAGAGAC
AATGCCAGGAACACCCTGTACCTGCAAGTGAGCAGTCTGAGGTCTGAGGACACG
GCCATGTATTACTGTGCAAGACATGTGGATTACTACGATGGGATTTCTTTGACT
ACTGGGGCCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCAT
CGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATC
AGGCGCTCTGACCAGCGGCGTGACACCTTCCAGCTGTCCTACAGTCCTCAGGA
CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGA
CCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAG
TTGAGCGCAAATGTTGTGTCGAGTGCCACCCGTGCCCAGCACCACTGTGGCAGG
ACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCTCACC GTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATT
ACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-1F8 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 193)

EVKLVESGGGLVKPGGSLKLSCAASGFTFSTYTMSWVRQTPAKRLEWVATISSIGVN
TYYPD SVKGRFTISRDNARNTLYLQVSSLRSED TAMYYCARHVDYYDGISFDYWGQ
GTTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSNFGTQYTCNV D HKPSNTKVDKTVERKCCVECP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVH
NAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPML
DSDGSFFLYSKLTVDKSRWQQGNV FSC SVMHEALHNHYTQKSLSLSPGKGGGGSGS
GGSGGGGSPICKGCLSCSKDNGCSRCQQLFFFLRREGMRQYGECLHSCPSGYYG
HRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETME
CVE

FIGURE 11AD

LP1-1N15 light chain polynucleotide (SEQ ID NO: 194)

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TTACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCCATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCATTTCGTGCAAACAGATTGGT
AGATGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAGCCCCGGAGTATGAAGAAATGGGAATTTATTACTGTCTACAGTAT
GATGAGTTTCCGTTTCAGTTTCGGAGGGGGGACCAAGCTGGAAATAAAACGTACG
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1N15 light chain polypeptide (SEQ ID NO: 195)

DIKMTQSPSSMYASLGERVTITCKASQDINSHLSWFQQKPGKSPKTLIIRANRLVDGV
PSRFSGSGSGQDYSLTISSPEYEEMGIYYCLQYDEFPTFGGGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 11AE

LPI-1N15 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 196)

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCAGTACTACTACATGAACTGGG
TGAAGCAGAGTCATGGAGAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCA
ATGGTGGTACTAACTACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCACCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAAGACTC
TGCGGTCTATTTCTGTGCAAGAGGGATGGACTACTGGGGTCCAGGAACCTCAGTC
ACCGTCTCCAGCGCTAGCACCAAGGGGCCATCGGTCTTCCCCCTGGCGCCCTGCT
CCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT
TCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGCGTGC
ACACCTTCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCAC
AAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAG
TGCCCACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCC
CAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGG
TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGC
ACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCA
AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCATCGAGAAAA
CCATCTCCAAAACCAAGGGCAGCCCCGAGAACACAGGTGTACACCTGCCCC
CATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA
ACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTA
CAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG
TCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGC
AGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCA
CGGTGCCAGCAAAAGCTGTTTTTCTTCCCTCCGGCGGGAAGGAATGCGGCAGTAC
GGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACA
TGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGG
ACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGA
CGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LPI-1N15 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 197)

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGESLEWIGRVIPSNG
GTNYNQKFKGKATLTVDKSLTTAYMQLNSLTSEDSAVYFCARGMDYWGPGETSVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVTPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMMLDSGGSF
FLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGSGSGG
GGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYIGHRAPD
MNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

FIGURE 11AF

LP1-1P13 light chain polynucleotide (SEQ ID NO: 198)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGACAAACTG
TTATCATCACATGTCTGAACAAGTGAGAATATTTACAGTAATTTAGCATGGTATCA
GCAGAAACAGGGGAAAATCTCCTCAGCTCCTGGTCTATGCTGCAACAAACTTAGC
AGATGGTGTGCCATCAAGGTTTCAGTGGCAGTGGTTCAGGCACACAGTATTACCTC
AAGATCAACAGCCTGCAGTCTGAAGATTTTGGGAGTTATTACTGTCAACATTTTT
GGGGTAGTACGTGGACGTTTCGGTGGAGGCACCAAGCTGGACATCAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1P13 light chain polypeptide (SEQ ID NO: 199)

DIQMTQSPASLSASVGQTVIITCRTSENIYSNLAWYQQKQGKSPQLLVYAATNLADG
VPSRFSGSGSGTQYYLKINSLSQSEDFGSYYCQHFVGSTWTFGGGKLDIK

FIGURE 11AG

LP1-1P13 Heavy chain IgG2, RSPO2 polynucleotide (SEQ ID NO: 200)

GAGGTTCAACTGCAGCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTG
AAGATATCCTGCAAGGCTTCTGGTTACTCATTTACTGACTACTTTATGAACTGGGT
GAAGCAGAGCCATGGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAAT
GGTCAAACCTTTCTACAATCAGGAGTTCAAGGGGCAAGGCCACATTAAGTGTAGAC
AAATCCTCTAGCACCGCCACATGGAGCTCCGGAGCCTGACATCTGAGGACTCTG
CAGTCTATTATTGTGCAAGAAGAGGAAGGTACGACGTTTACTATGTTCTGGACTA
CTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGGCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCA
GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGT
TGAGCGCAAATGTTGTGTGTCGAGTGCCCCACCGTGCCAGCACCACCTGTGGCAGG
ACCGTCAGTCTTCCCTTCCCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCTGTGGTTCAGCGTCTCACCCTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATT
ACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-1P13 Heavy chain IgG2, RSPO2 polypeptide (SEQ ID NO: 201)

EVQLQQSGPELVKPGASVKISKASGYSFTDYFMNWVKQSHGKSLEWIGRFNPFNG
QTFYNQEFK GKATLTVDKSSSTAHEMELRSLTSEDSAVYYCARRGRYDVYYVLDYW
GQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVRKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKIT
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
MLDSDSGFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGSGGGGSGNPICKGCLSCSKDNGCSRQKLFFFLRREGMRQYGECLHSCPSGY
GHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRGRGCFDECPDGFAPLEETM
ECVE

FIGURE 11AH

LP1-1P5 light chain polynucleotide (SEQ ID NO: 202)

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGG
GTCAGCGTCACCTGCAAGGCCAGTCAGAATGTGGGTACTAATGTAGCCTGGTATC
AACAGAAACCAGGACAATCTCCTAAAGCACTGATTTACTCGGCATCTTATCGGTA
CAGTGGAGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAACAATATA
ACAGCTATCCGCTCACGTTCCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1P5 light chain polypeptide (SEQ ID NO: 203)

DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKALIYSASYRYS
GVPDRFTGSGSGTDFLTISNVQSEDLAEYFCQQYNSYPLTFGAGTKLELKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 11AI

LP1-1P5 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 204)

CAGGTCCAGCTGCAGCAATCTGGACCTGAGCTGGTGAGGCCTGGGACTTCAGTG
AAGATATCCTGCAAGGCTTCTGGCTATACCTTCCTCACCTACTGGATGAACTGGG
TGAAGCAGAGGCCTGGACAGGGCCTTGAGTGGATTGGACAGATTTTCCCTGCAA
CTGGTATTACTTACTACAGTGAGATGTTCAAGGACAAGGCCACATTGACTGAAG
ACACATCCTCCACCACAGCCTACATGCAACTCAGCAGCCTGACATCTGAGGCCAC
TGCTGTCTATTTCTGTGCAAGAAGAAGGGCCTACCATAGTAACTTTTTTGACTACT
GGGGCCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGGGCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCAGCTGTCTACAGTCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCTGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACC
GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCTGTGGTTCAGCGTCTCACCCTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGG
AGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAG
CAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGG
GAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTAC
GGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGC
GATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTC
ACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGA
CTATGGAATGCGTGGAG

LP1-1P5 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 205)

QVQLQQSGPELVRPGTSVKISKASGYTFLTYWMNWVKQRPQGQLEWIGQIFPATGI
TYYSEMFKDKATLTEDTSSTTAYMQLSSLTSEATAVYFCARRRAYHSNFFDYWGQG
TTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS
DGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGSGG
SGGGGSPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHR
APDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECV
E

FIGURE 11AJ

LP1-2E12 light chain polynucleotide (SEQ ID NO: 206)

GATGTTGTGGTGACTCAAACCTCCACTCTCCCTGCCTGTCAGCTTTGGAGATCGAG
TTTCTATCTCTTGCAGGTCTAGTCAGAGTCTTGCAAACAGTTATGGGAACACCTA
TTTGTCTTGGTACCTGCACAAGCCTGGCCAGTCTCCACAGCTCCTCATCTATGGG
ATTTCCAACAGATTTTCTGGGGTGCCAGACAGGTTTCAGTGGCAGTGGTTCAGGGA
CAGATTTACACTCAAGATCAGCACATAAAGCCTGAGGACTTGGGAATGTATT
ACTGCTTACAAGGTACACATCAGCCTCTCACGTTTCGGTGCTGGGACCAAGCTGGA
GCTGAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-2E12 light chain polypeptide (SEQ ID NO: 207)

DVVVTQTPLSLPVSFGDRVSISCRSSQSLANSYGNTYLSWYLHKPGQSPQLLIYGISN
RFSGVDPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPLTFGAGTKLELKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AK

LP1-2E12 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 208)

GATGTACAACCTTCAGGAGTCAGGACCTGGCCTCGTGAAACCTTCTCAGTCTCTGT
CTCTCACCTGCTCTGTCACTGGCTACTCCATCACCAGTGGTTATTACTGGAACCTGG
ATCCGGCAGTTTCCAGGAAACAACTGGAATGGATGGGCTCCATAGGCTACGAT
GATACCAATCACTACAACCCATCTCTCAAAAATCGAATCTCCATCACTCGTGACA
CATCTAAGAACCAGTTTTTTCCTGAAGTTGAATTCTGTGACAACTGAGGACACAGC
CACATATTACTGTGCAGGTGACTACCCCTTTGCTTTCTGGGGCCAAGGGACTCTG
GTCAGTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCT
GCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT
ACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGCG
TGCACACCTTCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGCTAGAT
CACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC
GAGTGCCCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCC
CCCCAAAACCCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGT
GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACA
GCACGTTCCGTGTGGTCAGCGTCCTACCGTTGTGCACCAGGACTGGCTGAACGG
CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCCTCCAGCCCCCATCGAGAA
AACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGTCAA
AGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
GAACAACCTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
TGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTG
GCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTT
CACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGT
ACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGA
CATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAA
GGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTT
GACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-2E12 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 209)

DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGSIGYDDT
NHYNPSLKNRISITRDTSKNQFFLKLNSVTTEDTATYYCAGDYPFQFWGQGLVTVS
AASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPAPPV
AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGGSFF
LYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGSGSGSGG
GSNPICKGCLSCSKDNGCSRQCKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDM
NRCARCRINCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

FIG. 11AL

LP1-2I13 light chain polynucleotide (SEQ ID NO: 210)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAACTG
TCACCATCACATGTTCGAGCAAGTGAGAATATTTACAGTTATTTAGTATGGTATCA
GCAGAAACAGGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTAGC
AGAAGGTGTGCCATCAAGGTTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTG
AAGATCAACAGCCTGCAGCCTGAAGATTTTGGGAGTTATTACTGTCAACATCATT
ATGGTACTTGGACGTTTCGGTGGAGGCATAAAGCTGGAAATCAAACGTACGGTGG
CTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC
TGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAG
TGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-2I13 light chain polypeptide (SEQ ID NO: 211)

DIQMTQSPASLSASVGETVTITCRASENIYSYLVWYQQKQKGKSPQLLVYNAKTLAEG
VPSRFSGSGSGTQFSLKINSLOPEDFGSYQCQHHYGTWTFGGGIKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AM

LP1-2I13 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 212)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCCGG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTGACTATGGAATGCACTGGG
TCCGTCAGGCTCCAGAGAAGGGGCTGGAGTGGGTGCCTACATTAGTAGTGGCA
GTAGTACCATCTACTATGCAGACACAGTGAAGGGCCGATTACCATCTCCAGAG
ACAATGCCAAGAACACCCTGTTCTACAAATGACCAGTCTAAGGTCTGAGGACA
CAGCCATGTATTACTGTTCAAGGAAGGGAGGGTTTGGTGACTACGAGAAAAGCT
ATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGC
ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAAGTCAAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCTGTCCTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTT
CGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT
GGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCAGCACC
ACCTGTGGCAGGACCGTCAGTCTTCCCTCTTCCCCCAAAACCCAAGGACACCCTC
ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAA
GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCC
AAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTC
CTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC
TCCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGG
CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACC
AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCC
TCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGAC
AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGT
GGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAG
GGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTG
TTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCT
GCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGAT
GCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCA
AAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTT
CGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-2I13 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 213)

EVQLVESGGGLVKPGGSRKLSAASGFTFSDYGMHWVRQAPEKGLEWVAYISSGSS
TIYYADTVKGRFTISRDNKNTLFLQMTSLRSEDAMYYCSRKGGFGDYEKSYAMD
YWGQGTSTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKC
CVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTFRVVSVLTIVHQQDWLNGKEYKCKVSNKGLPAPIEKTI
SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVMEALHNHYTQKSLSLSPGKGG
GGSGSGSGGGGSGNPICKGCLSCSKDNGCSRQKQLFFFLRREGMRQYGECLHSCPS
GYYGHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLE
ETMECVE

FIG. 11AN

LP1-2I22 light chain polynucleotide (SEQ ID NO: 214)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAACTG
TTATCATCACATGTGCGAGCAAGTGAGAATATTTACAGTAATTTAGCATGGTATCA
GCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATGGTGCAACAACTTAGC
AGATGGTGTGACATCAAGGTTTCAGTGGCAGTGGTTCAGGCACACAGTTTTCCCTC
AAGATCGACAGCCTGCAGTCTGAAGATTTTGGGAGTTATTACTGTCAACATTTTT
GGGGTACTACGTGGACGTTCCGGTGGAGGCACCAAGCTGGAAATCAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-2I22 light chain polypeptide (SEQ ID NO: 215)

DIQMTQSPASLSASVGETVIITCRASENIYSNLAWYQQKQKGKSPQLLVYGATNLADG
VTSRFSGSGSGTQFSLKIDSLQSEDFGSYYCQHFHWGTTWTFGGGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AO

LP1-2I22 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 216)

GAGGTTCAACTGCAGCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTG
AAGATATCCTGCAAGGCTTCTGGTTACTCATTTACTGGCTACTTTATGAACTGGGT
GAAGCAGAGCCATGGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAAT
GGTCAAACCTTTCTACAATCAGGAGTTCAAGGGGCAAGGCCACATTAACCTGTTGAC
AAATCCTCTGACACCGCCACATGGAACCTCCGGAGCCTGACATCTGAGGACTCTG
CAGTCTATTATTGTGCAAGAAGAGGAAGGTACGACGTTTACTATGCTCTGGACTA
CTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGGCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCA
GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGT
TGAGCGCAAATGTTGTGTGTCGAGTGCCCCACCGTGCCAGCACCACTGTGGCAGG
ACCGTCAGTCTTCCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCTCACCCTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATT
ACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-2I22 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 217)

EVQLQQSGPELVKPGASVKISCKASGYSTGYFMNWVKQSHGKSLEWIGRFNPFNG
QTFYNQEFK GKATLTVDKSSDTAHMELRSLTSEDSAVYYCARRGRYDVYYALDYW
GQGTSTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
MLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSGNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGY
GHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETM
ECVE

FIG. 11AP

LP1-3A24 light chain polynucleotide (SEQ ID NO: 218)

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGG
GTCAGCGTCACCTGCAAGGCCAGTCAGAATGTGGGTAGTAATGTAGCCTGGTTTC
AACAGAAACCAGGGCAATCTCCTAAAGCACTGATTTACTCGTCATCCTACCGGTA
CAGTGGAGTCCCTGATCGCTTCACGGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCACCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAGCAATATA
ACAGCTTTTCCTCTCACGTTTCGGTGCTGGGACCAAGCTGGAAGTCAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-3A24 light chain polypeptide (SEQ ID NO: 219)

DIVMTQSQKFMSTSVGDRVSVTCKASQNVGSNVAWFQKPGQSPKALIYSSSYRYS
GVPDRFTGSGSGTDFTLTITNVQSEDLAEYFCQQYNSFPLTFGAGTKLELKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AQ

LP1-3A24 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 220)

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCAGTACTACTACATAAACTGGG
TGAGGCAGAGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCA
ATGGTGGTAGTAATAACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCAGTACAGCCTACATGCACCTCAACAGCCTGACATCTGAGGACTC
TGCGGTCTATTACTGTGCAACCCAGCTGGGACGGTGGGGCCAAGGGACTCTGGT
CACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGC
TCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC
TTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGCGGCGTG
CACACCTTCCCAGCTGTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGG
TGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCA
CAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGA
GTGCCACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCCCC
CCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACAGTGCCTG
GTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGAC
GGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAG
CACGTTCCGTGTGGTCAGCGTCTCACCGTTGTGCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAA
ACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
CCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAA
GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
AACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCT
ACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT
GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT
GTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGG
CAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTT
ACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTA
CGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGAC
ATGAACCGATGCGCCAGATGCCGGATCGAGAAGTGCATAGCTGCCGCAGCAAG
GACGCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTG
ACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-3A24 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 221)

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLEWIGRVIPSNG
GSNYNQKFKGKATLTVDKSLSTAYMHLNSLTSEDSAVYYCATQLGRWGQGLVTV
SAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDKTVRKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMILDSGGSF
FLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGKGGGGSGSGSGG
GGSNPICKGCLSCSKDNGCSRCQQKLFLLRREGMRQYGECLHSCPSGYYGHRAPD
MNRCARCRIENCDSRSDACTKCKVGFYLRGRCFDECPDGFAPLEETMECVE

FIG. 11AR

LP1-3E20 light chain polynucleotide (SEQ ID NO: 222)

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TCACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCTATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCTATCGTGCAAACAGATTGGT
AGATGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAGCCTAGAGTATGAAGATATGGGAATTTATTATTGTCTACAGTATG
ATGACTTGTGGACGTTTCGGTGGAGGCACCAAGCTGGAAATCAAACGTACGGTGG
CTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC
TGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTACAG
TGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-3E20 light chain polypeptide (SEQ ID NO: 223)

DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLVDG
VPSRFSGSGSGQDYSLTISSEYEDMGIYYCLQYDDLWTFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AS

LP1-3E20 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 224)

CAGGTCCAACCTGCAGCAGTCTGGGGCTGAACTGGCAAAACCTGGGGCCTCAGTG
AAGATGTCCTGCAAGGCTTCTGGCTACACCTTTACTAGCTACTGGATACACTGGG
TAAACAGAGGCCTGGACAGGGTCTGGAATGGATTGGATACATTAATCCTAGCA
GTGGTTATGCTGAGTACAATCAGAAGTTCAAGGTCAGGGCCACATTGACTGCAG
ACAAATCCTCCAGCACAGCCTACATGCAACTAAGCAGCCTGACATCTGAGGACT
CTGCAGTCTATTACTGTGCAAGAGAAAGTTACTATAGTTTCGACTATACTATGGA
CTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCC
ATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCC
CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGA
CAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTACAGTCTCAGG
ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAG
ACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACA
GTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCAGCACCACTGTGGCAG
GACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCTCATGATCTCCCG
GACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGT
CCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
ACGGGAGGAGCAGTTCAACAGCACGTTCCTGTGGTTCAGCGTCTCACCCTGTGTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGC
CTCCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAA
CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTC
AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGAC
TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATC
CGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTG
TAGCAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCCG
CGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTAT
TACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAAC
TGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTAC
CTTACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGG
AGACTATGGAATGCGTGGAG

LP1-3E20 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 225)

QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPGQGLEWIGYINPSSG
YAEYNQKFKVRATLTADKSSSTAYMQLSSLTSEDSAVYYCARESYYSFDYTMDYW
GQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVERKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
MLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSGNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGY
GHRAPDMNRCARCRIENCDSRSDACTKCKVGFYLRHGRCFDECPDGFAPLEETM
ECVE

FIG. 11AT

LP1-6H3 light chain polynucleotide (SEQ ID NO: 226)

GATGTTGTGATGACCCAGACTCCACTCACTTTGTCGGTTACCATTGGACAACCAG
CCTCCATCTCTTGCAAGTCAAGTCAGAGCCTCTTAGATAGTGATGGAAAGACATA
TTTGAATTGGTTGTTACAGAGGCCAGGCCAGTCTCCAAAGCGCCTAATCTATCTG
GTGTCTAAACTGGACTCTGGAGTCCCTGACAGGTTCACTGGCAGTGGATCAGGG
ACAGATTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATTTGGGAGTTTAT
TATTGCTGGCAAGGTACACATTTTCCTCACACGTTTCGGCTCGGGGACAAAGTTGG
AAATAAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGT

LP1-6H3 light chain (PN & PP) polypeptide (SEQ ID NO: 227)

DVVMTQTPLTSLVTIGQPASISCKSSQSLLDS DGKTYLNWLLQRPQGSPKR LIYLVSK
LD SGVPDRFTGSGSGTDFTLKISRVEAEDLG VYYCWQGTHFPHTFGSGTKLEIKRTV
AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AU

LP1-6H3 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 228)

CAGGCTTATCTACAGCAGTCTGGGGCTGAGCTGGTGAGGCCTGGGGCCTCAGTG
AAGATGTCCTGTAAGGCTTCTGGCTACACATTTTCCCGTTTCGATATGCACTGGG
TAAAGCAGACACCTAGACAGGGCCTGGAATGGATTGGAGTTATTTATCCAGGAA
ATGGTGATACTTCCTACAATCAGAAGTTCAGGGACAAGGCCTCACTGACTGTAG
ACAAATCCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTGACATCTGAAGACT
CTGCGGTCTATTTCTGTGCAAGCTCCTACTATGGTAACCCCTGGGGCCAAGGCAC
CACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGC
GGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCAACCGTGCCCAAGCACCTGTGGCAGGACCGTCAGTCTTCCTC
TTCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTCACGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAATAACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAAGTGCATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-6H3 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 229)

QAYLQQSGAELVRPGASVKMSCKASGYTFSRFDMHVVKQTPRQGLEWIGVIYPGN
GDTSYNQKFRDKASLTVDKSSSTAYMQLSSLTSEDSAVYFCASSYYGNPWGQGTTL
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDKTVRKCCVECPPCA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSFLTIVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFPSCSVMEALHNHYTQKSLSLSPGKGGGGSGSGSGS
GGGSNPICKGCLSCSKDNGCSRQKLFFFLRREGMRQYGECLHSCPSGYIGHRAP
DMNRCARCRIENCDSKRSKDACTKCKVGFYLRGRCFDECPDGFAPLEETMECVE

FIG. 11AV

LP1-7B13 light chain polynucleotide (SEQ ID NO: 230)

GATATTGTGCTAACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGATAGAG
TCAGTCTTTCTGTCAGGGCCAGTCAAAGTATTAGCAACTACCTACACTGGTATCA
ACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAGTTTGCTTCCCAGTCCATC
TCTGGGATCCCCCTCCAGGTTTCAGTGGCAGTGGATCAGGGACGGATTTCACTCTCA
CTATCAACAGTGTGGAGACTGAAGATTTTGGGAATGTATTTCTGTCAACAGAGTAA
CAGCTGGCCGCTCACGTTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-7B13 light chain polypeptide (SEQ ID NO: 231)

DIVLTQSPATLSVTPGDRVSLSCRASQSSISNYLHWYQOKSHESPRLLIKFASQSIGIPS
RFSGSGSGTDFLTINSVETEDFGMYFCQQSNSWPLTFGAGTKLELKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AW

LP1-7B13 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 232)

GAGGTCCAGCTGCAACAATCTGGACCTGAGGTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGACTTCTGGATTACATTCACTGACTACTACATGAACTGGG
TGAAGCAGGGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAGCA
ATGATGATACTAGGTACAATCAGAAGTTCAAGGGAAAGGCCACATTGACAGTAG
ACAAGTCCCTCAGCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACT
CTGCGGTCTATTACTGTACAAGGTGGTTCTACTTTGACTACTGGGGCCAAGGCAC
TACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCTGTTGAACTCAGGCGCTCTGACCAGC
GGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCAACCGTGCCCAAGCACCACTGTGGCAGGACCGTCAGTCTTCCTC
TCCCCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACAGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAATAACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAAGTGCATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-7B13 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 233)

EVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYYMNWVKQGHGKSLEWIGRVNPSN
DDTRYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCTRWFYFDYWQQT
LTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVTVPSNFQTQYTCNVDHKPSNTKVDKTVKCCVECPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPR
EPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSD
GSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGKGGGGSGSGGS
GGGGSNPICKGCLSCSKDNGCSRQCKLFFFLRREGMRQYGECLHSCPSGYGHRA
PDMNRCARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

FIG. 11AX

LP1-7I20 light chain polynucleotide (SEQ ID NO: 234)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAACTG
TCACCATCACATGTGGAACAAGTGAGAATATTTACAGTTATTTAGCATGGTATCA
GCAGAAACAGGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTAGC
AAAAGGTGTGCCATCAAGGTTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTG
AAGATCAACGGCCTGCAGCCTGAAGATTTTGGGAATTATTACTGTCAACATCATT
ATGGTACTCCGTACACGTTTCGGAGGGGGGACCAAGGTGGAAATAAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-7I20 light chain polypeptide (SEQ ID NO: 235)

DIQMTQSPASLSASVGETVTITCRTSENIYSYLAWYQQKQKGKSPQLLVYNAKTLAKG
VPSRFSGSGSGTQFSLKINGLQPEDFGNYCYQHGYGTPYTFGGGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11AY

LP1-7I20 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 236)

GAGGTGAAGCTGGTGGAGTCTGGAGGAGGCTTGGTACAGCCTGGGGGTTCTCTG
AGTCTCTCCTGTGCAGCTTCTGGATTACCTTCACTGATTACTACATGAGCTGGGT
CCGCCAGCCCCCAGGGAAGGCACTTGAGTGGTTGGCTTTGATTAGAAACAAAGC
TAATGGTTACACAACAGAGTACAGTGCATCTGTGAAGGGTTCGGTTCACCATCTCC
AGGGATAATTCCCAAAGCATCCTCTATCTTCAAATGAATGCCCTGAGAGCTGAGG
ACAGTGCCACTTATTACTGTGCAGTTACCTACGGGGCTTACTGGGGCCAAGGGAC
TCTGGTCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGC
GGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCAACCGTGCCCAAGCACCACTGTGGCAGGACCGTCAGTCTTCCTC
TTCCCCCCTCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTCACGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAATAACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCCCTCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAAGTGCATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-7I20 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 237)

EVKLVESGGGLVQPGGSLSLSCAASGFTFTDYYMSWVRQPPGKALEWLALIRNKAN
GYTTEYSASVKGRFTISRDNQSILYLQMNALRAEDSATYYCAVTYDAYWGQGLV
TVSAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSVTVPSNFGTQTYTCNVDPKPSNTKVDKTVERKCCVECPPCA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSIVLVVHVDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFPSCSVMEALHNHYTQKSLSLSPGKGGGGSGSGSGS
GGGSNPICKGCLSCSKDNGCSRQKLFFFLRREGMRQYGECLHSCPSGYIGHRAP
DMNRCARCRINCDSCRSDACTKCKVGFYLRGRCFDECPDGFAPLEETMECVE

FIG. 11AZ

LP1-8M24 light chain polynucleotide (SEQ ID NO: 238)

GAGGTTCAGCTGCAGCAGTCTGGGGCTGAGCTTGTGAGGCCAGGGGCCTCAGTC
AAGTTGTCCTGCACAGCTTCTGGCTTTACCATTAAAGACGACTATATTCAGTGGG
TGAAGCAGGGGCCTGAACAGGGCCTGGAGTGGATTGGAAGAATTGATCCTGCGG
ATGATGATACTAAATATGCCCCGAAGTTCCAGGACAAGGCCACTATAACTGCAG
ACACATCCTCCAACACAGCCTACCTGCAGCTCAGCAGCCTGACATCTGAGGACA
CTGCCGTCTATTACTGTGCTAGAAAGTTCCATGGCCTGGTTTGCTTACTGGGCCCCA
AGGGACTCTGGTCACTGTCTCTACAGCTAGCACCAAGGGCCCCATCGGTCTTCCCC
CTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGACACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGGATCCGGCTCCGGAcatcatcatcaccatcac

LP1-8M24 light chain polypeptide (SEQ ID NO: 239)

EVQLQQSGAELVRPGASVKLSCTASGFTIKDDYIHVVKQGPEQGLEWIGRIDPADDD
TKYAPKFQDKATITADTSSNTAYLQLSSLTSEDYAVYYCARSSMAWFAYWAQGLV
TVSTASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHH
HHH

FIG. 11BA

LP1-8M24 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 240)

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGA
GTGACCATCACCTGTCGGATCAGCGAGAACATCTACAGCAACCTGGCCTGGTATC
AGCAGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGCCGCCATCAATCTGG
CCGATGGCGTGCCAAGCAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCT
GACCATATCTAGCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCACTTT
TGGGGCACCCCTTTACCTTTTGGCCAGGGCACCAAGCTGGAAATCAAGCGTACG
GTGGCTGCACCATCTGTCTTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-8M24 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 241)

DIQMTQSPSSLASVSGDRVITTCRISENIYSNLAWYQQKPGKAPKLLIYAAINLADGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQHFHWGTPFTFGQGKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSLTLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11BB

LP1-9C3 light chain polynucleotide (SEQ ID NO: 242)

GATGTTGTGGTGACTCAAACCTCCACTCTCCCTGCCTGTCAGCTTTGGAGATCAAG
TTTCTATCTCTTGCAGGTCTAGTCAGAGTCTTGCAAACAGTTATGGGAACACCTA
TTTGTCTTGGTACCTGCACAAGCCTGGCCAGTCTCCACAGCTCCTCATCTATGGG
ATTTCCAACAGATTTTCTGGGGTGCCAGACAGGTTTCAGTGGCAGTGGTTCAGGGA
CAGATTTACACTCAAGATCAGCACATAAAGCCTGAGGACTTGGGAATCTATT
ACTGCTTACAAGCTACACATCAGCCGTGGACGTTCCGGTGGAGGCACCAAGCTGG
AAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGT

LP1-9C3 light chain polypeptide (SEQ ID NO: 243)

DVVVTQTPLSLPVSFGDQVSISCRSSQSLANSYGNTYLSWYLHKPGQSPQLLIYGISN
RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGIYYCLQATHQPWTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11BC

LP1-9C3 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SEQ ID NO: 244)

CAGGTTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCCCTCCCAGACCCTCA
GTCTGACTTGTTCTTTCTCTGGGTTTTCACTGAGCACTTCTTATATGGGTGTGAGC
TGGATTCGTAAGCCTTCAGGAAAGGGTCTGGAGTGGCTGGCACACATTTTCTGGG
ATGATGACAAGCGCTATAACCCATCCCTGAAGAGCCGGCTCACAACTCTCCAAGG
ATACCTCCAGCAACCAGGTATTCCTCATGATCACCAGTGTGGAACTGCAGATAC
TGCCACATACTACTGTGGGGGTCCCTACTATCCGTTTACTTACTGGGGCCAAGGG
ACTCTGGTCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGG
CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCA
AGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCA
GCGGCGTGCACACCTTCCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
GTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT
TGTGTGAGTGCCCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCC
TCTTCCCCCCTAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGT
TCAACAGCACGTTCCGTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC
CCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT
GGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTT
CTTCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGT
CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGC
CTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTG
GCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACG
GATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGGAAGGAATGCG
GCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCG
CCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGC
AGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGA
TGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCG
TGGAG

LP1-9C3 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 245)

QVTLKESGPGILQPSQTLSTCSFSGFSLSTSYMGVSWIRKPSGKGLEWLAHIFWDDD
KRYNPSLKSRLTISKDTSSNQVFLMITSVETADTATYYCGGPYYPFTYWGQGLVTV
SAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVRKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMILDSGGSF
FLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGKGGGGSGSGGSGG
GGSNPICKGCLSCSKDNGCSRQKQLFFFLRREGMRQYGECLHSCPSGYYGHRAPD
MNRCARCRIENCDSRSDACTKCKVGFYLRGRCFDECPDGFAPLEETMECVE

FIG. 11BD

LP1-9M16 light chain polynucleotide (SEQ ID NO: 246)

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TCACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCTATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCTATCGTGCAAACAGATTGGC
AGATGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAACCTGGAGTATGAAGATATGGGAATTTATTATTGTCTACAGTATG
ATGAGTTTCCGCTCACGTTCCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-9M16 light chain polypeptide (SEQ ID NO: 247)

DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLADG
VPSRFSGSGSGQDYSLTISNLEYEDMGIYYCLQYDEFPLTFGAGTKLELKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11BE

LP1-9M16 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SID NO: 248)

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCAGTACTACTACATGAACTGGG
TGAAGCAGAGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAACA
ATGGTGGTTCTAACTACAACCAGAAATTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCAGCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACT
CTGCGGTCTATTACTGTGCAAGTCGAACTTCGATGTCTGGGGGCGCAGGGACCAC
GGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCC
TGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGCGGC
GTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCG
TGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGA
TCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGT
CGAGTGCCCACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTC
CCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACAGTGC
GTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAA
CAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAAC
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCGAG
AAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG
CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTC
AAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCTCCCATGCTGGACTCCGACGGCTCCTTCTTCC
TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT
CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGG
TGGCAGCAACCCAAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATG
TTCACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGGAAGGAATGCGGCAG
TACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTG
ACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCA
AGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCGAGATGTTT
TGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGA
G

LP1-9M16 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 249)

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGKSLEWIGRVNPN
GGSNYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCASRNFDVWGAGTTV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVRKCCVECP
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSFLTIVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFPSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGSGS
GGGSNPICKGCLSCSKDNGCSRQKLFFFLRREGMRQYGECLHSCPSGYIGHRAP
DMNRCARCRIENCDSKRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

FIG. 11BF

LP1-10C22 light chain polynucleotide (SEQ ID NO: 250)

GATGTTTTGATGACCCAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAG
CCTCCATCTCTTGCAGATCTAGTCAGGGCATTGTACATAGTAATGGAAACATCTA
TTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACAAA
GTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGA
CAGATTTCACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATT
ACTGCTTTCAAGGTTACATGTTTCTCCACGTTTCGGAGGGGGGACCAAGCTGGA
AATAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-10C22 light chain polypeptide (SEQ ID NO: 251)

DVLMQTPLSLPVS LGDQASISCRSSQGIVHSNGNIYLEWYLQKPGQSPKLLIYKVS
NRFSGVPDRFSGSGSDFTLKISRVEAEDLGVYYCFQGSHVPPTFGGGTKLEIKRTVA
APSVFI FPPSDEQLKSGTASVVCLLNFPYFREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSLTSLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 11BG

LP1-10C22 Heavy chain IgG2, RSPO2 (F105R/F109A) polynucleotide (SID NO: 252)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAGTTATGGCATGTCTTGGGT
TCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCGCAAGTATTAGTAGTGGTGG
TAGTTATACCTACTATCCAGACAGTGTGAAGGGGCGATTACCATCTCCAGAGAC
AATGCCCAGAACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGGACACA
GCCATGTATTACTGTGTAAGACATGAGGAGTATGGTAAATCCGGATTGCTTACT
GGGGCCAAGGGACCCTGATTACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCAGCTGTCTACAGTCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCTGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACC
GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCTCACCCTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGG
AGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAG
CAAGGACAACGGATGTTACGGTGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGG
GAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCCTCGGGGTATTAC
GGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGC
GATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTC
ACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGA
CTATGGAATGCGTGGAG

LP1-10C22 Heavy chain IgG2, RSPO2 (F105R/F109A) polypeptide (SEQ ID NO: 253)

EVQLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVRQTPDKRLEWVASISSGGS
YTYYPDSVKGRFTISRDNQNTLYLQMSSLKSEDTAMYYCVRHEEYGKSGFAYWG
QGTLITVSAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVEC
PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPM
LDSGGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSG
SGSGGGGSGNPICKGCLSCSKDNGCSRQKQLFFFLRREGMRQYGECLHSCPSGYYG
HRAPDMNRCARCRIENCDSKRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETME
CVE

FIG. 11BH

RSPO2 (F105R/F109A), LP1-1N15 Heavy chain IgG1 N297G polynucleotide (SID NO: 254)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCACTGACTACTACATGAACTGGGTGAAGCAGAGTCAT
GGAGAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCAATGGTGGTACTAACT
ACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCACCA
CAGCCTACATGCAGCTCAACAGCCTGACATCTGAAGACTCTGCGGTCTATTTCTG
TGCAAGAGGGGATGGACTACTGGGGTCCAGGAACCTCAGTCACCGTCTCCAGCGC
TAGCACC AAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCT
GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCTGGAAGTCAAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGT
GTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA
GCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACACACATGCC
CACCGTGCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCAGCA
CGTACCGTGTGGTCAGCGTCCTACCGTCTGCAACCAGGACTGGCTGAATGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAAC
CATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGTCAAAGG
CTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-1N15 Heavy chain IgG1 N297G polypeptide (SID NO: 255)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGS
SGSGSGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYIMNWVKQSHGESL
EWIGRVIPSNNGTNYNQKFKGKATLTVDKSLTTAYMQLNSLTSEDSAVYFCARGMD
YWGPGETSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPG
K

FIG. 11BI

RSPO2 (F105R/F109A), LP1-1P13 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 256)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTTCAACTGCA
GCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAA
GGCTTCTGGTTACTCATTTACTGACTACTTTATGAACTGGGTGAAGCAGAGCCAT
GGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAATGGTCAAACCTTTCT
ACAATCAGGAGTTCAAGGGCAAGGCCACATTAAGTGTAGACAAATCCTCTAGCA
CCGCCACATGGAGCTCCGGAGCCTGACATCTGAGGACTCTGCAGTCTATTATTG
TGCAAGAAGAGGAAGGTACGACGTTTACTATGTTCTGGACTACTGGGGTCAAGG
AACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC
AAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA
ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAAT
CTTGTGACAAAACCTCACACATGCCACACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCTCTTCCCCCCTCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
GCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-1P13 Heavy chain IgG1 N297G polypeptide (SEQ ID NO: 257)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGS
SGSGSGGGSEVQLQQSGPELVKPGASVKISCKASGYSFTDYFMNWVKQSHGKSLE
WIGRFNPFNGQTFYNQEFKGKATLTVDKSSSTAHEMLRSLTSEDSAVYYCARRGRY
DVYYVLDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQ
KSLSLSPGK

FIG. 11BJ

RSPO2 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 258)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTCCAACCTCGT
AGAATCAGGTGGTGGTTTGGTCAAACCAGGTGGCTCTCGGAAGTTGTCCTGTGCT
GCCTCTGGATTTACATTCAGTGACTACGGTATGCACTGGGTCCGTCAGGCTCCAG
AGAAGGGGGCTGGAGTGGGTTCCTACATTAGTAGTGGCAGTAGTACCATCTACT
ATGCAGACACAGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACA
CCCTGTTCCCTACAAATGACCAGTCTAAGGTCTGAGGACACAGCCATGTATTACTG
TTCAAGGAAGGGAGGGTTTGGTGACTACGAGAAAAGCTATGCTATGGACTACTG
GGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGT
CTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGC
TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA
GCCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCCACAGCACCTGAACCTC
CTGGGGGGGACCGTCAGTCTTCTCTTCCCCCCTTCCCAAGGACACCCCTCATGA
TCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCA
ACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
CCCGAGAACCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG
TGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCCTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polypeptide (SID NO: 259)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECEVEGGGGS
GSGGSGGGGSEVQLVESGGGLVKPGGSRKLSAASGFTFSDYGMHWVRQAPEKGL
EWVAYISSGSSTIYYADTVKGRFTISRDNKNTLFLQMTSLRSEDAMYYCSRKGGF
GDYEKSYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH
YTQKSLSLSPGK

FIG. 11BK

RSPO2 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 260)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTTCAACTGCA
GCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAA
GGCTTCTGGTTACTCATTTACTGGCTACTTTATGAACTGGGTGAAGCAGAGCCAT
GGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAATGGTCAAACCTTTCT
ACAATCAGGAGTTCAAGGGCAAGGCCACATTAAGTGTGACAAATCCTCTGACA
CCGCCACATGGAAGTCCGGAGCCTGACATCTGAGGACTCTGCAGTCTATTATTG
TGCAAGAAGAGGAAGGTACGACGTTTACTATGCTCTGGACTACTGGGGTCAAGG
AACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC
AAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA
ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAAT
CTTGTGACAAAACCTCACACATGCCACACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCTCTTCCCCCCTCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
GCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAAGCGTCTCACCCTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polypeptide (SID NO: 261)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECEVEGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLE
WIGRFNPFNGQTFYNQEFK GKATLTVDKSSDTAHMELRSLTSEDSAVYYCARRGRY
DVYYALDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQ
KSLSLSPGK

FIG. 11BL

RSPO2 (F105R/F109A), LP1-3A24 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 262)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCAGTACTACTACATAAACTGGGTGAGGCAGAGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCAATGGTGGTAGTA
ACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCAGTA
CAGCCTACATGCACCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACTG
TGCAACCCAGCTGGGACGGTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGC
TAGCACCAGGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCT
GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCTGGAAGTCAAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA
GCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACACACATGCC
CACCGTGCCAGCACCTGAACCTCTGGGGGGACCGTCAGTCTTCTCTTCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCAGCA
CGTACCGTGTGGTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAATGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAAC
CATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGG
CTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-3A24 Heavy chain IgG1 N297G polypeptide (SEQ ID NO: 263)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGS
SGSGSGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLE
WIGRVIPSNNGGSNYNQKFKGKATLTVDKSLSTAYMHLNSLTSEDSAVYYCATQLGR
WGQGTILVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHREALHNHYTQKSLSLSPGK

FIG. 11BM

RSPO2 (F105R/F109A), LP1-3E20 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 264)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCCAGGTCCAAGTCA
GCAGTCTGGGGCTGAACTGGCAAAACCTGGGGCCTCAGTGAAGATGTCCTGCAA
GGCTTCTGGCTACACCTTTACTAGCTACTGGATACTGGGTAAAACAGAGGCCT
GGACAGGGTCTGGAATGGATTGGATACATTAATCCTAGCAGTGGTTATGCTGAGT
ACAATCAGAAGTTCAAGGTCAGGGCCACATTGACTGCAGACAAATCCTCCAGCA
CAGCCTACATGCAACTAAGCAGCCTGACATCTGAGGACTCTGCAGTCTATTACTG
TGCAAGAGAAAAGTTACTATAGTTTCGACTATACTATGGACTACTGGGGTCAAGGA
ACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGGCCCATCGGTCTTCCCCCTGG
CACCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCA
AGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCCCTGACCA
GCGGCGTGCACACCTTCCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC
GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCT
TGTGACAAAACCTCACACATGCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA
CCGTCAGTCTTCTCTTCCCCCCTCAAAACCAAGGACACCCTCATGATCTCCCGGA
CCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCA
AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC
TCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-3E20 Heavy chain IgG1 N297G polypeptide (SID NO: 265)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
SGSGSGGGGSQVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPQQGL
EWIGYINPSSGYAEYNQKFKVRATLTADKSSSTAYMQLSSLTSEDSAVYYCARESY
SFDYTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHENHNYTQ
KSLSLSPGK

FIG. 11BN

RSPO2 (F105R/F109A), LP1-7B13 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 266)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAATCTGGACCTGAGGTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GACTTCTGGATTACATTCCTGACTACTACATGAACTGGGTGAAGCAGGGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAGCAATGATGATACTAGG
TACAATCAGAAGTTCAAGGGAAAGGCCACATTGACAGTAGACAAGTCCCTCAGC
ACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACT
GTACAAGGTGGTTCTACTTTGACTACTGGGGCCAAGGCACTACTCTCACAGTCTC
CAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGC
ACCTCTGGGGGACACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA
CCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTC
CCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGC
CCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCA
GCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACA
CATGCCACCGTGCCAGCACCTGAACCTCGGGGGGACCGTCAGTCTTCTCTT
CCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGG
CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAT
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG
CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACAGCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACCTACAAGACCACGCTCCCGTGTGACTCCGACGGCTCCTTCTTCC
TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT
CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CTGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-7B13 Heavy chain IgG1 N297G polypeptide (SEQ ID NO: 267)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
SGSGSGGGGSEVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYIMNWVKQGHGKSL
EWIGRVNPSNDDTRYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCTRWF
YFDYWQGQTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFSVMSVMHEALHNHYTQKSLSL
SPGK

FIG. 11B0

RSPO2 (F105R/F109A), LP1-8M24 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 268)

CAGGTTTCAGCTGCAGCAGTCTGGAGCTGAGCTGGCGAGGCCTGGGGCTTCAGTG
AAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACAAATTATGGTATAAACTGGG
TGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAGATTTTTCCTAGAA
GTGATAATACTTTCTACAATGAGAAGTTCAAGGGCAAGGCCACACTGACTGCAG
ACAAATCCTCCACCACAGCGTACATGGAGCTCCGCAGCCTGACATCTGAGGACT
CTGCGGTCTATTTCTGTGCAAGAAAAGGCAGGGACTACGGTACTAGCCACTACTT
TGACTACTGGGGTCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG
GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGA
ACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGGCTGTCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACC
CAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAG
AAAGTTGAGCCCAAATCTTGTGGATCCGGCTCCGGACATCATCATCACCATCAC

RSPO2 (F105R/F109A), LP1-8M24 Heavy chain IgG1 N297G polypeptide (SEQ ID NO: 269)

QVQLQQSGAELARPGASVKLSCKASGYTFTNYGINWVKQRTGQGLEWIGEIFPRSD
NTFYNEKFKGKATLTADKSSTTAYMELRSLTSEDSAVYFCARKGRDYGTSHYFDYW
GQGTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGS
GSGHHHHHH

FIG. 11BP

RSPO2 (F105R/F109A), LP1-9M16 Heavy chain IgG1 N297G polynucleotide (SEQ ID NO: 270)

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTACGG
TGCCAGCAAAAGCTGTTTTTCTTCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CTGCACTAAGTGCAAAGTCGGCTTCTACCTTACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCAGTACTACTACATGAACTGGGTGAAGCAGAGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAACAATGGTGGTTCTAACT
ACAACCAGAAATTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCAGCA
CAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACTG
TGCAAGTCGAAACTTCGATGTCTGGGGCGCAGGGACCACGGTCACCGTCTCCAG
CGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACC
TCTGGGGGACACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTCTGGAAGTCAAGCGCCCTGACCAGCGGCGTGCACACCTTCCCG
GCTGTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT
CCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCA
ACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACACAT
GCCCACCGTGCCCAGCACCTGAACCTCCTGGGGGGACCGTCAGTCTTCCCTCTTCCC
CCCAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGT
GGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG
CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAA
AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
GAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
TGTCTCCGGGTAAA

RSPO2 (F105R/F109A), LP1-9M16 Heavy chain IgG1 N297G polypeptide (SID NO: 271)

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSRSDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
SGSGSGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYIMNWVKQSHGKSL
EWIGRVNPNNGGSNYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCASRNF
DVWGAGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVSMHEALHNHYTQKSLSLSP
GK

FIG. 11BQ

Anti-ASGR1 heavy chain polynucleotide (SEQ ID NO: 272)

GAAGTGCAGCTGCTGGAATCCGGGGGGCGGACTGGTGTCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCCTGGAAAAGGCCTCGAATGGGTGTGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCCTACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCCTTGTCACCGTGTGCGAGTGCTAGCACCAAGGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCTGGAACCTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCAGCTGTCTACAGTCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACC
GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCTGTGGTTCAGCGTCTCACCCTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Anti-ASGR1 heavy chain polypeptide (SEQ ID NO: 273)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKV DKTVERKCCVEC
PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPM
LSDGGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

FIG. 11BR

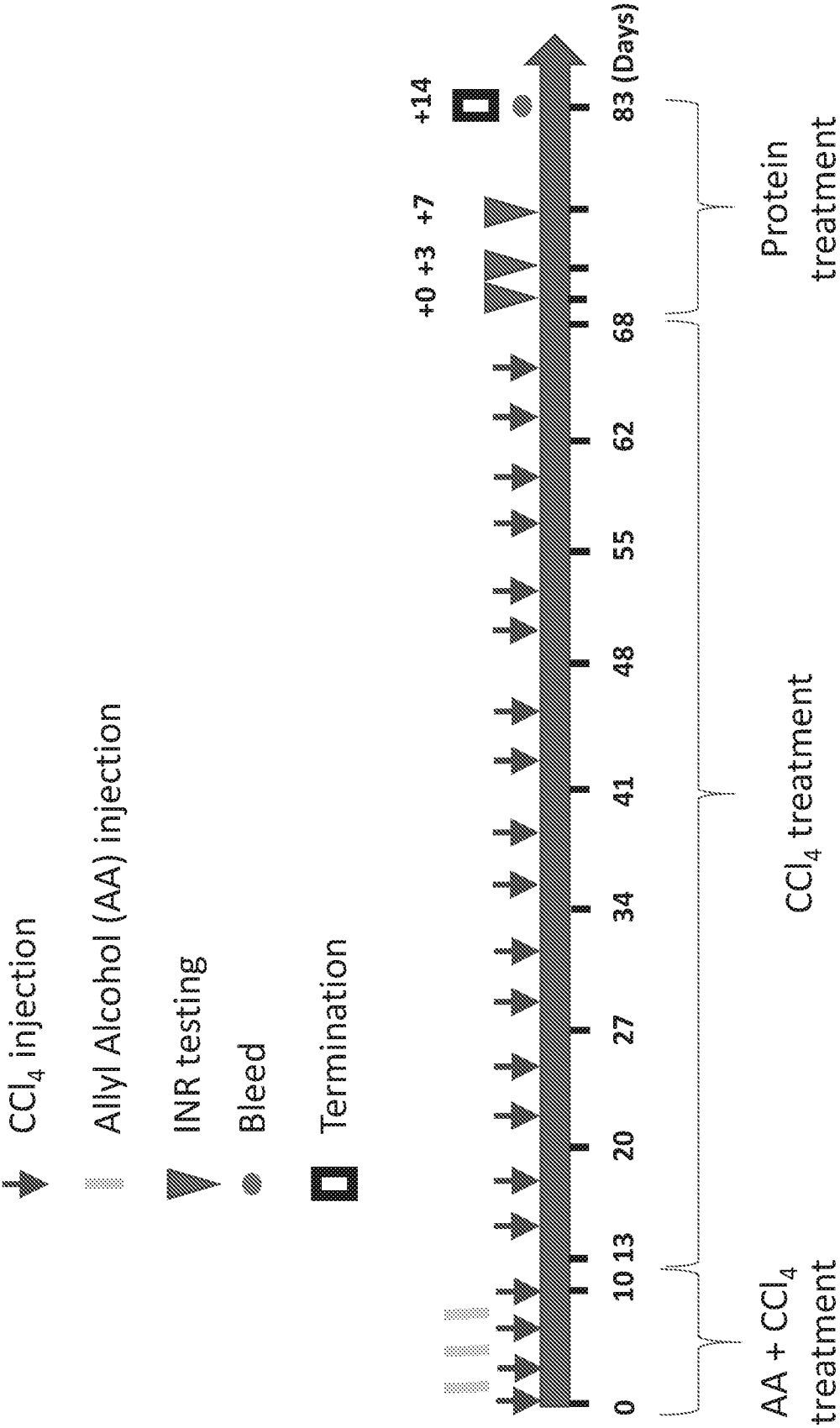


FIG. 12

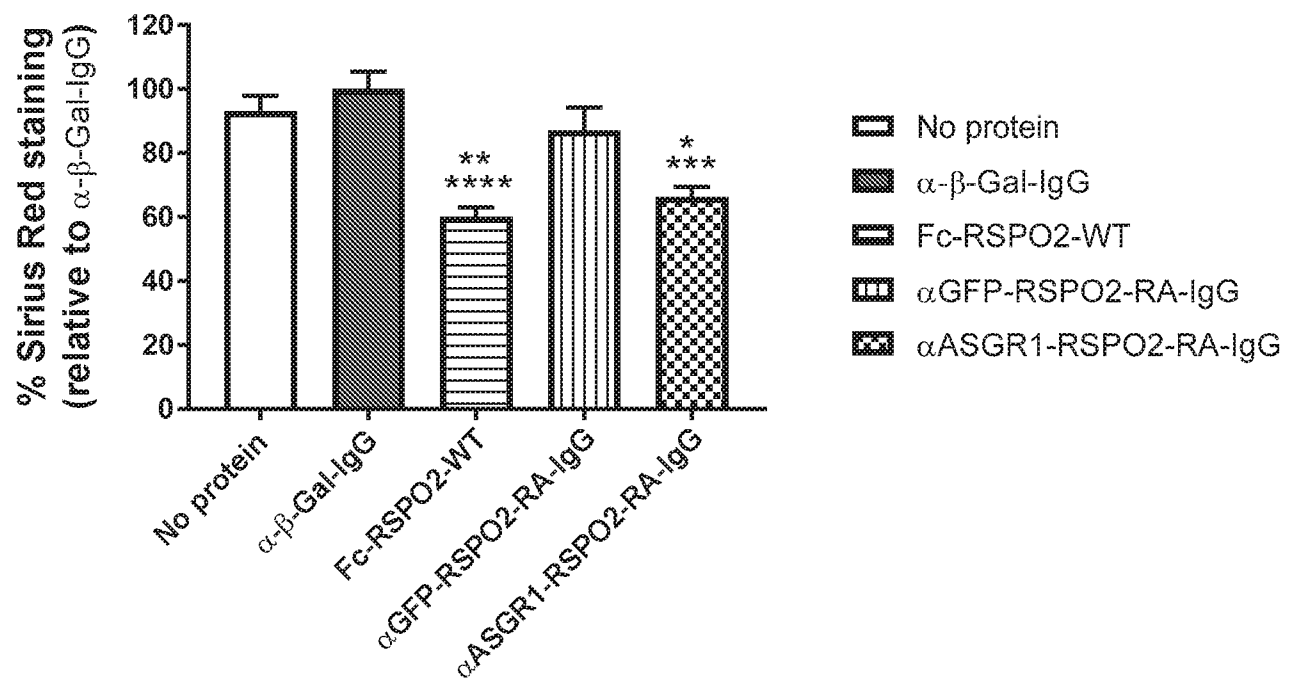
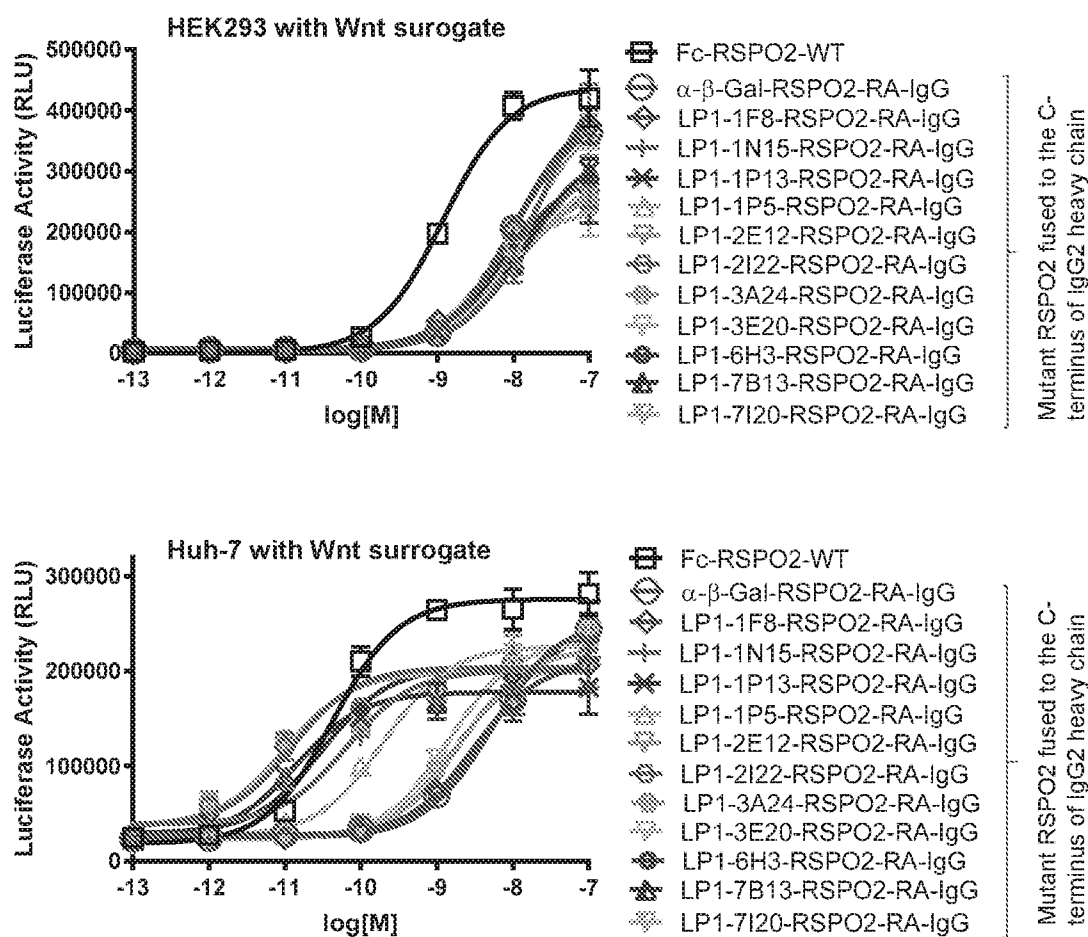
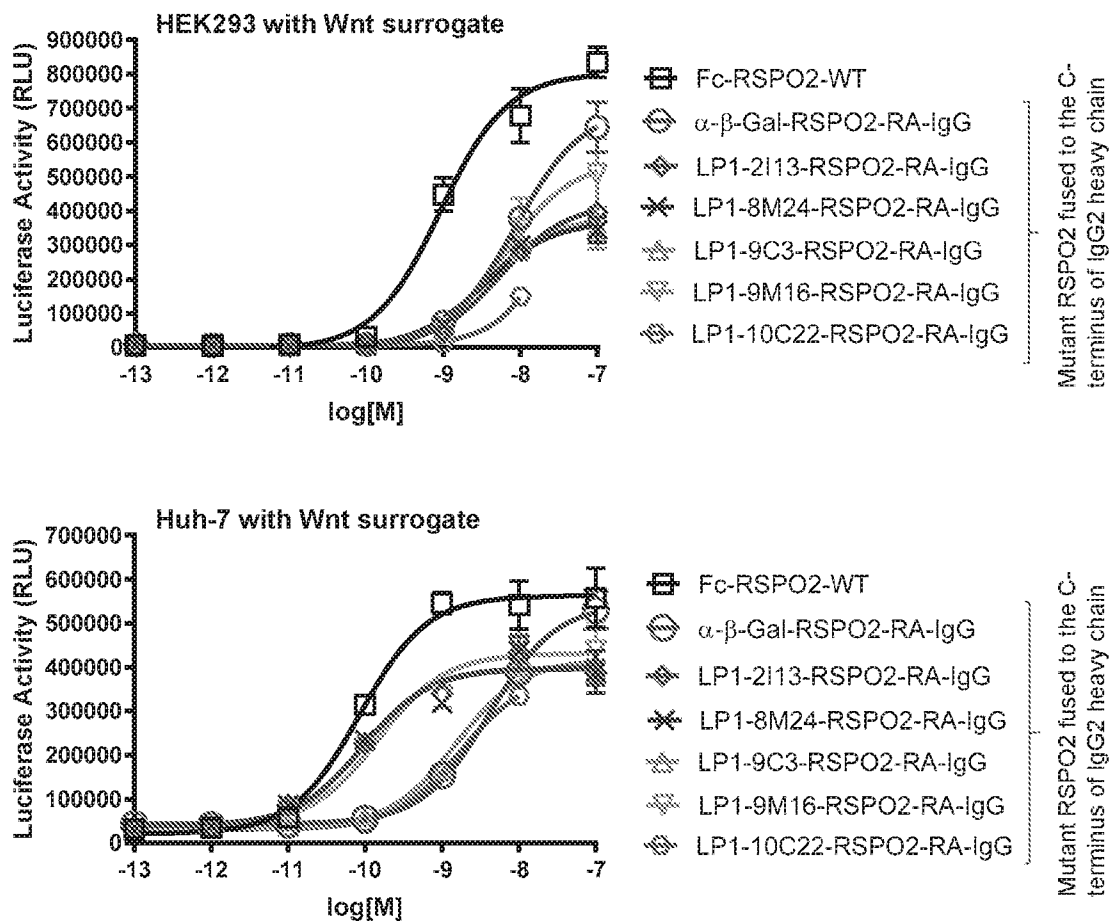


FIG 13



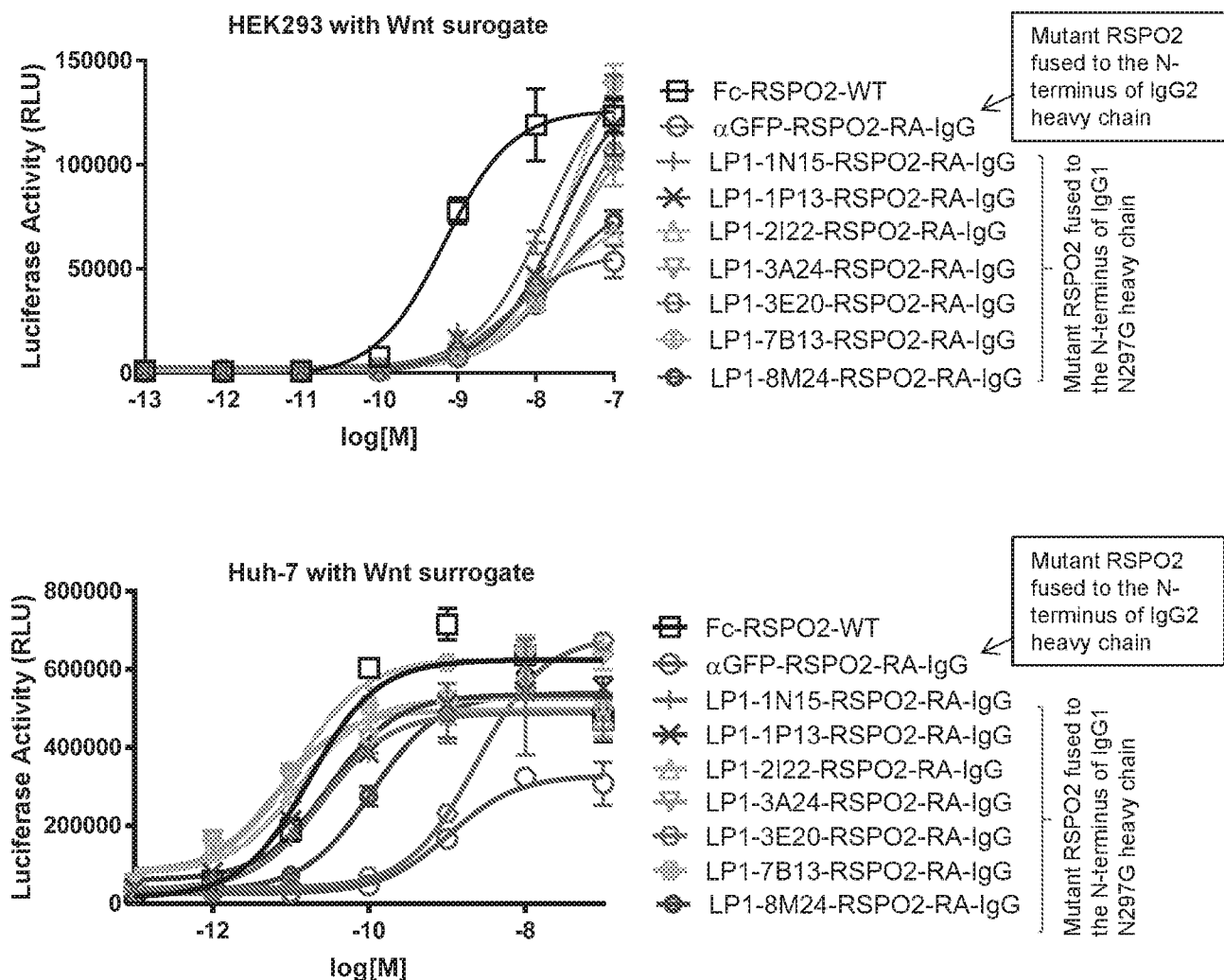
	HEK293		Huh-7	
	% Emax of RSPO	EC50 (M)	% Emax of RSPO	EC50 (M)
Fc-RSPO2-WT	100.0	1.2E-09	100.0	4.2E-11
α - β -Gal-RSPO2-RA-IgG	91.3	9.8E-09	92.0	5.4E-09
LP1-1F8-RSPO2-RA-IgG	94.1	1.0E-08	76.4	3.0E-09
LP1-1N15-RSPO2-RA-IgG	111.5	2.2E-08	72.8	6.5E-11
LP1-1P13-RSPO2-RA-IgG	78.1	1.4E-08	64.5	1.4E-11
LP1-1P5-RSPO2-RA-IgG	86.8	8.6E-09	82.1	2.0E-10
LP1-2E12-RSPO2-RA-IgG	93.7	1.5E-08	81.2	2.0E-09
LP1-2I22-RSPO2-RA-IgG	74.3	1.3E-08	74.1	1.2E-11
LP1-3A24-RSPO2-RA-IgG	62.9	9.6E-09	72.1	1.0E-11
LP1-3E20-RSPO2-RA-IgG	65.5	8.9E-09	84.0	1.4E-09
LP1-6H3-RSPO2-RA-IgG	59.9	5.0E-09	88.7	4.8E-09
LP1-7B13-RSPO2-RA-IgG	69.1	7.8E-09	74.0	3.1E-11
LP1-7I20-RSPO2-RA-IgG	54.6	4.6E-09	76.2	1.7E-09

FIG. 14A



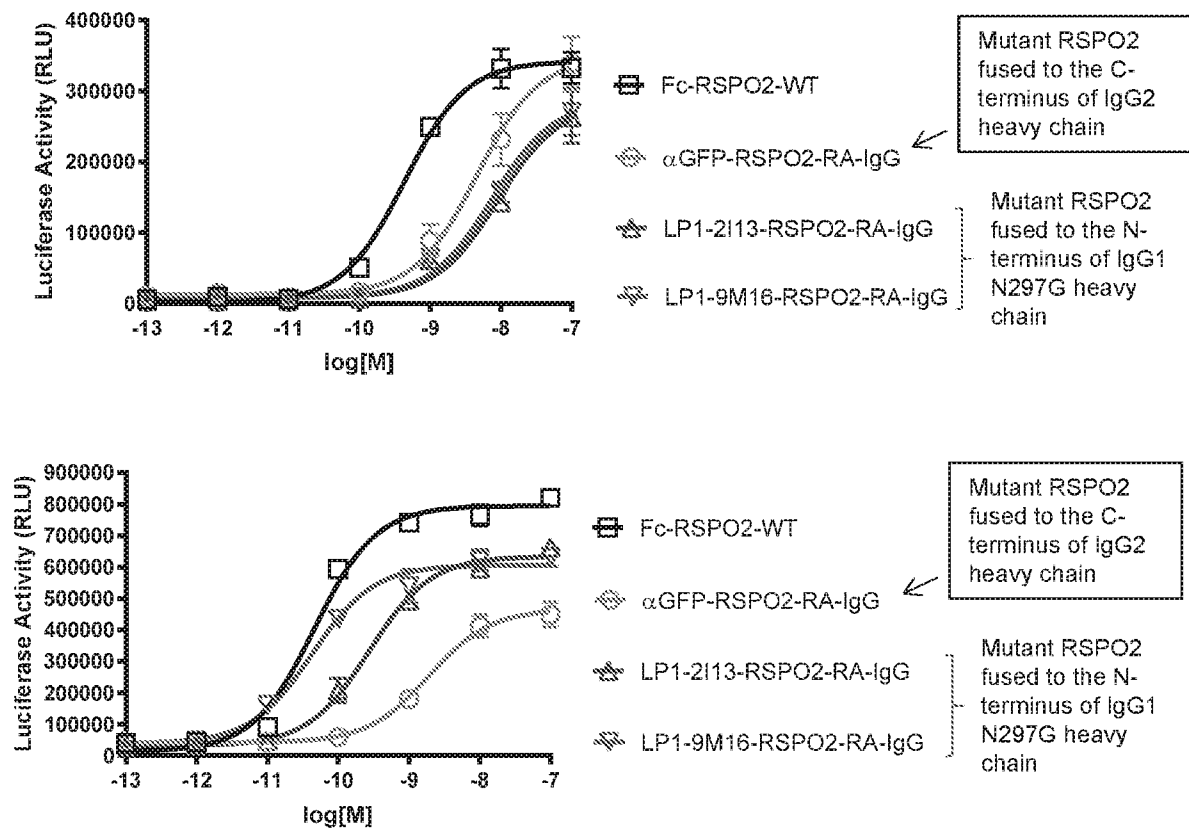
	HEK293		Huh-7	
	% Emax of RSPO	EC50 (M)	% Emax of RSPO	EC50 (M)
Fc-RSPO2-WT	148.4	9.1E-10	94.9	8.5E-11
α - β -Gal-RSPO2-RA-IgG	129.6	8.7E-09	91.8	4.1E-09
LP1-2I13-RSPO2-RA-IgG	78.2	5.6E-09	67.3	9.4E-11
LP1-8M24-RSPO2-RA-IgG	68.1	3.3E-09	66.9	9.4E-11
LP1-9C3-RSPO2-RA-IgG	70.5	3.4E-09	70.5	1.5E-09
LP1-9M16-RSPO2-RA-IgG	100.9	6.2E-09	72.8	1.5E-10
LP1-10C22-RSPO2-RA-IgG	N.D.	N.D.	65.4	1.7E-09

FIG. 14B



	HEK293		Huh-7	
	% Emax of RSPO	EC50 (M)	% Emax of RSPO	EC50 (M)
Fc-RSPO2-WT	144.7	6.752E-10	100.9	1.8E-11
αGFP-RSPO2-RA-IgG	65.3	4.399E-09	53.1	1.1E-09
LP1-1N15-RSPO2-RA-IgG	169.0	1.346E-08	78.9	2.5E-11
LP1-1P13-RSPO2-RA-IgG	163.3	2.056E-08	86.4	3.1E-11
LP1-2I22-RSPO2-RA-IgG	84.4	1.14E-08	84.7	1.3E-11
LP1-3A24-RSPO2-RA-IgG	141.0	2.49E-08	80.1	6.6E-12
LP1-3E20-RSPO2-RA-IgG	156.7	2.912E-08	110.5	2.4E-09
LP1-7B13-RSPO2-RA-IgG	210.1	3.202E-08	101.0	1.2E-11
LP1-8M24-RSPO2-RA-IgG	96.5	1.631E-08	87.0	1.1E-10

FIG. 14C



	HEK293		Huh-7	
	% Emax of RSPO	EC50 (M)	% Emax of RSPO	EC50 (M)
Fc-RSPO2-WT	116.9	4.3E-10	118.8	4.6E-11
αGFP-RSPO2-RA-IgG	118.9	4.6E-09	69.6	1.9E-09
LP1-2I113-RSPO2-RA-IgG	96.7	9.0E-09	94.8	2.7E-10
LP1-9M16-RSPO2-RA-IgG	98.1	7.6E-09	90.6	4.3E-11

FIG. 14D

SEQ ID NOs	Common Name	Dose mg/kg	# mice
155, 156, 159, 160	α - β -Gal	5	3
29, 30, 272, 273	α ASGR1-IgG	5	3
25-28	α GFP-RSPO2-RA-IgG NG	5	3
29 - 32	α ASGR1-RSPO2-RA-IgG	5	3
194, 195, 254, 255	LP1-1N15-RSPO2-RA-IgG	5	3
198, 199, 256, 257	LP1-1P13-RSPO2-RA-IgG	5	3
210, 211, 258, 259	LP1-2I13-RSPO2-RA-IgG	5	2
214, 215, 260, 261	LP1-2I22-RSPO2-RA-IgG	5	3
218, 219, 262, 263	LP1-3A24-RSPO2-RA-IgG	5	2
222, 223, 264, 265	LP1-3E20-RSPO2-RA-IgG	5	3
230, 231, 266, 267	LP1-7B13-RSPO2-RA-IgG	5	2
238, 239, 268, 269	LP1-8M24-RSPO2-RA-IgG	5	3
246, 247, 270, 271	LP1-9M16-RSPO2-RA-IgG	5	2

FIG. 15A

Axin2 induction at 24 hr

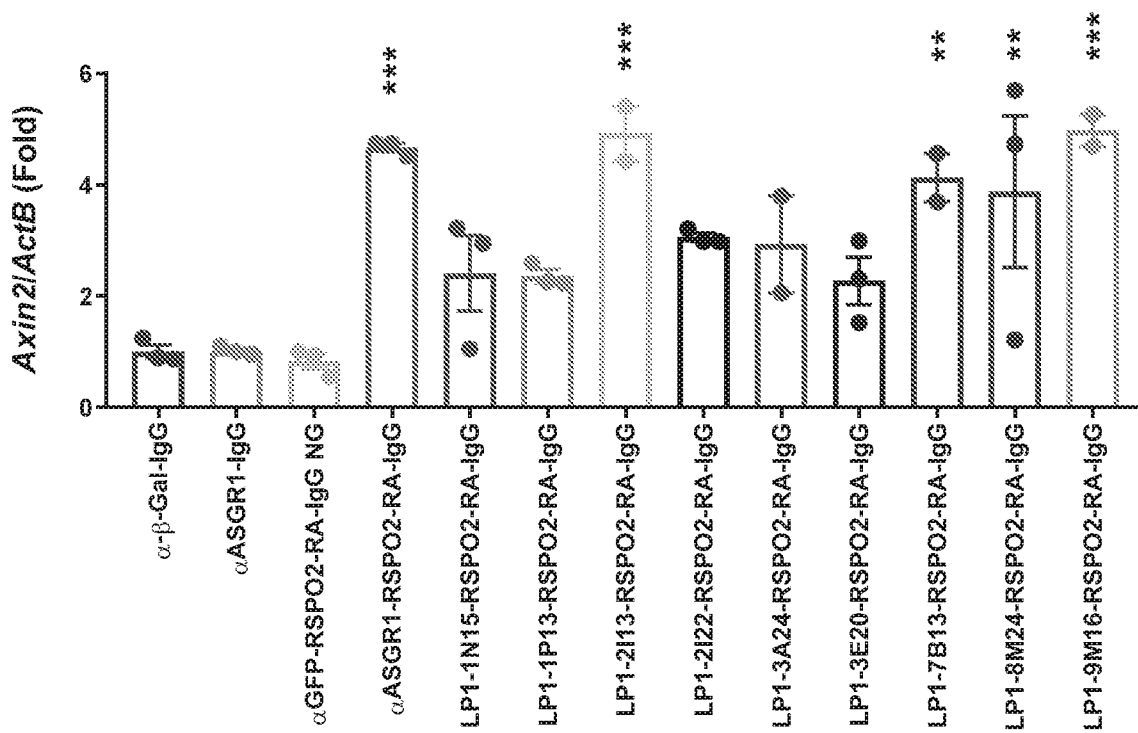


FIG. 15B

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<110> Surrozen, Inc.
Zhang, Zhengjian
Li, Yang
Yeh, Wen-Chen
Yuan, Tom Zhiye
Baribault, Helene

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<213> Homo sapiens

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35 40 45

Glu Val Asn Gly Cys Leu Lys Cys Ser Pro Lys Leu Phe Ile Leu Leu
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Glu Arg Asn Asp Ile Arg Gln Val Gly Val Cys Leu Pro Ser Cys Pro
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Pro Gly Tyr Phe Asp Ala Arg Asn Pro Asp Met Asn Lys Cys Ile Lys
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Lys Lys Gln Gln Leu Cys Gly Phe Arg Arg Gly Ser Glu Glu Arg Thr
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Arg Arg Val Leu His Ala Pro Val Gly Asp His Ala Ala Cys Ser Asp
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Thr Lys Glu Thr Arg Arg Cys Thr Val Arg Arg Val Pro Cys Pro Glu
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Gly Gln Lys Arg Arg Lys Gly Gly Gln Gly Arg Arg Glu Asn Ala Asn
210 215 220

Arg Asn Leu Ala Arg Lys Glu Ser Lys Glu Ala Gly Ala Gly Ser Arg
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20

25

30

Ser Tyr Val Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys
 35 40 45

Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg
 50 55 60

Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser
 65 70 75 80

Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys
 85 90 95

Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr Lys
 100 105 110

Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys
 115 120 125

Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly
 130 135 140

Cys Glu Val Gly His Trp Ser Glu Trp Gly Thr Cys Ser Arg Asn Asn
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Arg Thr Cys Gly Phe Lys Trp Gly Leu Glu Thr Arg Thr Arg Gln Ile
 165 170 175

Val Lys Lys Pro Val Lys Asp Thr Ile Leu Cys Pro Thr Ile Ala Glu
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Ser Arg Arg Cys Lys Met Thr Met Arg His Cys Pro Gly Gly Lys Arg
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Thr Pro Lys Ala Lys Glu Lys Arg Asn Lys Lys Lys Lys Arg Lys Leu
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Met His Pro Asn Val Ser Gln Gly Cys Gln Gly Gly Cys Ala Thr Cys
35 40 45

Ser Asp Tyr Asn Gly Cys Leu Ser Cys Lys Pro Arg Leu Phe Phe Ala
50 55 60

Leu Glu Arg Ile Gly Met Lys Gln Ile Gly Val Cys Leu Ser Ser Cys
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Pro Ser Gly Tyr Tyr Gly Thr Arg Tyr Pro Asp Ile Asn Lys Cys Thr
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Lys Cys Lys Ala Asp Cys Asp Thr Cys Phe Asn Lys Asn Phe Cys Thr
100 105 110

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Gly Glu Arg Gly Lys Lys Gly Arg Glu Arg Lys Arg Lys Lys Pro Asn
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Ser Cys Phe Ser Gln Asp Phe Cys Ile Arg Cys Lys Arg Gln Phe Tyr
100 105 110

Leu Tyr Lys Gly Lys Cys Leu Pro Thr Cys Pro Pro Gly Thr Leu Ala
115 120 125

His Gln Asn Thr Arg Glu Cys Gln Gly Glu Cys Glu Leu Gly Pro Trp
130 135 140

Gly Gly Trp Ser Pro Cys Thr His Asn Gly Lys Thr Cys Gly Ser Ala
145 150 155 160

Trp Gly Leu Glu Ser Arg Val Arg Glu Ala Gly Arg Ala Gly His Glu
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Glu Ala Ala Thr Cys Gln Val Leu Ser Glu Ser Arg Lys Cys Pro Ile
180 185 190

Gln Arg Pro Cys Pro Gly Glu Arg Ser Pro Gly Gln Lys Lys Gly Arg
195 200 205

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Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
      50              55              60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
      65              70              75              80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85              90              95

Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
      100              105              110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
      115              120              125

Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
      130              135              140

Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
      145              150              155              160

Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
      165              170              175

Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
      180              185              190

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
      195              200              205

Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser

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SRZN_010_03WO_ST25 (1).TXT

210

215

220

Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240

Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser
245 250 255

Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu
260 265 270

Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro
275 280 285

Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg
290 295 300

Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr
305 310 315 320

Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu
325 330 335

Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350

Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His His His
355 360 365

His His His His
370

<210> 7

<211> 1119

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-GFP and RSP02 mutant fusion sequence

<400> 7

SRZN_010_03WO_ST25 (1).TXT

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cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac      180
gccgactccg tgaagggaac gttcaccatt agccgggata acagcaagaa cactctgtac      240
ttgcaaata ga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtag      300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcatc cgggtggtag      360
ggatccggag gcggaggaag cggaggaggg gggtcagaca tcgaactcac ccagcccccg      420
tcagtgtccg tggcccctgg acagactgcg cgcattctct gctccggcga caacctgggg      480
aagaaatacg tgtactggta ccagcagaag ccaggtaag cccctgtgct ggtcatctac      540
ggcgacgacg aaaggccgtc aggcattcca gagcgcttct ccggctcaa ctccgggaat      600
actgccacc ttaccatttc cggaaccag gccgaggatg aagcggatta ctattgcgcg      660
agctacgata gcagccacat cctgatcgtg tttggaggcg gtactaagct gaccgtgctg      720
ggaagcggtg gatcaaacc aatttgcaag ggatgcctga gctgtagcaa ggacaacgga      780
tgttcacggg gccagcaaaa gctgtttttc ttctccggc gggaaggaat gcggcagtag      840
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac      900
cgatgcgcca gatgccggat cgagaactgc gatagctgcc gcagcaagga cgcctgcact      960
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc     1020
ttgccccgc tggaggagac tatggaatgc gtggaggggc gagactacaa ggacgacgat     1080
gacaagggt cccaccatca ccaccatcat caccactag                                1119

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<210> 8

<211> 372

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-GFP and RSP02 mutant fusion sequence

<400> 8

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
130 135 140

Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
145 150 155 160

Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
165 170 175

Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
180 185 190

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
195 200 205

Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser
210 215 220

SRZN_010_03WO_ST25 (1).TXT

Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240

Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser
245 250 255

Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu
260 265 270

Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro
275 280 285

Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg
290 295 300

Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr
305 310 315 320

Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu
325 330 335

Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350

Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His His His
355 360 365

His His His His
370

<210> 9
<211> 1119
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab: anti-GFP and RSP02 mutant fusion sequence

<400> 9
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SRZN_010_03WO_ST25 (1).TXT

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gccgactccg tgaaggacg gttcaccatt agccgggata acagcaagaa cactctgtac	240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac	300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcatc cgggtggtgga	360
ggatccggag gcggaggaag cggaggaggg ggttcagaca tcgaactcac ccagcccccg	420
tcagtgtccg tggcccctgg acagactgcg cgcatctcct gctccggcga caacctgggg	480
aagaaatacg tgtactggta ccagcagaag ccagggtcaag cccctgtgct ggtcatctac	540
ggcgacgacg aaaggccgtc aggcattcca gagcgcttct ccggctcaa ctccgggaat	600
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agctacgata gcagccacat cctgatcgtg tttggaggcg gtactaagct gaccgtgctg	720
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tgttcacggg gccagcaaaa gctgtttttc ttcctccggg ccgaaggaaat ggccgcatac	840
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac	900
cgatgcgcca gatgccggat cgagaactgc gatagctgcc gcagcaagga cgcctgcact	960
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc	1020
ttcgccccgc tggaggagac tatggaatgc gtggaggggc gagactacaa ggacgacgat	1080
gacaagggct cccaccatca ccaccatcat caccactag	1119

<210> 10

<211> 372

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-GFP and RSP02 mutant fusion sequence

<400> 10

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5					10					15	

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr

20

25

30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
 130 135 140

Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
 145 150 155 160

Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
 165 170 175

Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
 180 185 190

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
 195 200 205

Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser
 210 215 220

Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

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SRZN_010_03WO_ST25 (1).TXT

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cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac      180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac      240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc      300
agctcacgcc ggtggtacct tgagtactgg ggacaggga cccttgtcac cgtgtccagc      360
ggtggcggcg gaagcggcgg gggcggatcc ggtggcgggg gctcagagct caccaggac      420
cccgctgtgt ccgtggcctt gggacagacc gtgcgcatca catgccaggc cgatagcctg      480
cggagctatt acgcctcgtg gtaccagcag aagcctgggt aagcgccggt cctggtcac      540
tacggaaaga acaaccgccc gtccggaatt ccagacaggt tcagcggatc cagctcgggg      600
aacaccgcct cactgactat caccggagca caggccgaag atgaagccga ctactactgc      660
aactccctgg agcggattgg atacctgagc tacgtgtttg gtggcggcac gaagctcacc      720
gtgctgggaa gcggtggatc aaacccaatt tgcaagggat gcctgagctg tagcaaggac      780
aacggatggt caccgtgcca gaaaagctg tttttcttcc tccggcggga aggaatgcgg      840
cagtacggcg aatgtctcca ctctgcccc tcgggggtatt acggacaccg cgcgcctgac      900
atgaaccgat gcgccagatg ccgatcgag aactgcgata gctgcttcag caaggacttc      960
tgactaagt gcaaagtcgg cttctacctt caccggggca gatgttttga cgaatgcccc     1020
gatggcttcg ccccgctgga ggagactatg gaatgcgtgg agggcggaga ctacaaggac     1080
gacgatgaca agggctccca ccatcaccac catcatcacc actag                        1125

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<210> 12

<211> 374

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-ASGR1 and RSP02 wild type fusion sequence

<400> 12

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20           25           30

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SRZN_010_03WO_ST25 (1).TXT

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220

Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240

SRZN_010_03WO_ST25 (1).TXT

Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser
245 250 255

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
260 265 270

Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser
275 280 285

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
290 295 300

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe
305 310 315 320

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
325 330 335

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
340 345 350

Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
355 360 365

His His His His His His
370

<210> 13
<211> 1125
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab: anti-ASGR1 and RSP02 mutant fusion sequence

<400> 13
gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180

SRZN_010_03WO_ST25 (1).TXT

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gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac      240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc      300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc      360
ggtggcggcg gaagcggcgg gggcggatcc ggtggcgggg gctcagagct caccagggac      420
cccgctgtgt ccgtggcctt gggacagacc gtgcgcatca catgccaggg cgatagcctg      480
cggagctatt acgcctcgtg gtaccagcag aagcctgggtc aagcgccggt cctggtcatt      540
tacggaaaga acaaccgccc gtccggaatt ccagacaggt tcagcggatc cagctcgggg      600
aacaccgcct cactgactat caccggagca caggccgaag atgaagccga ctactactgc      660
aactccctgg agcggattgg atacctgagc tacgtgtttg gtggcggcac gaagctcacc      720
gtgctgggaa gcggtggatc aaacccaatt tgcaagggat gcctgagctg tagcaaggac      780
aacggatggt caggtgcca gcaaaagctg tttttcttcc tccggcggga aggaatgcgg      840
cagtacggcg aatgtctcca ctctgcccc tcgggggtatt acggacaccg cgcgctgac      900
atgaaccgat gcgccagatg ccggatcgag aactgcgata gctgccgcag caaggacgcc      960
tgcactaagt gcaaagtcgg cttctacctt caccggggca gatgttttga cgaatgcccc     1020
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gacgatgaca agggctccca ccataccacc catcatcacc actag                        1125

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<210> 14
 <211> 374
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab: anti-ASGR1 and RSP02 mutant fusion sequence

<400> 14

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220

Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240

Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser

245

250

255

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
 260 265 270

Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser
 275 280 285

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
 290 295 300

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
 305 310 315 320

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
 325 330 335

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
 340 345 350

Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
 355 360 365

His His His His His His
 370

<210> 15

<211> 1125

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-ASGR1 and RSP02 mutant fusion sequence

<400> 15

gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60

tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120

cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180

gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240

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cccgtgtgt	ccgtggcctt	gggacagacc	gtgcgcacat	catgccaggg	cgatagcctg	480
cggagctatt	acgcctcgtg	gtaccagcag	aagcctggtc	aagcgccggg	cctgggtcatc	540
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aacaccgcct	cactgactat	caccggagca	caggccgaag	atgaagccga	ctactactgc	660
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atgaaccgat	gcgccagatg	ccggatcgag	aactgcgata	gctgccgcag	caaggacgcc	960
tgactaagt	gcaaagtcgg	cttctacctt	caccggggca	gatgttttga	cgaatgcccc	1020
gatggcttcg	ccccgctgga	ggagactatg	gaatgcgtgg	agggcggaga	ctacaaggac	1080
gacgatgaca	agggctccca	ccatcaccac	catcatcacc	actag		1125

<210>	16
<211>	374
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Made in Lab: anti-ASGR1 and RSP02 mutant fusion sequence

<400> 16

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

SRZN_010_03WO_ST25 (1).TXT

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220

Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240

Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser
245 250 255

SRZN_010_03WO_ST25 (1).TXT

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
260 265 270

Phe Leu Arg Ala Glu Gly Met Ala Ala Tyr Gly Glu Cys Leu His Ser
275 280 285

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
290 295 300

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
305 310 315 320

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
325 330 335

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
340 345 350

Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
355 360 365

His His His His His His
370

<210> 17
<211> 1134
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab: anti-TFR1 and RSP02 wild type fusion sequence

<400> 17
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tcattgcaagg ggtccgggta taccttcact gactatgcaa tgcactgggt aaagcagagc 120
cacgccaagt ccttggagtg gatcggaggc attagtagct acttcggacg caccaactac 180
aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240
atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcgggttg 300

SRZN_010_03WO_ST25 (1).TXT

tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc	360
ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa	420
tcccctgcga gcctggcggt aagtttggga cagagagcca cgatttcctg ccgagcgagt	480
gaaagcgtag acgactacgg caattctttc atgcactggt atcaacagaa gccaggccaa	540
ccgccgaagc tgcttatcta tcgcgcgtcc aatttggagt cagggatccc tgcacgattt	600
tcaggttctg gaagtaggac agactttaca cttacgataa accccgtgga agcggatgac	660
gtcgcaacct actattgtca acaaagcaat gaagcaccac ctaccttcgg aggtggcact	720
aaattggaaa ttaggggaag cggtggatca aacccaattt gcaagggatg cctgagctgt	780
agcaaggaca acggatgttc acggtgccag caaaagctgt ttttcttcct ccggcgggaa	840
ggaatgcggc agtacggcga atgtctccac tcctgcccct cggggtatta cggacaccgc	900
gcgctgaca tgaaccgatg cgccagatgc cggatcgaga actgcgatag ctgcttcagc	960
aaggacttct gcactaagtg caaagtcggc ttctaccttc accggggcag atgttttgac	1020
gaatgcccg atggcttcgc cccgctggag gagactatgg aatgcgtgga gggcggagac	1080
tacaaggacg acgatgacaa gggctccac catcaccacc atcatcacca ctag	1134

<210> 18

<211> 377

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-TFR1 and RSP02 wild type fusion sequence

<400> 18

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Leu	Val	Arg	Pro	Gly	Val
1			5					10						15	

Ser	Val	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr
			20					25					30		

Ala	Met	His	Trp	Val	Lys	Gln	Ser	His	Ala	Lys	Ser	Leu	Glu	Trp	Ile
		35					40					45			

Gly	Gly	Ile	Ser	Thr	Tyr	Phe	Gly	Arg	Thr	Asn	Tyr	Asn	Gln	Lys	Phe

50

55

60

Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
 85 90 95

Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Phe Gln Ser Pro Ala Ser
 130 135 140

Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
 145 150 155 160

Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln
 165 170 175

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu
 180 185 190

Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp
 195 200 205

Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr
 210 215 220

Tyr Cys Gln Gln Ser Asn Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr
 225 230 235 240

Lys Leu Glu Ile Arg Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly
 245 250 255

Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys

260

265

270

Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
 275 280 285

Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
 290 295 300

Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser
 305 310 315 320

Lys Asp Phe Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
 325 330 335

Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
 340 345 350

Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
 355 360 365

Ser His His His His His His His His
 370 375

<210> 19

<211> 1134

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-TFR1 and RSP02 mutant fusion sequence

<400> 19

caagtgaac tccaacaaag cgggtccgag ttggtccgac ccggcgtagc tgtgaaaatc 60

tcatgcaagg ggtccgggta taccttact gactatgcaa tgcactgggt aaagcagagc 120

cacgccaagt ccttgagtg gatcggaggc attagtagct acttcggacg caccaactac 180

aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240

atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcgggttg 300

tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc 360

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ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa 420
tcccctgcga gcctggcggt aagtttggga cagagagcca cgatttcctg ccgagcgagt 480
gaaagcgtag acgactacgg caattctttc atgcactggg atcaacagaa gccaggccaa 540
ccgccgaagc tgcttatcta tcgcgcgtcc aatttggagt cagggatccc tgcacgattt 600
tcaggttctg gaagtaggac agactttaca cttacgataa accccttgga agcggatgac 660
gtcgcaacct actattgtca acaaagcaat gaagcaccac ctaccttcgg aggtggcact 720
aaattggaaa ttaggggaag cggtggatca aacccaattt gcaagggatg cctgagctgt 780
agcaaggaca acggatgttc acggtgccag caaaagctgt ttttcttcct ccggcgggaa 840
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gcgctgaca tgaaccgatg cgccagatgc cggatcgaga actgcgatag ctgccgcagc 960
aaggacgcct gcactaagtg caaagtcggc ttctaccttc accggggcag atgttttgac 1020
gaatgcccgg atggcttcgc cccgctggag gagactatgg aatgcgtgga gggcggagac 1080
tacaaggacg acgatgacaa gggctccac catcaccacc atcatcacca ctag 1134

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<210> 20
 <211> 377
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab: anti-TFR1 and RSP02 mutant fusion sequence

<400> 20

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
 1 5 10 15

Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
 35 40 45

Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
 50 55 60

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Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Phe Gln Ser Pro Ala Ser
130 135 140

Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
145 150 155 160

Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln
165 170 175

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu
180 185 190

Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp
195 200 205

Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr
210 215 220

Tyr Cys Gln Gln Ser Asn Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr
225 230 235 240

Lys Leu Glu Ile Arg Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly
245 250 255

Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
260 265 270

SRZN_010_03WO_ST25 (1).TXT

Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
275 280 285

Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
290 295 300

Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
305 310 315 320

Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
325 330 335

Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
340 345 350

Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
355 360 365

Ser His His His His His His His His
370 375

<210> 21
<211> 1134
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab: anti-TFR1 and RSP02 mutant fusion sequence

<400> 21
caagtgaac tccaacaaag cgggtcccgag ttgggtccgac ccggcgctcag tgtgaaaatc 60
tcatgcaagg ggtccgggta taccttcact gactatgcaa tgcactgggt aaagcagagc 120
cacgccaagt ccttggagtg gatcggaggc attagtacct acttcggacg caccaactac 180
aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240
atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcggtttg 300
tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc 360
ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa 420

SRZN_010_03WO_ST25 (1).TXT						
tcccctgcga	gcctggcggt	aagtttggga	cagagagcca	cgatttcctg	ccgagcgagt	480
gaaagcgtag	acgactacgg	caattctttc	atgcactggg	atcaacagaa	gccaggccaa	540
ccgccgaagc	tgcttatcta	tcgcgcgtcc	aatttggagt	cagggatccc	tgcacgattt	600
tcaggttctg	gaagtaggac	agactttaca	cttacgataa	accccgtgga	agcggatgac	660
gtcgcaacct	actattgtca	aaaagcaat	gaagcaccac	ctaccttcgg	aggtggcact	720
aaattggaaa	ttaggggaag	cggtggatca	aaccaattt	gcaagggatg	cctgagctgt	780
agcaaggaca	acggatgttc	acggtgccag	caaaagctgt	ttttcttcct	ccgggccgaa	840
ggaatggccg	catacggcga	atgtctccac	tcctgcccct	cgggggtatta	cggacaccgc	900
gcgcttgaca	tgaaccgatg	cgccagatgc	cggatcgaga	actgcgatag	ctgccgcagc	960
aaggacgcct	gcactaagtg	caaagtcggc	ttctaccttc	accggggcag	atgttttgac	1020
gaatgcccgg	atggcttcgc	cccgtggag	gagactatgg	aatgcgtgga	gggcgggagac	1080
tacaaggacg	acgatgacaa	gggctcccac	catcaccacc	atcatcacca	ctag	1134

<210>	22
<211>	377
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Made in Lab: anti-TFR1 and RSP02 mutant fusion sequence

<400> 22

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr

65					70					75					80
Met	Glu	Leu	Ala	Arg	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Leu	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Gly	Leu	Ser	Gly	Asn	Tyr	Val	Met	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Ser	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
		115					120					125			
Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Leu	Phe	Gln	Ser	Pro	Ala	Ser
	130					135					140				
Leu	Ala	Val	Ser	Leu	Gly	Gln	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser
145					150					155					160
Glu	Ser	Val	Asp	Asp	Tyr	Gly	Asn	Ser	Phe	Met	His	Trp	Tyr	Gln	Gln
			165						170					175	
Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Arg	Ala	Ser	Asn	Leu
			180					185					190		
Glu	Ser	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Arg	Thr	Asp
		195					200					205			
Phe	Thr	Leu	Thr	Ile	Asn	Pro	Val	Glu	Ala	Asp	Asp	Val	Ala	Thr	Tyr
	210					215					220				
Tyr	Cys	Gln	Gln	Ser	Asn	Glu	Ala	Pro	Pro	Thr	Phe	Gly	Gly	Gly	Thr
225					230					235					240
Lys	Leu	Glu	Ile	Arg	Gly	Ser	Gly	Gly	Ser	Asn	Pro	Ile	Cys	Lys	Gly
				245					250					255	
Cys	Leu	Ser	Cys	Ser	Lys	Asp	Asn	Gly	Cys	Ser	Arg	Cys	Gln	Gln	Lys
			260					265					270		
Leu	Phe	Phe	Phe	Leu	Arg	Ala	Glu	Gly	Met	Ala	Ala	Tyr	Gly	Glu	Cys

275

280

285

Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
 290 295 300

Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
 305 310 315 320

Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
 325 330 335

Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
 340 345 350

Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
 355 360 365

Ser His His His His His His His His
 370 375

<210> 23

<211> 1053

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: Fc-RSP02 fusion sequence

<400> 23

gacaaaactc acacatgccc accgtgcccga gcacctgaag ccgcgggggg accgtcagtc 60

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 120

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 180

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 240

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 300

tgcaaggtct ccaacaaagc cctcggagcc cccatcgaga aaaccatctc caaagccaaa 360

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 420

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 480

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tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc	540
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg	600
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc	660
ctctccctgt ctccgggtaa aggtggtggt ggctcgggag gaggaggctc cggtggcggt	720
ggcagctcaa atcccatttg caagggttgt ttgtcttggt caaaggacaa tgggtgtagc	780
cgatgtcaac agaagttggt cttcttcctt cgaagagaag ggatgcgcca gtatggagag	840
tgcttgcatc cctgcccac cgggtactat ggacaccgag cccagatat gaacagatgt	900
gcaagatgca gaatagaaaa ctgtgattct tgcttttagca aagacttttg taccaagtgc	960
aaagtaggct tttatttgca tagaggccgt tgctttgatg aatgtccaga tggttttgca	1020
ccattagaag aaaccatgga atgtgtggaa tga	1053

<210> 24
 <211> 350
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab: Fc-RSP02 fusion sequence

<400> 24

Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly
1				5					10					15	

Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			20					25					30		

Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
		35					40					45			

Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
	50					55					60				

His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
65					70					75					80

Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
 100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 225 230 235 240

Gly Ser Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp
 245 250 255

Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg
 260 265 270

Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly
 275 280 285

Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg

290

295

300

Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr Lys Cys
 305 310 315 320

Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro
 325 330 335

Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
 340 345 350

<210> 25

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-GFP light chain sequence

<400> 25

gacatcgaac tcacccagcc cccgtcagtg tccgtggccc ctggacagac tgcgcgcatc 60

tcctgctccg gcgacaacct ggggaagaaa tacgtgtact ggtaccagca gaagccaggt 120

caagcccctg tgctgggtcat ctacggcgac gacgaaaggc cgtcaggcat cccagagcgc 180

ttctccggct ccaactccgg gaatactgcc acccttacca tttccggaac ccaggccgag 240

gatgaagcgg attactattg cgcgagctac gatagcagcc acatcctgat cgtgtttgga 300

ggcgggtacca agcttaccgt cctaggtcag cccaaggctg ccccctcggc cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtac 420

ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 26

<211> 214

<212> PRT

<213> Artificial Sequence

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<220>

<223> Made in Lab: anti-GFP light chain sequence

<400> 26

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Lys Lys Tyr Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser Ser His Ile Leu
85 90 95

Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

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Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 27
<211> 1695
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab: RSP02 mutant and anti-GFP Heavy chain IgG2 fusion polynucleotide

<400> 27
aaccaattt gcaagggatg cctgagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga ggggtggtgg ggctcgggag gaggaggctc cgggtggcgg 360
ggcagccagg tccagttggg ggaatccgga gggggtttgg tccagcctgg tggaagcctg 420
cgctctcat gcgccgctag cggattcacc ttctcccgat acggcatgca ttgggtcaga 480
caggcaccg gaaaaggact cgaatgggtg tcgggcattt cctcgatcgg gtcaaacacc 540
tattacgccg actccgtgaa gggacggttc accattagcc gggataacag caagaacact 600
ctgtacttgc aaatgaactc cctgcgggct gaggacaccg ccgtgtacta ctgtgcgcgg 660
tggtacaaga cctatattga cgtctgggga cagggtaccc tcgtgaccgt gtcgagtgct 720
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acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 840
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga 900
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac 960
acctgcaacg tagatcaciaa gccagcaac accaaggtgg acaagacagt tgagcgcaaa 1020

SRZN_010_03WO_ST25 (1).TXT

```

tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc      1080
ttccccccaa aaccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg      1140
gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg      1200
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg      1260
gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag      1320
gtctccaaca aaggcctccc agccccatc gagaaaacca tctccaaaac caaagggcag      1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag      1440
gtcagcctga cctgcctggt caaaggcttc taccacagcg acatcgccgt ggagtggggag      1500
agcaatgggc agccggagaa caactacaag accacgcctc ccatgctgga ctccgacggc      1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc      1620
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc      1680
ctgtctccgg gtaaa                                                    1695

```

<210> 28

<211> 565

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: RSP02 mutant and anti-GFP Heavy chain IgG2 fusion polypeptide

<400> 28

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Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1           5           10          15

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Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
          20          25          30

```

```

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
          35          40          45

```

```

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
          50          55          60

```

SRZN_010_03WO_ST25 (1).TXT

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu
115 120 125

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
130 135 140

Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Gly Met His Trp Val Arg
145 150 155 160

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gly Ile Ser Ser Ile
165 170 175

Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
180 185 190

Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu
195 200 205

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Tyr Lys Thr
210 215 220

Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
225 230 235 240

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
245 250 255

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
260 265 270

SRZN_010_03WO_ST25 (1).TXT

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
275 280 285

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
290 295 300

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
305 310 315 320

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
325 330 335

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
340 345 350

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
355 360 365

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
370 375 380

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
385 390 395 400

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
405 410 415

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
420 425 430

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
435 440 445

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
450 455 460

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
465 470 475 480

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Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
485 490 495

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
500 505 510

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
515 520 525

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
530 535 540

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
545 550 555 560

Leu Ser Pro Gly Lys
565

<210> 29

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-ASGR1 light chain polynucleotide

<400> 29

gacatcgagc tcaccagga ccccgctgtg tccgtggcct tgggacagac cgtgcgcatc	60
acatgccagg gcgatagcct gcggagctat tacgcctcgt ggtaccagca gaagcctggt	120
caagcgccgg tcctgggtcat ctacggaaag aacaaccgcc cgtccggaat tccagacagg	180
ttcagcggat ccagctcggg gaacaccgcc tcttgacta tcaccggagc acaggccgaa	240
gatgaagccg actactactg caactccctg gagcggattg gatacctgag ctacgtgttt	300
ggtggcggtta ccaagcttac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg	360
ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactgggtgtg tctcataagt	420
gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg	480
ggagtggaga ccaccacacc ctccaacaa agcaacaaca agtacgcggc cagcagctat	540

SRZN_010_03WO_ST25 (1).TXT

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 30

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: anti-ASGR1 light chain polypeptide

<400> 30

Asp Ile Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu
85 90 95

Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala

<400>	31						
caggtccagt	tggtggaatc	cggaggggggt	ttgttccagc	ctggtggaag	cctgcgccctc		60
tcatgcgccg	ctagcggatt	caccttctcc	cgatacggca	tgcattgggt	cagacaggca		120
cccggaaaag	gactcgaatg	ggtgtcgggc	atttcctcga	tcgggtcaaa	cacctattac		180
gccgactccg	tgaagggacg	gttcaccatt	agccgggata	acagcaagaa	cactctgtac		240
ttgcaaatga	actccctgcg	ggctgaggac	accgccgtgt	actactgtgc	gcggtggtac		300
aagacctata	ttgacgtctg	gggacaggggt	accctcgtga	ccgtgtcgag	tgctagcacc		360
aagggcccat	cggctcttccc	cctggcaccc	tcctccaaga	gcacctctgg	gggcacagcg		420
gccctgggct	gcctggtcaa	ggactacttc	cccgaaccgg	tgacgggtgtc	gtggaactca		480
ggcgccctga	ccagcggcgt	gcacaccttc	ccggctgtcc	tacagtcctc	aggactctac		540
tccttcagca	gcgtggtgac	cgtgccctcc	agcagcttgg	gcaccagac	ctacatctgc		600
aacgtgaatc	acaagcccag	caacaccaag	gtggacaaga	aagttgagcc	caaatcttgt		660
gacaaaactc	acacatgccc	accgtgccc	gcacctgaac	tcctggggggg	accgtcagtc		720

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```

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca      780
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac      840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac      900
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag      960
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa     1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag     1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag     1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc     1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg     1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc     1320
ctctccctgt ctccgggtaa atga                                             1344

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<210> 32

<211> 568

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab: RSP02 mutant and anti-ASGR1 Heavy chain IgG2 fusion polypeptide

<400> 32

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Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1           5           10          15

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Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
          20          25          30

```

```

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
          35          40          45

```

```

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
          50          55          60

```

```

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly

```

65					70					75					80
Phe	Tyr	Leu	His	Arg 85	Gly	Arg	Cys	Phe	Asp 90	Glu	Cys	Pro	Asp	Gly 95	Phe
Ala	Pro	Leu	Glu 100	Glu	Thr	Met	Glu	Cys 105	Val	Glu	Gly	Gly	Gly	Gly	Ser
Gly	Gly	Gly 115	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Val	Gln 125	Leu	Leu	Glu
Ser	Gly 130	Gly	Gly	Leu	Val	Gln 135	Pro	Gly	Gly	Ser	Leu 140	Arg	Leu	Ser	Cys
Ala 145	Ala	Ser	Gly	Phe	Thr 150	Phe	Ser	Ser	Tyr	Ala 155	Met	Ser	Trp	Val	Arg
Gln	Ala	Pro	Gly	Lys 165	Gly	Leu	Glu	Trp	Val 170	Ser	Ala	Ile	Ser	Gly 175	Ser
Gly	Gly	Ser	Thr 180	Tyr	Tyr	Ala	Asp	Ser 185	Val	Lys	Gly	Arg	Phe 190	Thr	Ile
Ser	Arg	Asp 195	Asn	Ser	Lys	Asn	Thr 200	Leu	Tyr	Leu	Gln	Met 205	Asn	Ser	Leu
Arg	Ala 210	Glu	Asp	Thr	Ala	Val 215	Tyr	Tyr	Cys	Ala	Lys 220	Asp	Phe	Ser	Ser
Arg 225	Arg	Trp	Tyr	Leu	Glu 230	Tyr	Trp	Gly	Gln	Gly 235	Thr	Leu	Val	Thr	Val 240
Ser	Ser	Ala	Ser	Thr 245	Lys	Gly	Pro	Ser	Val 250	Phe	Pro	Leu	Ala	Pro 255	Cys
Ser	Arg	Ser	Thr 260	Ser	Glu	Ser	Thr	Ala 265	Ala	Leu	Gly	Cys	Leu	Val	Lys
Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu

275

280

285

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 290 295 300

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
 305 310 315 320

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 325 330 335

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
 340 345 350

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 355 360 365

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 370 375 380

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
 385 390 395 400

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 405 410 415

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
 420 425 430

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
 435 440 445

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
 450 455 460

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
 465 470 475 480

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

485

490

495

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 500 505 510

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 515 520 525

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 530 535 540

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 545 550 555 560

Ser Leu Ser Leu Ser Pro Gly Lys
 565

<210> 33

<211> 1344

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in Lab: SZC-09033-pFUSEss-aGFP-VH-CH1g-hG1 fusion
 polynucleotide

<400> 33

cagggtccagt tgggtggaatc cggaggggggt ttgggtccagc ctgggtggaag cctgcgccctc 60

tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120

cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180

gccgactccg tgaaggagc gttcaccatt agccgggata acagcaagaa cactctgtac 240

ttgcaaata gaactccctgc ggctgaggac accgccgtgt actactgtgc gcggtgggtac 300

aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcgag tgctagcacc 360

aaggggcccat cggctcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

tccctcagca gcgtgggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600

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aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt      660
gacaaaactc acacatgccc accgtgcccga gcacctgaac tcctggggggg accgtcagtc      720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca      780
tgcgtggtgg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtacgtggac      840
ggcgtggagg tgcataatgc caagacaaaag ccgcggggagg agcagtacaa cagcacgtac      900
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag      960
tgcaagggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa     1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag     1080
aaccagggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag     1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc     1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg     1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc     1320
ctctccctgt ctccgggtaa atga                                             1344

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<210> 34
 <211> 447
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab: SZC-09033-pFUSEss-aGFP-VH-CHlg-hG1 fusion polypeptide

<400> 34

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val

50

55

60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
 210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

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260

265

270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 35

<211> 693

<212> DNA

<213> Homo sapiens

SRZN_010_03WO_ST25 (1).TXT

```

<400> 35
cagaacagcc agctccagga agaactgagg ggcctccgcg aaaccttctc caacttcacg      60
gcttcgaccg aagctcaagt caaggggttg tccacacaag gcggcaacgt cggacgcaag      120
atgaagtcgc tggagtccca gctggaaaag cagcagaagg atctctccga ggatcacagc      180
tcactgctgt tgcacgtgaa gcagttcgtg tcggacctga ggtccctgag ctgtcagatg      240
gcggcactgc agggaaacgg ttccgaaaga acttgctgcc ctgtgaattg ggtggagcac      300
gagagaagct gctactgggt ctcgcggtcc ggcaaagcct gggcggacgc cgacaactat      360
tgtcggctgg aggatgcgca cctgggtggtc gtgacctcct gggaggaaca gaagtttgtg      420
cagcaccata tcggtcccgt gaacacttgg atggggctgc acgacaaaaa cggaccgtgg      480
aaatgggtgg atgggactga ttacgaaacc ggattcaaga actggcgccc agagcagccc      540
gacgattggt acggacatgg actggggggc ggagaggact gcgcccactt caccgacgac      600
ggccggtgga acgacgacgt gtgccagcgg ccgtaccgct gggctctgcga aaccgagctg      660
gacaaggcca gccaggagcc acctctcctt tga                                     693

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<210> 36
<211> 230
<212> PRT
<213> Homo sapiens

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```

<400> 36
Gln Asn Ser Gln Leu Gln Glu Glu Leu Arg Gly Leu Arg Glu Thr Phe
1          5          10         15
Ser Asn Phe Thr Ala Ser Thr Glu Ala Gln Val Lys Gly Leu Ser Thr
          20         25         30
Gln Gly Gly Asn Val Gly Arg Lys Met Lys Ser Leu Glu Ser Gln Leu
          35         40         45
Glu Lys Gln Gln Lys Asp Leu Ser Glu Asp His Ser Ser Leu Leu Leu
          50         55         60
His Val Lys Gln Phe Val Ser Asp Leu Arg Ser Leu Ser Cys Gln Met
65         70         75         80

```

SRZN_010_03WO_ST25 (1).TXT

Ala Ala Leu Gln Gly Asn Gly Ser Glu Arg Thr Cys Cys Pro Val Asn
85 90 95

Trp Val Glu His Glu Arg Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys
100 105 110

Ala Trp Ala Asp Ala Asp Asn Tyr Cys Arg Leu Glu Asp Ala His Leu
115 120 125

Val Val Val Thr Ser Trp Glu Glu Gln Lys Phe Val Gln His His Ile
130 135 140

Gly Pro Val Asn Thr Trp Met Gly Leu His Asp Gln Asn Gly Pro Trp
145 150 155 160

Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Lys Asn Trp Arg
165 170 175

Pro Glu Gln Pro Asp Asp Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190

Asp Cys Ala His Phe Thr Asp Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205

Gln Arg Pro Tyr Arg Trp Val Cys Glu Thr Glu Leu Asp Lys Ala Ser
210 215 220

Gln Glu Pro Pro Leu Leu
225 230

<210> 37
<211> 684
<212> DNA
<213> Homo sapiens

<400> 37
agggg'gcac agctgcaagc cgagctgcgg tccctgaagg aagctttctc aaactttctcg 60
agctcgaccc tcaccgaagt gcaggccatt agcaccacacg ggggttccgt gggggacaag 120
atcacctcgc tgggagcgaa gctggagaag cagcagcaag acctcaaggc cgaccacgac 180

SRZN_010_03WO_ST25 (1).TXT

```

gcgctgctgt tccacttgaa gcacttccca gtggacttgc ggttcgtggc gtgccagatg      240
gagctgctgc actccaatgg gagccagaga acttgttgcc ctgtgaactg ggtggaacac      300
cagggatcct gctactggtt tagccactcc ggaaaggcct gggccgaagc cgagaagtac      360
tgccagcttg agaacgcgca cctggtcgtg atcaactcct gggaagaaca gaagttcatt      420
gtgcaacaca ctaaccggtt caacacctgg atcggcctga ccgactccga cggctcatgg      480
aaatgggtgg acggaaccga ttaccggcat aactataaga actgggccgt gactcagccg      540
gataattggc acggacacga gctgggtgga tccgaggact gcgtcgaagt gcagcccgac      600
ggcagatgga acgatgactt ctgtctgcaa gtgtaccgct gggctctgca gaagcgccgc      660
aacgccactg gcgaagtggc ttga                                           684

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<210> 38
 <211> 227
 <212> PRT
 <213> Homo sapiens

<400> 38

Arg Gly Ala Gln Leu Gln Ala Glu Leu Arg Ser Leu Lys Glu Ala Phe
 1 5 10 15

Ser Asn Phe Ser Ser Ser Thr Leu Thr Glu Val Gln Ala Ile Ser Thr
 20 25 30

His Gly Gly Ser Val Gly Asp Lys Ile Thr Ser Leu Gly Ala Lys Leu
 35 40 45

Glu Lys Gln Gln Gln Asp Leu Lys Ala Asp His Asp Ala Leu Leu Phe
 50 55 60

His Leu Lys His Phe Pro Val Asp Leu Arg Phe Val Ala Cys Gln Met
 65 70 75 80

Glu Leu Leu His Ser Asn Gly Ser Gln Arg Thr Cys Cys Pro Val Asn
 85 90 95

Trp Val Glu His Gln Gly Ser Cys Tyr Trp Phe Ser His Ser Gly Lys

SRZN_010_03WO_ST25 (1).TXT

100 105 110

Ala Trp Ala Glu Ala Glu Lys Tyr Cys Gln Leu Glu Asn Ala His Leu
115 120 125

Val Val Ile Asn Ser Trp Glu Glu Gln Lys Phe Ile Val Gln His Thr
130 135 140

Asn Pro Phe Asn Thr Trp Ile Gly Leu Thr Asp Ser Asp Gly Ser Trp
145 150 155 160

Lys Trp Val Asp Gly Thr Asp Tyr Arg His Asn Tyr Lys Asn Trp Ala
165 170 175

Val Thr Gln Pro Asp Asn Trp His Gly His Glu Leu Gly Gly Ser Glu
180 185 190

Asp Cys Val Glu Val Gln Pro Asp Gly Arg Trp Asn Asp Asp Phe Cys
195 200 205

Leu Gln Val Tyr Arg Trp Val Cys Glu Lys Arg Arg Asn Ala Thr Gly
210 215 220

Glu Val Ala
225

<210> 39
<211> 690
<212> DNA
<213> Homo sapiens

<400> 39
caaaacgccc agctgcagcg ggagctgcgg ggcctgagag agacgctcag caacttcaca 60
gcgagcaccg aggcccaggt caagggcttg agcaccacagg gaggcaatgt gggaagaaaag 120
atgaagtcgc tggagtccca gctggagaaa cagcagaagg acttgagtga agatcactcc 180
agcctgctgc tccacgtgaa gcagttcgtg tctgacctgc ggagcctgag ctgtcagatg 240
gcggcgctcc agggcaatgg ctcggaaagg gcctgctgcc cagtcaactg ggtggagcac 300
gagcgcagct gctactggtt ctctcgctcc gggaaggcct gggccgacgc cgacaactac 360

SRZN_010_03WO_ST25 (1).TXT

tgccggctgg aggacgcgca cctggtggtg gtcacgtcct gggaggagca gaaatttgtc	420
cagcaccaca taggtcctgt gaacacctgg atgggcctcc acgaccaaaa cgggccctgg	480
aagtgggtgg acgggacgga ctacgagacg ggcttcaaga actggagacc ggagcagccg	540
gacgactggt acggccacgg gctcggggga ggggaggact gtgcccactt caccgacgac	600
ggccgctgga acgacgacgt ctgccagagg ccctaccgct gggctctgcga gacagagctg	660
gacaaggcca gtcaggagcc acctctcctt	690

<210> 40
 <211> 230
 <212> PRT
 <213> Homo sapiens

<400> 40

Gln Asn Ala Gln Leu Gln Arg Glu Leu Arg Gly Leu Arg Glu Thr Leu	
1 5 10 15	

Ser Asn Phe Thr Ala Ser Thr Glu Ala Gln Val Lys Gly Leu Ser Thr	
20 25 30	

Gln Gly Gly Asn Val Gly Arg Lys Met Lys Ser Leu Glu Ser Gln Leu	
35 40 45	

Glu Lys Gln Gln Lys Asp Leu Ser Glu Asp His Ser Ser Leu Leu Leu	
50 55 60	

His Val Lys Gln Phe Val Ser Asp Leu Arg Ser Leu Ser Cys Gln Met	
65 70 75 80	

Ala Ala Leu Gln Gly Asn Gly Ser Glu Arg Ala Cys Cys Pro Val Asn	
85 90 95	

Trp Val Glu His Glu Arg Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys	
100 105 110	

Ala Trp Ala Asp Ala Asp Asn Tyr Cys Arg Leu Glu Asp Ala His Leu	
115 120 125	

SRZN_010_03WO_ST25 (1).TXT

Val Val Val Thr Ser Trp Glu Glu Gln Lys Phe Val Gln His His Ile
130 135 140

Gly Pro Val Asn Thr Trp Met Gly Leu His Asp Gln Asn Gly Pro Trp
145 150 155 160

Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Lys Asn Trp Arg
165 170 175

Pro Glu Gln Pro Asp Asp Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190

Asp Cys Ala His Phe Thr Asp Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205

Gln Arg Pro Tyr Arg Trp Val Cys Glu Thr Glu Leu Asp Lys Ala Ser
210 215 220

Gln Glu Pro Pro Leu Leu
225 230

<210> 41
<211> 684
<212> DNA
<213> Homo sapiens

<400> 41
caaagtgcac agctgcaagc agagatgcgg agcctgaagg aagctttcag caacttctcc 60
tcgagcacgc tgggtggaggt ccatgctctc ggcacccacg gaggcagcgt ggggtgacaag 120
atcacatccc taggagacaa gttggagaaa cagcagcacg acctgaaagc agatcatgac 180
atcctgctcc tccatctgaa gcacttcccc gtggacctgc gcttcgtggc ctgccagatg 240
gagctcctcc acagcaacgg ctcccaaagg acctgctgcc ctgtcaactg ggtggagcac 300
caaggcagct gctactgggt ctctcgctcc gggaaggcct gggccgaggc ggagaagtac 360
tgccagctgg agaactcaca cctgggtggtc atcaactcct gggaggagca gaaattcatt 420
gtacaacaca cgaaccctt caatacctgg ataggtctca cggacagtga tggctcctgg 480
aaatgggtgg acggcacaga ctataggcac aactacaaga actgggctgt cactcagcca 540

SRZN_010_03WO_ST25 (1).TXT

gatgattggc acgggcatga gctgggcgga agtgaagact gtgttgaagt ccggccggat 600
 ggccgctgga acgatgattt ctgcctgcag gtgcaccgct ggggtgtgtga gaagaggcgg 660
 aatgccaccg gcgaggcagc ctga 684

<210> 42
 <211> 227
 <212> PRT
 <213> Homo sapiens

<400> 42

Gln Ser Ala Gln Leu Gln Ala Glu Met Arg Ser Leu Lys Glu Ala Phe
 1 5 10 15

Ser Asn Phe Ser Ser Ser Thr Leu Val Glu Val His Ala Leu Gly Thr
 20 25 30

His Gly Gly Ser Val Gly Asp Lys Ile Thr Ser Leu Gly Asp Lys Leu
 35 40 45

Glu Lys Gln Gln His Asp Leu Lys Ala Asp His Asp Ile Leu Leu Leu
 50 55 60

His Leu Lys His Phe Pro Val Asp Leu Arg Phe Val Ala Cys Gln Met
 65 70 75 80

Glu Leu Leu His Ser Asn Gly Ser Gln Arg Thr Cys Cys Pro Val Asn
 85 90 95

Trp Val Glu His Gln Gly Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys
 100 105 110

Ala Trp Ala Glu Ala Glu Lys Tyr Cys Gln Leu Glu Asn Ser His Leu
 115 120 125

Val Val Ile Asn Ser Trp Glu Glu Gln Lys Phe Ile Val Gln His Thr
 130 135 140

Asn Pro Phe Asn Thr Trp Ile Gly Leu Thr Asp Ser Asp Gly Ser Trp

SRZN_010_03WO_ST25 (1).TXT

Gln Lys Ala Ile Ile Arg Val Ile Pro Leu Lys Met Asp Pro Thr Gly
1 5 10 15

Lys Leu Asn Leu Thr Leu Glu Gly Val Phe Ala Gly Val Ala Glu Ile
20 25 30

Thr Pro Ala Glu Gly Lys Leu Met Gln Ser His Pro Leu Tyr Leu Cys
35 40 45

Asn Ala Ser Asp Asp Asp Asn Leu Glu Pro Gly Phe Ile Ser Ile Val
50 55 60

Lys Leu Glu Ser Pro Arg Arg Ala Pro Arg Pro Cys Leu Ser Leu Ala
65 70 75 80

Ser Lys Ala Arg Met Ala Gly Glu Arg Gly Ala Ser Ala Val Leu Phe
85 90 95

Asp Ile Thr Glu Asp Arg Ala Ala Ala Glu Gln Leu Gln Gln Pro Leu
100 105 110

Gly Leu Thr Trp Pro Val Val Leu Ile Trp Gly Asn Asp Ala Glu Lys
115 120 125

Leu Met Glu Phe Val Tyr Lys Asn Gln Lys Ala His Val Arg Ile Glu
130 135 140

Leu Lys Glu Pro Pro Ala Trp Pro Asp Tyr Asp
145 150 155

<210> 45
<211> 495
<212> DNA
<213> Homo sapiens

<400> 45
aaggagacgg cgttcgtgga ggtggtgctg ttcgagtcga gccaagcgg cgattacacc 60
acctacacca ccggcctcac gggccgcttc tcgcgggccg gggccacgct cagcgccgag 120
ggcgagatcg tgcagatgca cccactgggc ctatgtaata acaatgacga agaggacttg 180

SRZN_010_03WO_ST25 (1).TXT

tatgaatatg gctgggtagg agtgggtgaag ctggaacagc cagaattgga cccgaaacca	240
tgcctcactg tcctaggcaa ggccaagcga gcagtacagc ggggagctac tgcagtcac	300
tttgatgtgt ctgaaaaccc agaagctatt gatcagctga accagggctc tgaagaccg	360
ctcaagaggc cggtgggtgta tgtgaagggt gcagatgcca ttaagctgat gaacatcg	420
aacaagcaga aagtggctcg agcaaggatc cagcaccgcc ctcctcgaca acccactgaa	480
tactttgaca tgtga	495

<210> 46
 <211> 164
 <212> PRT
 <213> Homo sapiens

<400> 46

Lys	Glu	Thr	Ala	Phe	Val	Glu	Val	Val	Leu	Phe	Glu	Ser	Ser	Pro	Ser
1				5					10					15	

Gly	Asp	Tyr	Thr	Thr	Tyr	Thr	Thr	Gly	Leu	Thr	Gly	Arg	Phe	Ser	Arg
			20					25					30		

Ala	Gly	Ala	Thr	Leu	Ser	Ala	Glu	Gly	Glu	Ile	Val	Gln	Met	His	Pro
		35					40					45			

Leu	Gly	Leu	Cys	Asn	Asn	Asn	Asp	Glu	Glu	Asp	Leu	Tyr	Glu	Tyr	Gly
	50					55					60				

Trp	Val	Gly	Val	Val	Lys	Leu	Glu	Gln	Pro	Glu	Leu	Asp	Pro	Lys	Pro
65					70					75				80	

Cys	Leu	Thr	Val	Leu	Gly	Lys	Ala	Lys	Arg	Ala	Val	Gln	Arg	Gly	Ala
			85						90					95	

Thr	Ala	Val	Ile	Phe	Asp	Val	Ser	Glu	Asn	Pro	Glu	Ala	Ile	Asp	Gln
			100					105					110		

Leu	Asn	Gln	Gly	Ser	Glu	Asp	Pro	Leu	Lys	Arg	Pro	Val	Val	Tyr	Val
	115						120					125			

SRZN_010_03WO_ST25 (1).TXT

Lys Gly Ala Asp Ala Ile Lys Leu Met Asn Ile Val Asn Lys Gln Lys
130 135 140

Val Ala Arg Ala Arg Ile Gln His Arg Pro Pro Arg Gln Pro Thr Glu
145 150 155 160

Tyr Phe Asp Met

<210> 47
<211> 103
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 47

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45

Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
85 90 95

Gly Thr Lys Leu Glu Ile Lys
100

<210> 48

SRZN_010_03WO_ST25 (1).TXT

<211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 48

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30

Ser Ala Ala Trp Asn Trp Met Arg Gln Ser Pro Ser Arg Gly Leu Glu
 35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60

Val Ser Val Lys Ser Arg Met Thr Ile Asn Pro Asp Thr Ser Arg Asn
 65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Leu Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 49
 <211> 103
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 49

Asp Val Val Met Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly

SRZN_010_03WO_ST25 (1).TXT

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
 35 40 45

Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
 85 90 95

Gly Thr Lys Leu Glu Ile Lys
 100

<210> 50
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 50

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Ala Ser Val Ser Ser Asn
 20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
 35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60

SRZN_010_03WO_ST25 (1).TXT

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Gly Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 51
<211> 103
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 51

Asp Ile Gln Leu Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45

Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
85 90 95

Gly Thr Lys Leu Glu Ile Lys

100

<210> 52
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 52

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30

Ser Val Ala Trp Asn Trp Met Arg Gln Ser Pro Ser Arg Gly Leu Glu
 35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Tyr Asp Tyr Ala
 50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95

Tyr Tyr Cys Ala Ser Trp Thr Arg Gly Ala Phe Asp Ile Trp Gly Gln
 100 105 110

Gly Thr Met Val Thr Val Ser Ser
 115 120

<210> 53
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 53

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Leu Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 54

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 54

Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

SRZN_010_03WO_ST25 (1).TXT

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Val Ser Asp Gly Tyr Asp Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 55
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 55

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

His Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ile Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Val

85

90

95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 56

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 56

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ser Phe Gly Val Gly Ala Pro Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 57

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 57

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly His Asn Tyr Leu Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Leu Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Thr His Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 58

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 58

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Ala Gly Gly Gly Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 59

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 59

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Tyr Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 — — — 75 \ , / 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Tyr Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210>	60
<211>	117
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 60

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Gly Ile Ile Pro Val Phe Gly Ala Pro Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> 61
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Asp Phe Pro Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 62
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 62

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Gly Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Ala Thr Ala Glu Tyr Phe Gln His Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 63

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 63

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Thr Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 64

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 64

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Asn
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Gly Ile Ile Pro Met Phe Gly Thr Val Lys Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Arg Gly Tyr Arg Phe Asp Phe Asp Leu Trp Gly Arg Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 65
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 65

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ala Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Val
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 66
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 66

SRZN_010_03WO_ST25 (1).TXT

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Tyr Asn Ser His Thr Asn Asp Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ala Val Ala Ala Gly Gly Gln Tyr Tyr Tyr Met Asp Val
100 105 110

Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 67
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 67

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35

40

45

Tyr Asp Ala Ser Asn Leu Arg Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Thr Ile Pro Ile
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 68

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 68

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Tyr
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Pro Lys Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ala Arg Asp Arg Gly Ile Thr Met Val Arg Gly Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 69
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 69

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gln Ala Ser Asn Lys Asp Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 70
<211> 122
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 70

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Gly Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Thr Ala Met Ala Pro Glu Gly Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 71

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 71

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr

20

25

30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 72

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 72

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
 20 25 30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asn Pro Arg Asn Gly Arg Thr Ser Tyr Ala Gln Arg Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp His Leu Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 73
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 73

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 74

SRZN_010_03WO_ST25 (1).TXT

<211> 127
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 74

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
 20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ser Pro Ile Val Arg Arg Gly Glu Arg Gly Arg Tyr Tyr
 100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 75
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 75

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

SRZN_010_03WO_ST25 (1).TXT

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1           5           10           15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
      20                25                30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35                40                45

Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50                55                60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65                70                75                80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ala Ile Pro Leu
      85                90                95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100                105

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<210> 76
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 76

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1           5           10           15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
      20                25                30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35                40                45

Gly Trp Met Asn Pro Asn Thr Gly Asn Thr Ala Tyr Ala Gln Lys Phe
      50                55                60

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SRZN_010_03WO_ST25 (1).TXT

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Lys Asn Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 77
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 77

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly His Thr Phe Ser Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Ser Gln Ser Gly Tyr Val Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Asn Ala Arg Trp Gly Ala Gly Ser Leu Phe Ala Ser Trp Gly Gln Gly

100

105

110

Thr Gln Val Thr Val Ser Ser
115

<210> 78
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 78

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Ile Arg Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 79
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 79

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Gln Gly Val Trp Asp Tyr Trp Gly Arg Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 80

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 80

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Val Ser Gln Gly Ile Ser Ser Tyr
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 81
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 81

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Asn Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85

90

95

Ala Arg Gly Asp Phe Trp Ser Gly Tyr Tyr Pro Tyr Tyr Tyr Tyr Tyr
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 82

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 82

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
 85 90 95

Leu His Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 83

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 83

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Asn Gly Gly Arg Thr Thr Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Phe Gly Val Ala Gly Thr Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 84

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 84

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Asp Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 85
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 85

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asn Pro Gly Gly Ser Asp Thr Thr Tyr Ala Gln Lys Phe

50

55

60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 86

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 86

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile His Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 87
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 87

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro His Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Asp Tyr Asn Trp Asn Asp Gly Trp Phe Asp Pro Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 88
<211> 107
<212> PRT
<213> Artificial Sequence

SRZN_010_03WO_ST25 (1).TXT

<220>

<223> Made in lab - synthesized chain

<400> 88

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Tyr Asp Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 89

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 89

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ser Gly Tyr Cys Ser Ser Thr Ser Cys Tyr Asp Gly Gly
 100 105 110

Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 90
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 90

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
 20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 91
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 91

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Thr Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95

Asp Gln Gly His Asp Tyr Gly Asp Tyr Glu Ile Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 92

SRZN_010_03WO_ST25 (1).TXT

<211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 92

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asp Tyr Pro Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 93
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 93

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr

20

25

30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Pro Val Arg Gly Ile Ser Ala Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 94

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 94

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Val Ile Asn Ser Gly Gly Gly Ser Thr Ser Tyr Ala Glu Ser Val
 50 55 60

SRZN_010_03WO_ST25 (1).TXT

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Tyr Tyr Ser Gly Ser Tyr Tyr Tyr Pro Ala Leu Tyr
100 105 110

Tyr Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 95

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 95

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100

105

<210> 96
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 96

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Thr Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Leu Met Val Arg Gly Gly Pro Pro Phe Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 97
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 97

Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Ser Arg
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Thr
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Arg
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 98

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 98

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

SRZN_010_03WO_ST25 (1).TXT

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr His Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Ala Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Val Val Arg Ala Val Asp Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 99
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 99

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Ala Thr Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro

85

90

95

Ile Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 100
 <211> 124
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 100

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Arg Val Val Arg Gly Val Ile Ile Ser Tyr Gly Met Asp
 100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 101
 <211> 107
 <212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 101

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Arg Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 102

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 102

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Gly Tyr
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Asp Ala Ala Thr Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Arg Gly Gln Arg Ser Gly Tyr Ser Tyr Phe Asp Leu Trp
100 105 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 103
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 103

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser Arg Phe
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

$\langle 210 \rangle$	104
$\langle 211 \rangle$	119
$\langle 212 \rangle$	PRT
$\langle 213 \rangle$	Artificial Sequence

<220>
<223> Made in lab - synthesized chain

$\langle 400 \rangle$ 104

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Thr Ser
20 25 30

Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Thr Gly Gly Ile Lys Tyr Ser Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Arg Ala Leu Lys Gly Ser Tyr Thr Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

SRZN_010_03WO_ST25 (1).TXT

<210> 105
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 105

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 106
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 106

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Thr
20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Gly Gly Arg Ser Gly Trp Ile Trp Tyr Phe Asp Leu Trp Gly Arg
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 107
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 107

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Arg Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Arg Pro Phe
 85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 108
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 108

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
 20 25 30

Ser Leu Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asn Pro Arg Arg Gly Ser Thr Arg Tyr Ala Gln Asn Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Gly Leu Gly Val Asp Ala Phe Asp Ile Trp Gly Gln Gly
 100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 109
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 109

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Ser
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Pro Pro His
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 110
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 110

SRZN_010_03WO_ST25 (1).TXT

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Arg Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Asp Gly Tyr Asn Trp Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 111
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Phe Ile Ser Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35

40

45

Tyr Asp Ala Ser Ser Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Ser Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 112

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 112

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Ile Lys Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ala Arg Gly Arg Arg Ser Arg Gly Ser Ser Ser Leu Gly Tyr Tyr Tyr
100 105 110

Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 113
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 113

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
85 90 95

Leu Glu Ala Pro Leu Ala Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 114
<211> 123
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 114

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Tyr
20 25 30

Phe Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Arg Tyr Ala Gln Asn Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gln Lys Gly Lys Ser Ser Ser Trp Phe Arg Phe Asp Pro
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 115

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Tyr Arg Tyr

20

25

30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Phe Ala Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Ile
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 116

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 116

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Lys Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Lys Ile Asn Pro Ser Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Ala Gly Met Trp Tyr Phe Asp Leu Trp Gly Arg Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 117
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 117

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 118

SRZN_010_03WO_ST25 (1).TXT

<211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 118

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Arg Tyr
 20 25 30

Pro Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Lys Val Gly Ala Ile Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 119
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 119

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

SRZN_010_03WO_ST25 (1).TXT

```

1           5           10           15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Trp
      20                25                30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35                40                45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50                55                60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65                70                75                80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Leu
      85                90                95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100                105

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<210> 120
<211> 117
<212> PRT
<213> Artificial Sequence

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<220>
<223> Made in lab - synthesized chain

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<400> 120

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1           5           10           15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
      20                25                30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35                40                45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
      50                55                60

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SRZN_010_03WO_ST25 (1).TXT

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ser Gly Trp Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 121
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 121

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100

105

<210> 122
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 122

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Ile Ser Pro Asn Arg Gly Gly Thr Lys Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Ser Trp Leu Arg Gly Ala Trp Gly Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 123
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 123

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Thr Ser Ser Gln Ser Val Leu His Ser
20 25 30

Ser Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Ala Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr His Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 124

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 124

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Phe
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Ala Ser Gly Arg Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Arg Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Thr Arg His Gly Ser Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 125
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 125

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

$\langle 210 \rangle$	126
$\langle 211 \rangle$	125
$\langle 212 \rangle$	PRT
$\langle 213 \rangle$	Artificial Sequence

<400> 126

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Gly Tyr
20 25 30

Gly Trp Val Asn Pro Lys Asn Gly His Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Page 123

SRZN_010_03WO_ST25 (1).TXT

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 127
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 127

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105 110

<210> 128
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 128

SRZN_010_03WO_ST25 (1).TXT

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Asn Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Pro Asn Ser Gly Ala Thr Asn Tyr Ala Gln Asn Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Arg Thr Thr Val Thr Thr Met Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 129
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 129

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35

40

45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 130

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 130

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Asn Phe
 20 25 30

Ala Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ala Arg Leu Arg Ala Asn Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 131
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 131

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Ser
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Phe Ser Pro Pro Met
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 132
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 132

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly His Ala Gly Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Arg Ser Gly Leu Ser Pro Pro Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 133

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 133

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Tyr Ile Gly Ser Tyr

20

25

30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Pro Pro Phe
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 134

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 134

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Ser Ala Asp Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Ser Gly Asn Trp Lys Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 135
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 135

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr His Trp Pro Tyr Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

<210> 136

SRZN_010_03WO_ST25 (1).TXT

<211> 116
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 136

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Leu Met
 35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Ser Asn Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
 100 105 110

Thr Val Ser Ser
 115

<210> 137
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 137

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

SRZN_010_03WO_ST25 (1).TXT

```

1              5              10              15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Trp
      20              25              30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35              40              45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
      50              55              60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65              70              75              80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Thr Phe Pro Ile
      85              90              95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
      100              105

```

<210> 138
 <211> 116
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 138

```

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1              5              10              15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asn Tyr
      20              25              30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35              40              45

Ser Ala Ile Ser Gly Ser Gly Arg Thr Thr Tyr Tyr Ala Asp Ser Val
      50              55              60

```

SRZN_010_03WO_ST25 (1).TXT

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Thr Ser Ser Phe Ser Leu Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 139
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 139

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile

100

105

110

Lys

<210> 140

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 140

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Ala Gly Thr Phe Ser Asn Tyr
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Gly Ile Ile Pro Ile Phe Asp Ala Thr Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Arg Gln Tyr Ser Gly Tyr Asp Thr His Phe Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 141

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 141

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Ala Ala Ser Ala Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Arg Ser Pro
85 90 95

Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 142

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 142

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Lys Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Arg Ser Tyr Gly Tyr Trp Tyr Phe Asp Leu Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 143
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 143

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 — — — , 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210>	144
<211>	117
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Made in lab - synthesized chain

$\langle 400 \rangle$ 144

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Leu Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 145
 <211> 106
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 145

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Arg Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Val Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Leu Gln Pro Glu
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Ser Pro Tyr Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 146
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized chain

<400> 146

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Thr Gly Gly Thr Lys Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Leu Arg Gly Ser Leu Gly Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 147
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 147

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 148

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 148

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Gly Val Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asn Pro Arg Gly Gly Ser Thr Ser Tyr Ala Gln Asn Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Ser Ser Ser Trp Ser Trp Pro Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 149
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 149

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ser Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 150
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 150

SRZN_010_03WO_ST25 (1).TXT

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Arg Gly Gly Thr Ser Tyr Ala Gln Asn Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Met Tyr Ser Ser Ser Trp Leu Arg Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 151
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 151

Glu Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser

35

40

45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
 50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
 85 90 95

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 152

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 152

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
 1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Thr Tyr
 20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Ser Met
 65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Tyr Cys Val Arg Pro Arg Tyr Asp Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110

Thr Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 153
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized chain

<400> 153

Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ala Ala Ser Leu Gly
1 5 10 15

Gln Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Phe Leu His Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Pro Leu
35 40 45

Ile His Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65 70 75 80

Ala Glu Asp Asp Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Gly Tyr Pro
85 90 95

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 154
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in lab - synthesized chain

<400> 154

Asp Val Lys Leu Val Glu Ser Gly Glu Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Gly Asp Tyr Ile Tyr Tyr Val Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Glu Gly Thr Gly Gly Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 155

<211> 648

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized variable light chain polynucleotide
sequence

<400> 155

cagagcgtgt taaccagcc cgccagcgtg agcggcagcc ccggccagag catcaccatc 60

agctgcgccg gcaccagcag cgacgtgggc ggctacaact acgtgagctg gtaccagcag 120

caccccgga aggccccaa gctgatgatc tacgaggaca gcaagagacc cagcggcgtg 180

SRZN_010_03WO_ST25 (1).TXT

```

agcaacagat tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg      240
caggccgagg acgaggccga ctactactgc agcagctaca ccaccagaag caccagagtg      300
ttcggcggcg gcaccaagct ggccgtgctg ggtcagccca aggctgcccc ctcggtcact      360
ctgttcccg cctcctctga ggagcttcaa gccaacaagg ccacactggg gtgtctcata      420
agtgacttct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag      480
gcgggagtg agaccaccac accctcaaaa caaagcaaca acaagtacgc ggccagcagc      540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg      600
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca      648

```

<210> 156
 <211> 216
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized variable light chain polypeptide sequence

<400> 156

```

Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1           5           10          15

```

```

Ser Ile Thr Ile Ser Cys Ala Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20           25           30

```

```

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
          35           40           45

```

```

Met Ile Tyr Glu Asp Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
          50           55           60

```

```

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65           70           75           80

```

```

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg
          85           90           95

```

SRZN_010_03WO_ST25 (1).TXT

Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Ala Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 157
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized anti-beta-Gal Heavy chain IgG1-LALAPG
construct

<400> 157
gaggtgcagc tggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60
agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300

SRZN_010_03WO_ST25 (1).TXT

atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctggt gaccgtgagc	360
agcgctagca ccaagggccc atcgggtcttc cccctggcac cctcctccaa gagcacctct	420
gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg	480
tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc	540
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcagctt gggcacccag	600
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gaaagttgag	660
cccaaattct gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg	720
ggaccgtcag tcttcctctt cccccaaaaa cccaaggaca ccctcatgat ctcccggacc	780
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac	840
tggtagtggt acggcgtgga ggtgcataat gccaaagaca agccgcggga ggagcagtac	900
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc	960
aaggagtaca agtgcaaggt ctccaacaaa gccctcggag ccccatcga gaaaaccatc	1020
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgggag	1080
gagatgacca agaaccaggt cagcctgacc tgcctgggtca aaggcttcta tcccagcgac	1140
atgcccggtg agtgggagag caatgggcag ccggagaaca actacaagac cagcctccc	1200
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg	1260
tggcagcagg ggaacgtctt ctcatgtctc gtgatgcatg aggctctgca caaccactac	1320
acgcagaaga gcctctccct gtctccgggt aaa	1353

<210> 158

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized anti-beta-Gal Heavy chain IgG1-LALAPG
construct construct

<400> 158

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Ser	Leu	Val	Lys	Pro	Gly	Gly
1				5					10					15	

SRZN_010_03WO_ST25 (1).TXT

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Arg Ser Ser Ile Thr Ile Phe Gly Gly Gly Met Asp Val Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

SRZN_010_03WO_ST25 (1).TXT

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

SRZN_010_03WO_ST25 (1).TXT

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 159
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab - Synthesized anti-Beta-Gal Heavy chain IgG2
polynucleotide sequence

<400> 159
gaggtgcagc tggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60
agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300
atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctgggt gaccgtgagc 360
agcgctagca ccaagggccc atcgggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacgggtg 480
tcgtggaact caggcgtctt gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgaaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtgggtg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtgggtc gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggctc ccaacaaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaa 1020

SRZN_010_03WO_ST25 (1).TXT

```

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag      1080
aaccagggtca gcctgacctg cctgggtcaaa ggcttctacc ccagcgacat cgccgtggag      1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc      1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggtg gcagcagggg      1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc      1320
ctctccctgt ctccgggtaa a                                              1341

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<210> 160
 <211> 447
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - Synthesized anti-Beta-Gal Heavy chain IgG2
 polypeptide sequence

<400> 160

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Lys Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Val Arg Ser Ser Ile Thr Ile Phe Gly Gly Gly Met Asp Val Trp Gly
 100 105 110

SRZN_010_03WO_ST25 (1).TXT

Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

SRZN_010_03WO_ST25 (1).TXT

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 161
<211> 702
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in Lab - Synthesized Anti-ASGR1 VH-CH1 polynucleotide
sequence

<400> 161
gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cggggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300

SRZN_010_03WO_ST25 (1).TXT

```

agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc      360
gctagcacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg      420
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg      480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca      540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg caccagacc      600
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc      660
aaatcttggt gatccggctc cggacatcat catcaccatc ac                          702

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<210> 162
 <211> 234
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - Synthesized Anti-ASGR1 VH-CH1 polynpeptide sequence

<400> 162

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
 100 105 110

SRZN_010_03WO_ST25 (1).TXT

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

Ser Gly Ser Gly His His His His His His
225 230

<210> 163
<211> 765
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized murine ASGR1 Extracellular domain - polynucleotide

<400> 163
caaaattccc aactccggga agatctgctg gctctaaggc agaatttcag caacctcact 60
gtgagcactg aggaccaggt caaggccctg agcaccaggc gaagtagtgt gggaagaaag 120
atgaagttag tggagtcgaa gctggaaaaa cagcagaagg atctgactga agatcactcc 180
agtttgctac tgcacgtgaa gcagtttagt tctgacgtgc gaagcttgag ctgccagatg 240
gctgcatttc ggggcaatgg ctctgaaagg acctgctgcc ccatcaactg ggtggagtat 300

SRZN_010_03WO_ST25 (1).TXT

```

gaaggcagct gctactgggt ctccagctct gtgaggcctt ggactgaagc tgacaagtac      360
tgccagctgg aaaatgcccc tctgggtggtg gtgacctcca gggatgagca gaacttcctc      420
cagcgccaca tgggcccctt aaacacttgg attggcctaa ctgaccagaa cgggcccttg      480
aaatgggtgg atggaacaga ctacgagaca ggcttccaga attggagacc agagcagcca      540
gataactggt acggacatgg gcttggagga ggcgaggact gtgcccactt cacgacggat      600
ggccgctgga atgacgacgt ctgcaggagg ccctaccgct gggctctgtga gacaaagttg      660
gataaggcta attccggctc cggaggtctt aatgatattt tcgaggctca gaagattgag      720
tggcatagaag gatccggctc ccaccaccat catcaccacc accac                        765

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<210> 164
 <211> 255
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthesized murine ASGR1 Extracellular domain - polypeptide

<400> 164

Gln Asn Ser Gln Leu Arg Glu Asp Leu Leu Ala Leu Arg Gln Asn Phe
 1 5 10 15

Ser Asn Leu Thr Val Ser Thr Glu Asp Gln Val Lys Ala Leu Ser Thr
 20 25 30

Gln Gly Ser Ser Val Gly Arg Lys Met Lys Leu Val Glu Ser Lys Leu
 35 40 45

Glu Lys Gln Gln Lys Asp Leu Thr Glu Asp His Ser Ser Leu Leu Leu
 50 55 60

His Val Lys Gln Leu Val Ser Asp Val Arg Ser Leu Ser Cys Gln Met
 65 70 75 80

Ala Ala Phe Arg Gly Asn Gly Ser Glu Arg Thr Cys Cys Pro Ile Asn
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Trp Val Glu Tyr Glu Gly Ser Cys Tyr Trp Phe Ser Ser Ser Val Arg
100 105 110

Pro Trp Thr Glu Ala Asp Lys Tyr Cys Gln Leu Glu Asn Ala His Leu
115 120 125

Val Val Val Thr Ser Arg Asp Glu Gln Asn Phe Leu Gln Arg His Met
130 135 140

Gly Pro Leu Asn Thr Trp Ile Gly Leu Thr Asp Gln Asn Gly Pro Trp
145 150 155 160

Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Gln Asn Trp Arg
165 170 175

Pro Glu Gln Pro Asp Asn Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190

Asp Cys Ala His Phe Thr Thr Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205

Arg Arg Pro Tyr Arg Trp Val Cys Glu Thr Lys Leu Asp Lys Ala Asn
210 215 220

Ser Gly Ser Gly Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu
225 230 235 240

Trp His Glu Gly Ser Gly Ser His His His His His His His His
245 250 255

<210> 165
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 165

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Asp Ser Tyr
20 25 30

Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Asn Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 166
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 166

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Ala Asn Gly Lys Ala Asn Tyr Asp Pro Lys Phe
50 55 60

SRZN_010_03WO_ST25 (1).TXT

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Phe Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Leu Gly Gly Gly Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 167
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 167

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Ser Val Arg Pro Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 168
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized variable heavy chain sequence

<400> 168

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
 20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Lys Tyr Ala Ser Lys Phe
 50 55 60

Pro Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
 65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Thr Ala Ser Arg Thr Thr Ala Leu Asp Tyr Trp Gly Pro Gly Thr Thr
 100 105 110

Leu Thr Val Ser Ser
 115

<210> 169
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized variable light chain sequence

<400> 169

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
 1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Ser Leu Gly Ser Tyr Tyr Val
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45

Arg Asn Lys Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Trp Met Tyr Ser Ser
 85 90 95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 170

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized variable heavy chain sequence

<400> 170

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
 20 25 30

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

SRZN_010_03WO_ST25 (1).TXT

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Ile Thr Glu Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Ala Ile Tyr Tyr Leu Glu Ala Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 171
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 171

Asp Ile Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu
85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 172
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 172

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu
85 90 95

Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 173
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

SRZN_010_03WO_ST25 (1).TXT

<400> 173

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 174

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized variable light chain sequence

<400> 174

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Leu Arg Ser Gly Lys Met
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 175
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 175

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Trp Tyr Leu Pro Gly Arg Gly Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 176
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 176

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Lys Ser Ser Ser Lys Asn
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 177
<211> 120
<212> PRT
<213> Artificial Sequence

SRZN_010_03WO_ST25 (1).TXT

<220>

<223> Made in lab - synthesized variable heavy chain sequence

<400> 177

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ser Phe Thr Phe Gly Arg Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 178

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized variable light chain sequence

<400> 178

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Arg Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Arg Arg Gly Tyr Ser
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 179
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 179

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ser Phe Ser Tyr Leu Arg Ala Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 180
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 180

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 181
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 181

Asp Ile Val Leu Phe Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asp Tyr
20 25 30

Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 182
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 182

SRZN_010_03WO_ST25 (1).TXT

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> 183
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 183

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

SRZN_010_03WO_ST25 (1).TXT

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Ala Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 184
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable heavy chain sequence

<400> 184

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Ser Tyr
20 25 30

Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ser Ile Tyr Pro Gly Asn Ser Asp Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Val Val Thr Ser Ala Ser Ser Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

SRZN_010_03WO_ST25 (1).TXT

Thr Glu Pro Thr Tyr Tyr Ser Tyr Asp Asp Tyr Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 185
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized variable light chain sequence

<400> 185

Glu Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ala Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
20 25 30

Asn Leu His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Pro Trp
35 40 45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Thr Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 186
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>

SRZN_010_03WO_ST25 (1).TXT

<223> Made in lab - synthesized Anti-beta-Gal Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 186
gaggtgcagc tgggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60
agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300
atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctgggt gaccgtgagc 360
agcgctagca ccaagggccc atcgggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacgggtg 480
tcgtggaact caggcgtctt gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtgggtg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtgggtc gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccagggtc gcctgacctg cctgggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggt gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggg ggctcgggat ccggaggctc cgggtggcggg 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440

SRZN_010_03WO_ST25 (1).TXT						
tgccagcaaa	agctgttttt	cttcctccgg	cgggaaggaa	tgcggcagta	cggcgaatgt	1500
ctccactcct	gcccctcggg	gtattacgga	caccgcgcgc	ctgacatgaa	ccgatgcgcc	1560
agatgccgga	tcgagaactg	cgatagctgc	cgcagcaagg	acgcctgcac	taagtgcaaa	1620
gtcggcttct	accttcaccg	gggcagatgt	tttgacgaat	gcccggatgg	cttcgccccg	1680
ctggaggaga	ctatggaatg	cgtgggag				1707

<210>	187
<211>	569
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Made in lab - synthesized Anti-beta-Gal Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 187

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val	Arg	Ser	Ser	Ile	Thr	Ile	Phe	Gly	Gly	Gly	Met	Asp	Val	Trp	Gly
			100					105					110		

Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

SRZN_010_03WO_ST25 (1).TXT

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

SRZN_010_03WO_ST25 (1).TXT

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
 545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
 565

<210> 188
 <211> 1707
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized Anti-GFP Heavy chain IgG2, RSP02
 (F105R/F109A) polynucleotide sequence

<400> 188
 caggtccagt tggtggaatc cggaggggggt ttggtccagc ctggtggaag cctgcgcctc 60
 tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
 cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
 gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
 ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
 aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtctag cgctagcacc 360
 aaggggcccat cggctcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
 gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
 aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
 gacaaaactc acacatgccc accgtgcccga gcacctgaac tcctgggggg accgtcagtc 720
 ttctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
 tgcgtggtgg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtacgtggac 840
 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac 900
 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960

SRZN_010_03WO_ST25 (1).TXT

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccggt gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cgggtggcgggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt ttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707

<210> 189

<211> 569

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized Anti-GFP Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 189

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

SRZN_010_03WO_ST25 (1).TXT

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

SRZN_010_03WO_ST25 (1).TXT

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

SRZN_010_03WO_ST25 (1).TXT

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 190
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1F8 light chain polynucleotide
sequence

<400> 190
gacattgtga tgtcacagtc tccatcctcc ctggctgtgt cagcaggaga gaaggtcact 60
atgagctgca agtccagtca gagtctgttc aacagtagaa cccgaaagaa ctacttggtc 120
tggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 180
gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240
atcagcagtg tgcaggctga agacctggca gtttattact gcaagcaatc ttattatctg 300
ctcacgttcg gtgctgggac caagctggag ctgaaacgta cggctggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

SRZN_010_03WO_ST25 (1).TXT

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
 agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
 gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 191
 <211> 219
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-1F8 light chain polypeptide sequence

<400> 191

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
 1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
 20 25 30

Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
 85 90 95

Ser Tyr Tyr Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140

SRZN_010_03WO_ST25 (1).TXT

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 192
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1F8 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 192
gaagtgaac tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60
tcctgtgcag cctctggatt cactttcagt acctatacca tgtcttgggt tcgccagact 120
ccggcgaaga ggctggagtg ggtcgcaacc attagtagta ttggtgttaa cacctactat 180
ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaggaa caccctgtac 240
ctgcaagtga gcagtctgag gtctgaggac acggccatgt attactgtgc aagacatgtg 300
gattactacg atgggatttc ctttgactac tggggccaag gcaccactct cacagtctcc 360
agcgctagca ccaagggccc atcggctcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgtctt gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600

SRZN_010_03WO_ST25 (1).TXT

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
 cgcaaagtgt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
 tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
 ggctgtggagg tgcataatgc caagacaaaag ccacgggagg agcagttcaa cagcacgttc 900
 cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
 tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaa 1020
 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
 aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
 tgggagagca atgggcagcc ggagaacaac tacaagacca cgctcccat gctggactcc 1200
 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
 ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cgggtggcgg 1380
 ggagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
 tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
 ctccactcct gccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
 agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
 gtcggcttct accttcaccg gggcagatgt ttgacgaat gcccggatgg cttcgccccg 1680
 ctggaggaga ctatggaatg cgtggag 1707

<210> 193

<211> 569

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-1F8 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 193

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Ala Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ile Gly Val Asn Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Val Asp Tyr Tyr Asp Gly Ile Ser Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

SRZN_010_03WO_ST25 (1).TXT

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

SRZN_010_03WO_ST25 (1).TXT

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 194
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1N15 light chain polynucleotide
sequence

<400> 194
gacatcaaga tgaccagtc tccatcttcc atgtatgcat ctctaggaga gagagttact 60
atcacttgca aggcgagtca ggacattaat agccatttaa gctgggtcca gcagaaacca 120

SRZN_010_03WO_ST25 (1).TXT

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gggaaatctc ctaagaccct gatcattcgt gcaaacagat tggtagatgg ggtcccatca      180
aggttcagtg gcagtggatc tgggcaagat tatttctctca ccatcagcag cccggagtat      240
gaagaaatgg gaatttatta ctgtctacag tatgatgagt ttccggtcac gttcggaggg      300
gggaccaagc tggaaataaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca      360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat      420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag      480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg      540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc      600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642

```

<210> 195
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-1N15 light chain polypeptide sequence

<400> 195

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
 1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser His
 20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
 35 40 45

Ile Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Pro Glu Tyr
 65 70 75 80

Glu Glu Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 196
<211> 1683
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1N15 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 196
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagt 120
catggagaga gccttgagtg gattggacgt gttattccta gcaatgggtgg tactaactac 180
aaccagaagt tcaagggcaa ggccacattg acagtagaca aatccctcac cacagcctac 240

SRZN_010_03WO_ST25 (1).TXT

atgcagctca acagcctgac atctgaagac tctgcggtct atttctgtgc aagagggatg	300
gactactggg gtccaggaac ctcagtcacc gtctccagcg ctagcaccaa gggcccatcg	360
gtcttcccc tggcgccctg ctccaggagc acctccgaga gcacagcggc cctgggctgc	420
ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgctctgacc	480
agcggcgtgc acaccttccc agctgtccta cagtcctcag gactctactc cctcagcagc	540
gtggtgaccg tgccctccag caacttcggc acccagacct acacctgcaa cgtagatcac	600
aagcccagca acaccaaggt ggacaagaca gttgagcgca aatgttgtgt cgagtgccca	660
ccgtgcccag caccacctgt ggcaggaccg tcagtcttcc tcttcccccc aaaacccaag	720
gacaccctca tgatctcccc gaccctgag gtcacgtgcg tgggtggtgga cgtgagccac	780
gaagaccccg aggtccagtt caactggtac gtggacggcg tggaggtgca taatgccaag	840
acaaagccac gggaggagca gttcaacagc acgttccgtg tggtcagcgt cctcaccgtt	900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aggtctccaa caaaggcctc	960
ccagccccca tcgagaaaac catctccaaa accaaagggc agccccgaga accacaggtg	1020
tacaccctgc ccccatcccc ggaggagatg accaagaacc aggtcagcct gacctgcctg	1080
gtcaaaggct tctaccccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag	1140
aacaactaca agaccacgcc tcccatgctg gactccgacg gctccttctt cctctacagc	1200
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg	1260
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaagggt	1320
ggtggtggct cgggatccgg aggctccggt ggcggtggca gcaacccaat ttgcaaggga	1380
tgcttaagct gtagcaagga caacggatgt tcacggtgcc agcaaaagct gtttttcttc	1440
ctccggcggg aaggaatgcg gcagtacggc gaatgtctcc actcctgccc ctggggtat	1500
tacggacacc gcgcgcctga catgaaccga tgcgccagat gccggatcga gaactgcgat	1560
agctgccgca gcaaggacgc ctgcactaag tgcaaagtcg gcttctacct tcaccggggc	1620
agatgttttg acgaatgccc ggatggcttc gcccgcgtgg aggagactat ggaatgcgtg	1680
gag	1683

<210> 197

<211> 561

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-1N15 Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 197

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu Glu Trp Ile
 35 40 45

Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr
 65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95

Ala Arg Gly Met Asp Tyr Trp Gly Pro Gly Thr Ser Val Thr Val Ser
 100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
 115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175

SRZN_010_03WO_ST25 (1).TXT

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
210 215 220

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
275 280 285

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

SRZN_010_03WO_ST25 (1).TXT

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly
435 440 445

Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys
450 455 460

Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe
465 470 475 480

Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys
485 490 495

Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala
500 505 510

Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys
515 520 525

Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp
530 535 540

Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val
545 550 555 560

Glu

<210> 198

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-1P13 light chain polynucleotide sequence

<400> 198

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gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaca aactgttattc      60
atcacatgtc gaacaagtga gaatatttac agtaatttag catggtatca gcagaaacag      120
ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca      180
aggttcagtg gcagtggttc aggcacacag tattacctca agatcaacag cctgcagtct      240
gaagattttg ggagttatta ctgtcaacat ttttggggta gtacgtggac gttcgggtgga      300
ggcaccaagc tggacatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgccca      360
tctgatgagc agttgaaatc tggaactgcc tctgtttgtgt gcctgctgaa taacttctat      420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag      480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg      540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc      600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642

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<210> 199

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-1P13 light chain polypeptide sequence

<400> 199

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1           5           10           15

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Gln Thr Val Ile Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Asn
20           25           30

```

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Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35           40           45

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SRZN_010_03WO_ST25 (1).TXT

Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Tyr Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Ser Thr Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 200
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1P13 Heavy chain IgG2, RSP02
polynucleotide sequence

<400> 200
gaggttcaac tgcagcagtc tggacctgaa ctggtgaagc ctggggcttc agtgaagata 60
tcctgcaagg cttctggtta ctcatttact gactacttta tgaactgggt gaagcagagc 120
catggaaaga gccttgagtg gattggacgt tttaatcctt tcaatgggtca aactttctac 180
aatcaggagt tcaagggcaa ggccacatta actgtagaca aatcctctag caccgcccac 240
atggagctcc ggagcctgac atctgaggac tctgcagtct attattgtgc aagaagagga 300
aggtacgacg ttactatgt tctggactac tggggtaag gaacctcagt caccgtctcc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaagtgt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720

SRZN_010_03WO_ST25 (1).TXT

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg	780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac	840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc	900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag	960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaa	1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag	1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag	1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc	1200
gacggctcct tcttctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg	1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc	1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cgggtggcgg	1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg	1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt	1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc	1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa	1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg	1680
ctggaggaga ctatggaatg cgtggag	1707

<210> 201
 <211> 569
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-1P13 Heavy chain IgG2, RSP02 polypeptide sequence

<400> 201

Glu	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Leu	Val	Lys	Pro	Gly	Ala
1				5				10						15	

Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Asp	Tyr
			20					25					30		

SRZN_010_03WO_ST25 (1).TXT

Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala His
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

SRZN_010_03WO_ST25 (1).TXT

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 202
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1P5 light chain polynucleotide
sequence

<400> 202
gacattgtga tgaccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60
gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggatatca acagaaacca 120
ggacaatctc ctaaagcact gatttactcg gcatcttatac ggtacagtgg agtccctgat 180
cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

SRZN_010_03WO_ST25 (1).TXT

gaagacttgg cagagtat	ctgtcaacaa tataacagct atccgctcac gttcgg	gtgct	300
gggaccaagc tggagctgaa acgtacggtg gctgcac	cat ctgtcttcat cttcccgc		360
tctgatgagc agttgaaatc tggaactgcc tctgtt	gtgt gcctgctgaa taacttctat		420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc	tccaatcggg taactcccag		480
gagagtgtca cagagcagga cagcaaggac agcacctaca	gcctcagcag caccctgacg		540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct	gcgaagtcac ccatcagggc		600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt	gt		642

<210> 203
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-1P5 light chain polpeptide sequence

<400> 203

Asp	Ile	Val	Met	Thr	Gln	Ser	Gln	Lys	Phe	Met	Ser	Thr	Ser	Val	Gly
1				5					10					15	

Asp	Arg	Val	Ser	Val	Thr	Cys	Lys	Ala	Ser	Gln	Asn	Val	Gly	Thr	Asn
			20					25					30		

Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Ala	Leu	Ile
		35					40					45			

Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Ser	Gly	Val	Pro	Asp	Arg	Phe	Thr	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Asn	Val	Gln	Ser
65					70					75				80	

Glu	Asp	Leu	Ala	Glu	Tyr	Phe	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Pro	Leu
				85					90					95	

Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Thr	Val	Ala	Ala
			100					105					110		

SRZN_010_03WO_ST25 (1).TXT

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 204
<211> 1704
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-1P5 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 204
caggtccagc tgcagcaatc tggacctgag ctggtgaggc ctgggacttc agtgaagata 60
tcctgcaagg cttctggcta taccttcctc acctactgga tgaactgggt gaagcagagg 120
cctggacagg gccttgagtg gattggacag attttcctg caactggtat tacttactac 180
agtgagatgt tcaaggacaa ggccacattg actgaagaca catcctccac cacagcctac 240
atgcaactca gcagcctgac atctgaggcc actgctgtct atttctgtgc aagaagaagg 300
gcctaccata gtaacttttt tgactactgg ggccaaggca ccactctcac agtctccagc 360
gctagcacca agggccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420

SRZN_010_03WO_ST25 (1).TXT

agcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggt gacgggtgtcg	480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca	540
ggactctact ccctcagcag cgtgggtgacc gtgccctcca gcaacttcgg caccagacc	600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc	660
aaatgttggtg tcgagtgtccc accgtgtcca gcaccacctg tggcaggacc gtcagtcttc	720
ctcttcccc caaaaccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc	780
gtgggtgggtg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc	840
gtggaggtgc ataatgcaa gacaaagcca cgggaggagc agttcaacag cacgttccgt	900
gtggtcagcg tcctcacctg tgtgcaccag gactggctga acggcaagga gtacaagtgc	960
aaggtctcca acaaaggcct ccagcccc atcgagaaaa ccatctcaa aaccaaaggg	1020
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac	1080
caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcg cgtggagtgg	1140
gagagcaatg ggagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac	1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac	1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc	1320
tccctgtctc cgggtaaagg tgggtgggtg cgggatccg gaggtccgg tggcggtggc	1380
agcaaccaa tttgcaagg atgcttaagc tgtagcaagg acaacggatg ttcacgggtgc	1440
cagcaaaagc tgtttttctt cctccggcgg gaaggaatgc ggcagtacgg cgaatgtctc	1500
cactcctgcc cctcggggta ttacggacac cgcgcgcctg acatgaaccg atgcgccaga	1560
tgccggatcg agaactgcga tagctgccgc agcaaggacg cctgcactaa gtgcaaagtc	1620
ggcttctacc ttcaccgggg cagatgtttt gacgaatgcc cggatggctt cgccccgtg	1680
gaggagacta tggaatgcgt ggag	1704

<210> 205
 <211> 568
 <212> PRT
 <213> Artificial Sequence

<220>

SRZN_010_03WO_ST25 (1).TXT

<223> Made in lab - synthesized LP1-1P5 Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 205

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Leu Thr Tyr
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser Glu Met Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Glu Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Ala Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

SRZN_010_03WO_ST25 (1).TXT

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385 390 395 400

SRZN_010_03WO_ST25 (1).TXT

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
435 440 445

Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile
450 455 460

Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys
465 470 475 480

Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr
485 490 495

Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala
500 505 510

Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser
515 520 525

Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu
530 535 540

His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu
545 550 555 560

Glu Glu Thr Met Glu Cys Val Glu
565

<210> 206
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-2E12 light chain polynucleotide

SRZN_010_03WO_ST25 (1).TXT

sequence

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<400> 206
gatgttgtgg tgactcaaac tccactctcc ctgcctgtca gctttggaga tcgagtttct      60
atctcttgca ggtctagtca gagtcttgca aacagttatg ggaacaccta tttgtcttgg      120
tacctgcaca agcctggcca gtctccacag ctctcatct atgggatttc caacagattt      180
tctgggggtgc cagacaggtt cagtggcagt gggttcaggga cagatttcac actcaagatc      240
agcacaataa agcctgagga cttgggaatg tattactgct tacaaggtag acatcagcct      300
ctcacgttcg gtgctgggac caagctggag ctgaaacgta cggtaggctgc accatctgtc      360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg      420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa      480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc      540
agcagcaccg tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa      600
gtcacccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg agagtgt      657
```

```
<210> 207
<211> 219
<212> PRT
<213> Artificial Sequence
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<220>
<223> Made in lab - synthesized LP1-2E12 light chain polypeptide
sequence
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```
<400> 207

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1           5           10           15

Asp Arg Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
          20           25           30

Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
          35           40           45

Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
          50           55           60
```

SRZN_010_03WO_ST25 (1).TXT

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Thr Ile Lys Pro Glu Asp Leu Gly Met Tyr Tyr Cys Leu Gln Gly
85 90 95

Thr His Gln Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 208
<211> 1689
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-2E12 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 208
gatgtacaac ttcaggagtc aggacctggc ctcgtgaaac cttctcagtc tctgtctctc 60

SRZN_010_03WO_ST25 (1).TXT

acctgctctg tcaactggcta ctccatcacc agtgggttatt actggaactg gatccggcag	120
tttccaggaa acaaaactgga atggatgggc tccataggct acgatgatac caatcactac	180
aacccatctc tcaaaaatcg aatctccatc actcgtgaca catctaagaa ccagtttttc	240
ctgaagttga attctgtgac aactgaggac acagccacat attactgtgc aggtgactac	300
ccctttgctt tctggggcca agggactctg gtcactgtct ctgcagctag caccaagggc	360
ccatcgggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg	420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct	480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc	540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcaccc agacctacac ctgcaacgta	600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaag ttgtgtcgag	660
tgcccaccgt gccagcacc acctgtggca ggaccgtcag tcttcctctt cccccaaaa	720
cccaaggaca ccctcatgat ctcccggacc cctgagggtca cgtgcgtggg ggtggacgtg	780
agccacgaag accccgaggt ccagttcaac tgggtacgtgg acggcgtgga ggtgcataat	840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggg cagcgtcctc	900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa	960
ggcctcccag ccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca	1020
cagggtgtaca ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc	1080
tgcttggtca aaggcttcta cccagcgac atcgccgtgg agtgggagag caatgggcag	1140
ccggagaaca actacaagac cacgcctccc atgctggact ccgacggctc cttcttcctc	1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcagtctcc	1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt	1320
aaagggtgtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc	1380
aagggtgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt	1440
ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg	1500
gggtattacg gacaccgcgc gcctgacatg aaccgatgcg ccagatgccg gatcgagaac	1560
tgcatagct gccgcagcaa ggacgcctgc actaagtga aagtcggctt ctaccttcac	1620

cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa 1680

tgcgtggag 1689

<210> 209

<211> 563

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-2E12 Heavy chain IgG2, RSP02
(F105R/F109A) polypeptide sequence

<400> 209

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Ser Ile Gly Tyr Asp Asp Thr Asn His Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

Leu Lys Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Gly Asp Tyr Pro Phe Ala Phe Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

SRZN_010_03WO_ST25 (1).TXT

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

SRZN_010_03WO_ST25 (1).TXT

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445

Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu
450 455 460

Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480

Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495

Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510

Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525

Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540

Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560

Cys Val Glu

<210> 210
 <211> 639
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-2I13 light chain polynucleotide sequence

<400> 210
 gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60
 atcacatgtc gagcaagtga gaatatttac agttatttag tatggtatca gcagaaacag 120
 ggaaaatctc ctcagctcct ggtctataat gcaaaaacct tagcagaagg tgtgccatca 180
 aggttcagtg gcagtggatc aggcacacag ttttctctga agatcaacag cctgcagcct 240
 gaagattttg ggagttatta ctgtcaacat cattatggta cttggacgtt cgggtggaggc 300
 ataaagctgg aaatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
 gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
 agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
 agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
 agcaaagcag actacagaaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
 agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 211
 <211> 213
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-2I13 light chain polypeptide sequence

<400> 211

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
20 25 30

Leu Val Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His His Tyr Gly Thr Trp Thr
85 90 95

Phe Gly Gly Gly Ile Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 212
 <211> 1716
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-2I13 Heavy chain IgG2, RSP02
 (F105R/F109A) polynucleotide sequence

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<400> 212
gaggtgcagc tgggtggagtc tgggggaggc ttagtgaagc ctggagggtc ccggaaactc      60
tcctgtgcag cctctggatt cactttcagt gactatggaa tgcactgggt ccgtcaggct      120
ccagagaagg ggctggagtg ggttgccctac attagtagtg gcagtagtac catctactat      180
gcagacacag tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgttc      240
ctacaaatga ccagtctaag gtctgaggac acagccatgt attactgttc aaggaaggga      300
gggtttggtg actacgagaa aagctatgct atggactact ggggtcaagg aacctcagtc      360
accgtctcca gcgctagcac caagggccca tcggtcttcc ccctggcgcc ctgctccagg      420
agcacctccg agagcacagc ggccctgggc tgcctgggtca aggactactt ccccgaaccg      480
gtgacggtgt cgtggaactc aggcgctctg accagcggcg tgcacacctt cccagctgtc      540
ctacagtcct caggactcta ctccctcagc agcgtgggtga ccgtgccctc cagcaacttc      600
ggcacccaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag      660
acagttgagc gcaaattgtg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga      720
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccctt      780
gaggtcacgt gcgtgggtgt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg      840
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac      900
agcacgttcc gtgtgggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag      960
gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc     1020
aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag     1080
atgaccaaga accaggtcag cctgacctgc ctgggtcaaag gcttctaccc cagcgacatc     1140
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccatg     1200
ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg     1260

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SRZN_010_03WO_ST25 (1).TXT

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320
cagaagagcc tctccctgtc tccgggtaaa ggtggtggtg gctcgggatc cggaggctcc 1380
ggtggcggtg gcagcaaccc aatttgcaag ggatgcttaa gctgtagcaa ggacaacgga 1440
tgttcacggt gccagcaaaa gctgtttttc ttcctccggc gggaaggaat gcggcagtac 1500
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac 1560
cgatgcgcca gatgccgat cgagaactgc gatagctgcc gcagcaagga cgcctgcact 1620
aagtgcaaag tcggcttcta ctttcaccgg ggcagatgtt ttgacgaatg cccggatggc 1680
ttgccccgc tggaggagac tatggaatgc gtggag 1716

<210> 213
<211> 572
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-2I13 Heavy chain IgG2, RSP02
(F105R/F109A) polypeptide sequence

<400> 213

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ser Arg Lys Gly Gly Phe Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
210 215 220

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
290 295 300

SRZN_010_03WO_ST25 (1).TXT

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly
450 455 460

Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly
465 470 475 480

Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly
485 490 495

Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr
500 505 510

SRZN_010_03WO_ST25 (1).TXT

Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu
515 520 525

Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val
530 535 540

Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly
545 550 555 560

Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
565 570

<210> 214
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-2I22 light chain polynucleotide
sequence

<400> 214
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgttattc 60
atcacatgtc gagcaagtga gaatattttac agtaatttag catggtatca gcagaaacag 120
ggaaaatctc ctgagctcct ggtctatggg gcaacaaact tagcagatgg tgtgacatca 180
aggttcagtg gcagtgggtc aggcacacag ttttccctca agatcgacag cctgcagtct 240
gaagattttg ggagttatta ctgtcaacat ttttggggta ctacgtggac gttcggtgga 300
ggcaccaagc tggaaatcaa acgtacggtg gctgcacat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgtttgtg gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 215
<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-2I22 light chain polypeptide sequence

<400> 215

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10					15		

Glu	Thr	Val	Ile	Ile	Thr	Cys	Arg	Ala	Ser	Glu	Asn	Ile	Tyr	Ser	Asn
		20					25					30			

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Gln	Gly	Lys	Ser	Pro	Gln	Leu	Leu	Val
	35					40						45			

Tyr	Gly	Ala	Thr	Asn	Leu	Ala	Asp	Gly	Val	Thr	Ser	Arg	Phe	Ser	Gly
	50				55						60				

Ser	Gly	Ser	Gly	Thr	Gln	Phe	Ser	Leu	Lys	Ile	Asp	Ser	Leu	Gln	Ser
65					70					75				80	

Glu	Asp	Phe	Gly	Ser	Tyr	Tyr	Cys	Gln	His	Phe	Trp	Gly	Thr	Thr	Trp
			85						90					95	

Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
		100						105					110		

Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
		115					120					125			

Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130					135					140				

Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145				150						155					160

Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
			165						170					175	

SRZN_010_03WO_ST25 (1).TXT

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 216
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-2I22 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 216
gaggttcaac tgcagcagtc tggacctgaa ctggtgaagc ctggggcttc agtgaagata 60
tcctgcaagg cttctggtta ctcatttact ggctacttta tgaactgggt gaagcagagc 120
catggaaaga gccttgagtg gattggacgt tttaatcctt tcaatgggtca aactttctac 180
aatcaggagt tcaagggcaa ggccacatta actgttgaca aatcctctga caccgcccac 240
atggaactcc ggagcctgac atctgaggac tctgcagtct attattgtgc aagaagagga 300
aggtacgacg tttactatgc tctggactac tggggtaag gaacctcagt caccgtctcc 360
agcgctagca ccaagggccc atcggctctt cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcaccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc cccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900

SRZN_010_03WO_ST25 (1).TXT

```

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag      960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaaa      1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag      1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag      1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc      1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggtg gcagcagggg      1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc      1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt      1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg      1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt      1500
ctccactcct gccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc      1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa      1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg      1680
ctggaggaga ctatggaatg cgtggag                                           1707

```

<210> 217
 <211> 569
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-2I22 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 217

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Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1              5              10              15

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Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
          20              25              30

```

```

Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
          35              40              45

```

SRZN_010_03WO_ST25 (1).TXT

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asp Thr Ala His
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

SRZN_010_03WO_ST25 (1).TXT

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

SRZN_010_03WO_ST25 (1).TXT

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 218
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-3A24 light chain polynucleotide
sequence

<400> 218
gacattgtga tgaccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60
gtcacctgca aggccagtc gaatgtgggt agtaatgtag cctggtttca acagaaacca 120
gggcaatctc ctaaagcact gatttactcg tcatcctacc ggtacagtgg agtccctgat 180
cgcttcacgg gcagtggatc tgggacagat ttcactctca ccatcaccaa tgtgcagtct 240
gaagacttgg cagagtatct ctgtcagcaa tataacagct ttcctctcac gttcggtgct 300
gggaccaagc tggaactgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcga 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

SRZN_010_03WO_ST25 (1).TXT

```

cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag      480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg      540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc      600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642

```

<210> 219
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-3A24 light chain polypeptide sequence

<400> 219

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
 1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
 20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
 35 40 45

Tyr Ser Ser Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
 65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Phe Pro Leu
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

SRZN_010_03WO_ST25 (1).TXT

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 220
<211> 1683
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-3A24 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 220
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca taaactgggt gaggcagagt 120
catggaaaga gccttgagtg gattggacgt gttattccta gcaatgggtg tagtaactac 180
aaccagaagt tcaagggcaa ggccacattg acagtagaca aatccctcag tacagcctac 240
atgcacctca acagcctgac atctgaggac tctgcggtct attactgtgc aaccagctg 300
ggacggtggg gccaaaggac tctggtcact gtctctgcag ctagcaccaa gggcccatcg 360
gtcttcccc tggcgccctg ctccaggagc acctccgaga gcacagcggc cctgggctgc 420
ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgctctgacc 480
agcggcgtgc acaccttccc agctgtccta cagtcctcag gactctactc cctcagcagc 540

SRZN_010_03WO_ST25 (1).TXT

gtggtgaccg tgccctccag caacttcggc acccagacct acacctgcaa cgtagatcac	600
aagcccagca acaccaaggt ggacaagaca gttgagcgca aatgttgtgt cgagtgccca	660
ccgtgcccag caccacctgt ggcaggaccg tcagtcttcc tcttcccccc aaaaccaag	720
gacaccctca tgatctcccg gaccctgag gtcacgtgcg tggtggtgga cgtgagccac	780
gaagaccccg aggtccagtt caactggtac gtggacggcg tggaggtgca taatgccaag	840
acaaagccac gggaggagca gttcaacagc acgttccgtg tggtcagcgt cctcaccgtt	900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aggtctccaa caaaggcctc	960
ccagccccca tcgagaaaac catctccaaa accaaagggc agccccgaga accacaggtg	1020
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg	1080
gtcaaaggct tctaccccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag	1140
aacaactaca agaccacgcc tcccatgctg gactccgacg gctccttctt cctctacagc	1200
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg	1260
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaaggt	1320
ggtggtggct cgggatccgg aggtccggt ggcggtggca gcaacccaat ttgcaaggga	1380
tgcttaagct gtagcaagga caacggatgt tcacggtgcc agcaaaagct gtttttcttc	1440
ctccggcggg aaggaatgcg gcagtacggc gaatgtctcc actcctgccc ctccgggtat	1500
tacggacacc gcgcgctga catgaaccga tgcgccagat gccggatcga gaactgcgat	1560
agctgccgca gcaaggacgc ctgcactaag tgcaaagtcg gcttctacct tcaccggggc	1620
agatgttttg acgaatgccc ggatggcttc gcccgcctgg aggagactat ggaatgcgtg	1680
gag	1683

<210> 221
 <211> 561
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-3A24 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 221

SRZN_010_03WO_ST25 (1).TXT

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Ile Asn Trp Val Arg Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gln Leu Gly Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

SRZN_010_03WO_ST25 (1).TXT

Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
210 215 220

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
275 280 285

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

SRZN_010_03WO_ST25 (1).TXT

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly
435 440 445

Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys
450 455 460

Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe
465 470 475 480

Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys
485 490 495

Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala
500 505 510

Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys
515 520 525

Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp
530 535 540

Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val
545 550 555 560

Glu

<210> 222
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-3E20 light chain polynucleotide
sequence

<400> 222
gacatcaaga tgaccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

SRZN_010_03WO_ST25 (1).TXT

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atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca      120
gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca      180
aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctagagtat      240
gaagatatgg gaatttatta ttgtctacag tatgatgact tgtggacgtt cgggtggaggc      300
accaagctgg aaatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct      360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc      420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag      480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg      540
agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg      600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt                               639

```

<210> 223
 <211> 213
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-3E20 light chain polypeptide
 sequence

<400> 223

```

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1           5           10           15

```

```

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
          20           25           30

```

```

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
          35           40           45

```

```

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
          50           55           60

```

```

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
          65           70           75           80

```


SRZN_010_03WO_ST25 (1).TXT

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 224
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-3E20 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 224
caggtccaac tgcagcagtc tggggctgaa ctggcaaaac ctggggcctc agtgaagatg 60
tcctgcaagg cttctggcta cacctttact agctactgga tacactgggt aaaacagagg 120
cctggacagg gtctggaatg gattggatac attaataccta gcagtgggta tgctgagtac 180

SRZN_010_03WO_ST25 (1).TXT

aatcagaagt tcaaggtcag ggccacattg actgcagaca aatcctccag cacagcctac	240
atgcaactaa gcagcctgac atctgaggac tctgcagtct attactgtgc aagagaaagt	300
tactatagtt tcgactatac tatggactac tgggggtcaag gaacctcagt caccgtctcc	360
agcgctagca ccaagggccc atcgggtcttc cccctggcgc cctgctccag gagcacctcc	420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg	480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc	540
tcaggactct actccctcag cagcgtgggtg accgtgccct ccagcaactt cggcacccag	600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag	660
cgcaaagtgt gtgtcgagtgc cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc	720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg	780
tgctgtgggtg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac	840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc	900
cgtgtgggtca gcgtcctcac cggtgtgcac caggactggc tgaacggcaa ggagtacaag	960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaacaaa	1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag	1080
aaccaggtca gcctgacctg cctgggtcaaa ggcttctacc ccagcgacat cgccgtggag	1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgctcccat gctggactcc	1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggtg gcagcagggg	1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc	1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cgggtggcgg	1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg	1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt	1500
ctccactcct gccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc	1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa	1620
gtcggcttct accttcaccg gggcagatgt tttagacgaat gcccggatgg cttcgccccg	1680
ctggaggaga ctatggaatg cgtggag	1707

SRZN_010_03WO_ST25 (1).TXT

<210> 225
 <211> 569
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in lab - synthesized LP1-3E20 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

 <400> 225

 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
 1 5 10 15

 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

 Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

 Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe
 50 55 60

 Lys Val Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

 Ala Arg Glu Ser Tyr Tyr Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly
 100 105 110

 Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125

 Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
 130 135 140

 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

SRZN_010_03WO_ST25 (1).TXT

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

SRZN_010_03WO_ST25 (1).TXT

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 226
 <211> 657
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-6H3 light chain polynucleotide sequence

<400> 226
 gatgttgtga tgaccagac tccactcact ttgtcgggta ccattggaca accagcctcc 60
 atctcttgca agtcaagtca gagcctctta gatagtgatg gaaagacata tttgaattgg 120
 ttgttacaga ggccaggcca gtctccaaag cgcctaattct atctgggtgtc taaactggac 180
 tctggagtcc ctgacagggt cactggcagt ggatcaggga cagatttcac actgaaaatc 240
 agcagagtgg aggctgagga tttgggagtt tattattgct ggcaaggtag acattttcct 300
 cacacgttcg gctcggggac aaagttggaa ataaaacgta cggtaggctgc accatctgtc 360
 ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
 ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
 tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
 agcagcacc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
 gtcacccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 227
 <211> 219
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-6H3 light chain polypeptide sequence

<400> 227

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
 1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
 20 25 30

SRZN_010_03WO_ST25 (1).TXT

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro His Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 228
<211> 1689
<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-6H3 Heavy chain IgG2, RSP02 (F105R/F109A) polynucleotide sequence

<400> 228

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caggcttatc tacagcagtc tggggctgag ctggtgaggc ctggggcctc agtgaagatg      60
tcctgtaagg cttctggcta cacatcttcc cgtttcgata tgcactgggt aaagcagaca      120
cctagacagg gcctggaatg gattggagtt atttatccag gaaatgggtga tacttcctac      180
aatcagaagt tcagggacaa ggcctcactg actgtagaca aatcctccag cacagcctac      240
atgcagctca gcagcctgac atctgaagac tctgcggtct atttctgtgc aagctcctac      300
tatggtaacc cctggggcca aggcaccact ctcacagtct ccagcgctag caccaagggc      360
ccatcgggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg      420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct      480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc      540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcaccc agacctacac ctgcaacgta      600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaatg ttgtgtcgag      660
tgcccaccgt gcccagcacc acctgtggca ggaccgtcag tcttcctctt cccccaaaaa      720
cccaaggaca ccctcatgat ctcccggacc cctgagggtca cgtgcgtggt ggtggacgtg      780
agccacgaag accccgaggt ccagttcaac tggtagctgg acggcgtgga ggtgcataat      840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggt cagcgtcctc      900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa      960
ggcctcccag ccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca     1020
caggtgtaca ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc     1080
tgcttggtca aaggcttcta cccagcgac atcgccgtgg agtgggagag caatgggcag     1140
ccggagaaca actacaagac cagcctccc atgctggact ccgacggctc cttcttcctc     1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc     1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt     1320
aaagtggtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc     1380

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SRZN_010_03WO_ST25 (1).TXT

aagggatgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt 1440
 ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg 1500
 gggattacg gacaccgcgc gcctgacatg aaccgatgcg ccagatgccg gatcgagaac 1560
 tgcgatagct gccgcagcaa ggacgcctgc actaagtgca aagtcggctt ctaccttcac 1620
 cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa 1680
 tgcgtggag 1689

<210> 229
 <211> 563
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-6H3 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 229

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Phe
 20 25 30

Asp Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Val Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

Arg Asp Lys Ala Ser Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95

Ala Ser Ser Tyr Tyr Gly Asn Pro Trp Gly Gln Gly Thr Thr Leu Thr
 100 105 110

SRZN_010_03WO_ST25 (1).TXT

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

SRZN_010_03WO_ST25 (1).TXT

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445

Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu
450 455 460

Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480

Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495

Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510

Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525

SRZN_010_03WO_ST25 (1).TXT

Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540

Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560

Cys Val Glu

<210> 230
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-7B13 light chain polynucleotide
sequence

<400> 230
gatattgtgc taactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtcagt 60
ctttcctgca gggccagtca aagtattagc aactacctac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaagttt gcttcccagt ccatctctgg gatccccctc 180
aggttcagtg gcagtggatc agggacggat ttcactctca ctatcaacag tgtggagact 240
gaagattttg gaatgtattt ctgtcaacag agtaacagct ggccgctcac gttcggtgct 300
gggaccaagc tggagctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 231
<211> 214
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-7B13 light chain polypeptide sequence

<400> 231

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15

Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30

Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45

Lys Phe Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Thr
65 70 75 80

Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

SRZN_010_03WO_ST25 (1).TXT

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 232
<211> 1689
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-7B13 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 232
gaggtccagc tgcaacaatc tggacctgag gtggtgaagc ctggggcttc agtgaagatg 60
tcctgtaaga cttctggatt cacattcact gactactaca tgaactgggt gaagcagggt 120
catggaaaga gccttgagtg gattggacgt gttaatccta gcaatgatga tactaggtac 180
aatcagaagt tcaagggaaa ggccacattg acagtagaca agtccctcag cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcggtct attactgtac aaggtgggtc 300
tactttgact actggggcca aggcactact ctcacagtct ccagcgctag caccaagggc 360
ccatcggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg 420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct 480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcacc agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaatg ttgtgtcgag 660
tgcccaccgt gcccagcacc acctgtggca ggaccgtcag tcttcctctt cccccaaaa 720
cccaaggaca ccctcatgat ctcccggacc cctgagggtca cgtgcgtggt ggtggacgtg 780
agccacgaag accccgaggt ccagttcaac tggtagctgg acggcgtgga ggtgcataat 840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggt cagcgtcctc 900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa 960
ggcctcccag ccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca 1020

SRZN_010_03WO_ST25 (1).TXT

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caggtgtaca ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc      1080
tgcctgggtca aaggcttcta ccccagcgac atcgccgtgg agtgggagag caatgggcag      1140
ccggagaaca actacaagac cacgcctccc atgctggact ccgacggctc cttcttcctc      1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcagtctcc      1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt      1320
aaaggtgggtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc      1380
aagggatgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt      1440
ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg      1500
gggtattacg gacaccgcg gcctgacatg aaccgatgcg ccagatgccg gatcgagaac      1560
tgcgatagct gccgcagcaa ggacgcctgc actaagtgca aagtcgggctt ctaccttcac      1620
cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa      1680
tgcgtggag                                         1689

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<210> 233

<211> 563

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-7B13 Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 233

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Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
1              5              10              15

```

```

Ser Val Lys Met Ser Cys Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr
          20              25              30

```

```

Tyr Met Asn Trp Val Lys Gln Gly His Gly Lys Ser Leu Glu Trp Ile
          35              40              45

```

```

Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe
          50              55              60

```

SRZN_010_03WO_ST25 (1).TXT

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Trp Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270

SRZN_010_03WO_ST25 (1).TXT

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445

Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu
450 455 460

Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480

SRZN_010_03WO_ST25 (1).TXT

Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495

Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510

Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525

Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540

Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560

Cys Val Glu

<210> 234
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-7I20 light chain polynucleotide
sequence

<400> 234
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60
atcacatgtc gaacaagtga gaatatttac agttatttag catggtatca gcagaaacag 120
ggaaaatctc ctgagctcct ggtctataat gcaaaaacct tagcaaaaagg tgtgccatca 180
aggttcagtg gcagtggatc aggcacacag ttttctctga agatcaacgg cctgcagcct 240
gaagattttg ggaattatta ctgtcaacat cattatggta ctccgtacac gttcggaggg 300
gggaccaagg tggaaataaa acgtacggtg gctgcacat ctgtcttcat cttcccgcga 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 235

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-7I20 light chain polypeptide sequence

<400> 235

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Lys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Gly Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Asn Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

SRZN_010_03WO_ST25 (1).TXT

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 236
<211> 1692
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-7I20 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 236
gaggtgaagc tgggtggagtc tggaggaggc ttggtacagc ctgggggttc tctgagtctc 60
tcctgtgcag cttctggatt caccttcact gattactaca tgagctgggt ccgccagccc 120
ccagggaagg cacttgagtg gttggctttg attagaaaca aagctaattg ttacacaaca 180
gagtacagtg catctgtgaa gggtcggttc accatctcca gggataattc ccaaagcatc 240
ctctatcttc aaatgaatgc cctgagagct gaggacagtg ccacttatta ctgtgcagtt 300
acctacgggg cttactgggg ccaagggact ctggtcactg tctctgcagc tagcaccaag 360
ggcccatcgg tcttccccct ggcgccctgc tccaggagca cctccgagag cacagcggcc 420
ctgggctgcc tgggtcaagga ctacttcccc gaaccgggtga cgggtgtcgtg gaactcaggc 480
gctctgacca gcggcgtgca caccttccca gctgtcctac agtcctcagg actctactcc 540
ctcagcagcg tggtgaccgt gccctccagc aacttcggca cccagaccta cacctgcaac 600
gtagatcaca agcccagcaa caccaaggtg gacaagacag ttgagcgcaa atgttgtgtc 660

SRZN_010_03WO_ST25 (1).TXT

gagtgtccac cgtgtccagc accacctgtg gcaggaccgt cagtcttcct cttcccccca	720
aaaccaagg acaccctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac	780
gtgagccacg aagaccccga ggtccagttc aactggtacg tggacggcgt ggaggtgcat	840
aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc	900
ctcaccgttg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac	960
aaaggcctcc cagcccccat cgagaaaacc atctccaaaa ccaaaggga gccccgagaa	1020
ccacaggtgt acaccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg	1080
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg	1140
cagccggaga acaactacaa gaccacgcct cccatgctgg actccgacgg ctctttcttc	1200
ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc	1260
tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg	1320
ggtaaagggtg gtggtggctc gggatccgga ggctccggtg gcggtggcag caaccaatt	1380
tgcaagggat gcttaagctg tagcaaggac aacggatgtt cacggtgcca gaaaagctg	1440
tttttcttcc tccggcggga aggaatgcgg cagtacggcg aatgtctcca ctctgcccc	1500
tcgggggtatt acggacaccg cgcgcctgac atgaaccgat gcgccagatg ccggatcgag	1560
aactgcgata gctgccgcag caaggacgcc tgcactaagt gcaaagtcgg cttctacctt	1620
caccgggggca gatgttttga cgaatgcccg gatggcttcg ccccgtgga ggagactatg	1680
gaatgcgtgg ag	1692

<210> 237
 <211> 564
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-7I20 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 237

Glu	Val	Lys	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5				10						15	

SRZN_010_03WO_ST25 (1).TXT

Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
35 40 45

Ala Leu Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
65 70 75 80

Leu Tyr Leu Gln Met Asn Ala Leu Arg Ala Glu Asp Ser Ala Thr Tyr
85 90 95

Tyr Cys Ala Val Thr Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220

SRZN_010_03WO_ST25 (1).TXT

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

SRZN_010_03WO_ST25 (1).TXT

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
435 440 445

Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys
450 455 460

Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu
465 470 475 480

Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu
485 490 495

His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn
500 505 510

Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys
515 520 525

Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg
530 535 540

Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met
545 550 555 560

Glu Cys Val Glu

<210> 238

<211> 693

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-8M24 light chain polynucleotide
sequence

<400> 238

gaggttcagc tgcagcagtc tggggctgag cttgtgaggc caggggcctc agtcaagttg 60

tcctgcacag cttctggctt taccattaaa gacgactata ttactgggt gaagcagggg 120

cctgaacagg gcctggagtg gattggaaga attgatcctg cggatgatga tactaaatat 180

SRZN_010_03WO_ST25 (1).TXT

```

gccccgaagt tccaggacaa ggccactata actgcagaca catcctccaa cacagcctac      240
ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtgc tagaagttcc      300
atggcctggt ttgcttactg ggcccaaggg actctgggtca ctgtctctac agctagcacc      360
aaggggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg      420
gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca      480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac      540
tccctcagca gcgtgggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc      600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt      660
ggatccggct ccggacatca tcatcaccat cac                                  693

```

<210> 239
 <211> 231
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesizedLP1-8M24 light chain polypeptide
 sequence

<400> 239

```

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1              5              10              15

```

```

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Thr Ile Lys Asp Asp
              20              25              30

```

```

Tyr Ile His Trp Val Lys Gln Gly Pro Glu Gln Gly Leu Glu Trp Ile
              35              40              45

```

```

Gly Arg Ile Asp Pro Ala Asp Asp Asp Thr Lys Tyr Ala Pro Lys Phe
              50              55              60

```

```

Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65              70              75              80

```

```

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys

```

Ala Arg Ser Ser Met Ala Trp Phe Ala Tyr Trp Ala Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Thr Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Ser Gly Ser
 210 215 220

Gly His His His His His His
 225 230

<210> 240

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-8M24 Heavy chain IgG2, RSP02
 (F105R/F109A) polynucleotide sequence

<400> 240

gacatccaga tgacacagag ccctagcagc ctgtctgccca gcgtgggaga cagagtgacc 60

atcacctgtc ggatcagcga gaacatctac agcaacctgg cctgggtatca gcagaagcct 120

SRZN_010_03WO_ST25 (1).TXT

```

ggcaaggccc ctaagctgct gatctacgcc gccatcaatc tggccgatgg cgtgccaagc      180
agattttctg gcagcggctc tggcaccgac ttcaccctga ccatacttag cctgcagcct      240
gaggacttcg ccacctacta ctgccagcac ttttggggca cccctttcac ctttggccag      300
ggcaccaagc tggaaatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca      360
tctgatgagc agttgaaatc tggaactgcc tctgtttgtg gcctgctgaa taacttctat      420
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag      480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg      540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc      600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642

```

<210> 241
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-8M24 Heavy chain IgG2, RSP02
 (F105R/F109A) polypeptide sequence

<400> 241

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15

```

```

Asp Arg Val Thr Ile Thr Cys Arg Ile Ser Glu Asn Ile Tyr Ser Asn
          20           25           30

```

```

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35           40           45

```

```

Tyr Ala Ala Ile Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
          50           55           60

```

```

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65           70           75           80

```

```

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Phe

```

85

90

95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 242
 <211> 657
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-9C3 light chain polynucleotide
 sequence

<400> 242
 gatgttgtgg tgactcaaac tccactctcc ctgcctgtca gctttggaga tcaagtttct 60
 atctcttgca ggtctagtca gagtcttgca aacagttatg ggaacaccta tttgtcttgg 120
 tacctgcaca agcctggcca gtctccacag ctctcatct atgggatttc caacagattt 180
 tctgggggtgc cagacaggtt cagtggcagt ggttcaggga cagatttcac actcaagatc 240

SRZN_010_03WO_ST25 (1).TXT

agcacaataa agcctgagga cttgggaatc tattactgct tacaagctac acatcagccg 300
 tggacgttcg gtggaggcac caagctggaa atcaaacgta cggtggctgc accatctgtc 360
 ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
 ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
 tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
 agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
 gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 243
 <211> 219
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-9C3 light chain polypeptide
 sequence

<400> 243

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
 1 5 10 15

Asp Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
 20 25 30

Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Thr Ile Lys Pro Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Ala
 85 90 95

Thr His Gln Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

SRZN_010_03WO_ST25 (1).TXT

100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 244
<211> 1695
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-9C3 Heavy chain IgG2, RSP02
(F105R/F109A) polynucleotide sequence

<400> 244
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60
acttgttctt tctctgggtt ttactgagc acttcttata tgggtgtgag ctggattcgt 120
aagccttcag gaaagggtct ggagtggctg gcacacattt tctgggatga tgacaagcgc 180
tataacccat ccctgaagag cgggtcaca atctccaagg atacctccag caaccaggta 240
ttcctcatga tcaccagtgt ggaaactgca gatactgcca catactactg tgggggtccc 300
tactatccgt ttacttactg gggccaaggg actctgggtca ctgtctctgc agctagcacc 360

SRZN_010_03WO_ST25 (1).TXT

aagggcccat cggtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcg	420
gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca	480
ggcgtcttga ccagcggcgt gcacaccttc ccagctgtcc tacagtcctc aggactctac	540
tccctcagca gcgtgggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc	600
aacgtagatc acaagcccag caacaccaag gtggacaaga cagttgagcg caaatgttgt	660
gtcgagtgcc caccgtgccc agcaccacct gtggcaggac cgtcagtctt cctcttcccc	720
ccaaaacca aggacacctt catgatctcc cggacccctg aggtcacgtg cgtgggtggtg	780
gacgtgagcc acgaagacct cgaggtccag ttcaactggc acgtggacgg cgtggaggtg	840
cataatgcca agacaaagcc acgggaggag cagttcaaca gcacgttccg tgtgggtcagc	900
gtcctcaccg ttgtgcacca ggactggctg aacggcaagg agtacaagtg caaggtctcc	960
aacaaaggcc tcccagcccc catcgagaaa accatctcca aaaccaaagg gcagccccga	1020
gaaccacagg tgtacacctt gccccatcc cgggaggaga tgaccaagaa ccaggtcagc	1080
ctgacctgcc tgggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat	1140
gggcagccgg agaacaacta caagaccacg cctcccatgc tggactccga cggctccttc	1200
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca	1260
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct	1320
ccgggtaaag gtgggtggtg ctcgggatcc ggaggctccg gtggcgggtg cagcaacca	1380
atttgcaagg gatgcttaag ctgtagcaag gacaacggat gttcacgggtg ccagcaaaag	1440
ctgtttttct tcctccggcg ggaaggaatg cggcagtagc gcgaatgtct ccactcctgc	1500
ccctcgggggt attacggaca ccgcgcgcct gacatgaacc gatgcgccag atgccggatc	1560
gagaactgcg atagctgccg cagcaaggac gcctgcacta agtgcaaagt cggcttctac	1620
cttcaccggg gcagatgttt tgacgaatgc ccggatggct tcgccccgct ggaggagact	1680
atggaatgcg tggag	1695

<210> 245
 <211> 565
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-9C3 Heavy chain IgG2, RSP02 (F105R/F109A) polypeptide sequence

<400> 245

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Tyr Met Gly Val Ser Trp Ile Arg Lys Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80

Phe Leu Met Ile Thr Ser Val Glu Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Gly Gly Pro Tyr Tyr Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn

180

185

190

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
 195 200 205

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
 210 215 220

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 245 250 255

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
 260 265 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
 290 295 300

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 305 310 315 320

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
 325 330 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
 340 345 350

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe

385 390 395 400

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
405 410 415

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
420 425 430

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
435 440 445

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly
450 455 460

Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
465 470 475 480

Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
485 490 495

Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
500 505 510

Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
515 520 525

Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
530 535 540

Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
545 550 555 560

Met Glu Cys Val Glu
565

<210>	246
<211>	642
<212>	DNA
<213>	Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-9M16 light chain polynucleotide sequence

<400> 246

```

gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact      60
atcacttgca aggcgagtcg ggacattaat agctatttaa gctgggtcca gcagaaacca      120
gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggcagatgg ggtcccatca      180
agggttcagt gcagtggatc tgggcaagat tattctctca ccatcagcaa cctggagtat      240
gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgctcac gttcggtgct      300
gggaccaagc tggagctgaa acgtacggtg gctgcacat ctgtcttcat cttcccacca      360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat      420
cccagagagg ccaaagtaca gtggaagggt gataacgccc tccaatcggg taactcccag      480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg      540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc      600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                          642

```

<210> 247

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-9M16 light chain polypeptide sequence

<400> 247

```

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1           5           10           15

```

```

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
          20           25           30

```

```

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
          35           40           45

```

```

Tyr Arg Ala Asn Arg Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly

```

50

55

60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Tyr
 65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 248

<211> 1686

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-9M16 Heavy chain IgG2, RSP02
 (F105R/F109A) polynucleotide sequence

SRZN_010_03WO_ST25 (1).TXT

<400> 248

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catggaaaga gccttgagtg gattggacgt gttaatccta acaatgggtgg ttctaactac	180
aaccagaaat tcaagggcaa ggccacattg acagtagaca aatccctcag cacagcctac	240
atgcagctca acagcctgac atctgaggac tctgcggtct attactgtgc aagtcgaaac	300
ttcgatgtct gggg'gcagcagg gaccacggtc accgtctcca gcgctagcac caagggccca	360
tcggtcttcc ccctggcgcc ctgctccagg agcacctccg agagcacagc ggccctgggc	420
tgcctggtca aggactactt ccccgaaccg gtgacgggtg cgtggaaactc aggcgctctg	480
accagcggcg tgcacacctt cccagctgtc ctacagtcct caggactcta ctccctcagc	540
agcgtggtga ccgtgccctc cagcaacttc ggcacccaga cctacacctg caacgtagat	600
cacaagccca gcaacaccaa ggtggacaag acagttgagc gcaaagtgtg tgtcgagtgc	660
ccaccgtgcc cagcaccacc tgtggcagga ccgtcagtct tcctcttccc cccaaaaccc	720
aaggacaccc tcatgatctc ccggaccctt gaggtcacgt gcgtgggtgg ggacgtgagc	780
cacgaagacc ccgaggtcca gttcaactgg tacgtggacg gcgtggaggt gcataatgcc	840
aagacaaagc cacgggagga gcagttcaac agcacgttcc gtgtgggtcag cgtcctcacc	900
gttgtgcacc aggactggct gaacggcaag gagtacaagt gcaaggctc caacaaaggc	960
ctcccagccc ccatcgagaa aacctctcc aaaaccaaag ggcagccccg agaaccacag	1020
gtgtacaccc tgccccatc ccgggaggag atgaccaaga accaggctcag cctgacctgc	1080
ctggtcaaag gcttctaccc cagcgacatc gccgtggagt gggagagcaa tgggcagccg	1140
gagaacaact acaagaccac gcctcccatg ctggactccg acggctcctt cttcctctac	1200
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg	1260
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa	1320
ggtggtggtg gctcgggac cggaggctcc ggtggcggtg gcagcaaccc aatttgcaag	1380
ggatgcttaa gctgtagcaa ggacaacgga tgttcacggt gccagcaaaa gctgtttttc	1440
ttcctccggc gggaaggaat gcggcagtac ggcgaatgtc tccactcctg cccctcgggg	1500
tattacggac accgcgcgcc tgacatgaac cgatgcgcca gatgccggat cgagaactgc	1560

SRZN_010_03WO_ST25 (1).TXT

gatagctgcc gcagcaagga cgcctgcact aagtgcaaag tcggcttcta ccttcaccgg 1620
ggcagatgtt ttgacgaatg cccggatggc ttcgccccgc tggaggagac tatggaatgc 1680
gtggag 1686

<210> 249
<211> 562
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-9M16 Heavy chain IgG2, RSP02
(F105R/F109A) polypeptide sequence

<400> 249

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Arg Asn Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
100 105 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
115 120 125

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys

130

135

140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 145 150 155 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 165 170 175

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
 180 185 190

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 195 200 205

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
 210 215 220

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 245 250 255

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
 260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 275 280 285

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
 290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
 305 310 315 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
 325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr

340

345

350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 355 360 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 370 375 380

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 385 390 395 400

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly
 435 440 445

Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser
 450 455 460

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
 465 470 475 480

Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser
 485 490 495

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
 500 505 510

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
 515 520 525

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
 530 535 540

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys

545

550

555

560

Val Glu

<210> 250

<211> 657

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-10C22 light chain polynucleotide sequence

<400> 250

gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gggcattgta catagtaatg gaaacatcta ttagaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctctgatct acaaagtttc caaccgattt 180

tctgggggtcc cagacagggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300

cccacgttcg gaggggggac caagctggaa ataaaacgta cggtaggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtggga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcacc tgacgtgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcaccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 251

<211> 219

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized LP1-10C22 light chain polypeptide sequence

<400> 251

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly

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1              5              10              15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Gly Ile Val His Ser
      20              25              30

Asn Gly Asn Ile Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35              40              45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
      50              55              60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
      85              90              95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
      100             105             110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
      115             120             125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
      130             135             140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
      145             150             155             160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
      165             170             175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
      180             185             190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
      195             200             205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

```

210

215

<210> 252
 <211> 1704
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized LP1-10C22 Heavy chain IgG2, RSP02
 (F105R/F109A) polynucleotide sequence

<400> 252
 gaggtgcagc tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctgaaactc 60
 tcctgtgcag cctctggatt cactttcagt agttatggca tgtcttgggt tcgccagact 120
 ccagacaaga ggctggagtg ggtcgcaagt attagtagtg gtggtagtta tacctactat 180
 ccagacagtg tgaaggggcg attcaccatc tccagagaca atgcccagaa caccctgtac 240
 ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgt aagacatgag 300
 gagtatggta aatccggatt tgcttactgg ggccaaggga ccctgattac tgtctctgca 360
 gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
 agcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggg gacgggtgtcg 480
 tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
 ggactctact ccctcagcag cgtgggtgacc gtgccctcca gcaacttcgg caccagacc 600
 tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
 aaatgttgtg tcgagtgtcc accgtgtcca gcaccacctg tggcaggacc gtcagtcttc 720
 ctcttcccc caaaaccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc 780
 gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
 gtggaggtgc ataatgcaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
 gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960
 aaggtctcca acaaaggcct ccagcccc atcgagaaaa ccatctcaa aaccaaaggg 1020
 cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1080
 caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg 1140
 gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac 1200

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ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
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tccctgtctc cgggtaaagg tgggtggtggc tcgggatccg gaggctccgg tggcggtggc 1380
agcaacccaa tttgcaaggg atgcttaagc tgtagcaagg acaacggatg ttcacgggtgc 1440
cagcaaaagc tgtttttctt cctccggcgg gaaggaatgc ggcagtacgg cgaatgtctc 1500
cactcctgcc cctcggggta ttacggacac cgcgcgcctg acatgaaccg atgcgccaga 1560
tgccggatcg agaactgcga tagctgccgc agcaaggacg cctgcactaa gtgcaaagtc 1620
ggcttctacc ttcaccgggg cagatgtttt gacgaatgcc cggatggctt cgccccgctg 1680
gaggagacta tggaatgcgt ggag 1704

<210> 253
<211> 568
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized LP1-10C22 Heavy chain IgG2, RSP02
(F105R/F109A) polypeptide sequence

<400> 253

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys

Val Arg His Glu Glu Tyr Gly Lys Ser Gly Phe Ala Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Ile Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
 210 215 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val

290

295

300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
 385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
 435 440 445

Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile
 450 455 460

Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys
 465 470 475 480

Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr
 485 490 495

Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala

500

505

510

Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser
 515 520 525

Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu
 530 535 540

His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu
 545 550 555 560

Glu Glu Thr Met Glu Cys Val Glu
 565

<210> 254
 <211> 1695
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-1N15 Heavy
 chain IgG1 N297G polynucleotide sequence

<400> 254
 aacccaattt gcaagggatg ctttaagctgt agcaaggaca acggatgttc acggtgccag 60
 caaaagctgt ttttcttcct cgggcgggaa ggaatgcggc agtacggcga atgtctccac 120
 tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
 cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
 ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
 gagactatgg aatgcgtgga ggggtggtggt ggctcgggat ccggaggctc cgggtggcggt 360
 ggacgcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagtg 420
 aagatgtcct gtaaggcttc tggatacaca ttcactgact actacatgaa ctgggtgaag 480
 cagagtcatg gagagagcct tgagtggatt ggacgtgtta ttcctagcaa tgggtgtact 540
 aactacaacc agaagttcaa gggcaaggcc acattgacag tagacaaatc cctcaccaca 600
 gcctacatgc agctcaacag cctgacatct gaagactctg cggctctattt ctgtgcaaga 660
 gggatggact actggggtcc aggaacctca gtcaccgtct ccagcgctag caccaagggc 720

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ccatcgggtct tccccctggc accctcctcc aagagcacct ctgggggcac agcggccctg      780
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc      840
ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc      900
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg      960
aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaadc ttgtgacaaa     1020
actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc     1080
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg     1140
gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg     1200
gaggtgcata atgccaagac aaagccgcgg gaggagcagt acggcagcac gtaccgtgtg     1260
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgaag      1320
gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag     1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag     1440
gtcagcctga cctgcctggg caaaggcttc tatcccagcg acatcgccgt ggagtgggag     1500
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc     1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc     1620
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc     1680
ctgtctccgg gtaaa                                           1695

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<210> 255
 <211> 565
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-1N15 Heavy chain IgG1 N297G polypeptide sequence

<400> 255

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
 1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met

20

25

30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
 35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
 50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
 65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
 85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
 100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
 115 120 125

Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
 130 135 140

Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
 145 150 155 160

Gln Ser His Gly Glu Ser Leu Glu Trp Ile Gly Arg Val Ile Pro Ser
 165 170 175

Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
 180 185 190

Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr Met Gln Leu Asn Ser Leu
 195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Gly Met Asp Tyr
 210 215 220

Trp Gly Pro Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly

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225                               230                235                240

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
                245                250                255

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                260                265                270

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                275                280                285

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
                290                295                300

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
305                310                315                320

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
                325                330                335

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
                340                345                350

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                355                360                365

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                370                375                380

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
385                390                395                400

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser
                405                410                415

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                420                425                430

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala

```

435

440

445

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 450 455 460

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
 465 470 475 480

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 485 490 495

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 500 505 510

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 515 520 525

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 530 535 540

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 545 550 555 560

Leu Ser Pro Gly Lys
 565

<210> 256
 <211> 1719
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-1P13 Heavy
 chain IgG1 N297G polynucleotide sequence

<400> 256
 aacccaattt gcaagggatg ctttaagctgt agcaaggaca acggatgttc acggtgccag 60
 caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
 tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
 cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240

SRZN_010_03WO_ST25 (1).TXT

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ggcagcgagg ttcaactgca gcagtctgga cctgaactgg tgaagcctgg ggcttcagt	420
aagatatacct gcaaggcttc tggttactca tttactgact actttatgaa ctgggtgaag	480
cagagccatg gaaagagcct tgagtggatt ggacgtttta atcctttcaa tgggtcaaact	540
ttctacaatc aggagttcaa gggcaaggcc acattaactg tagacaaatc ctctagcacc	600
gcccacatgg agctccggag cctgacatct gaggactctg cagtctatta ttgtgcaaga	660
agaggaaggt acgacgttta ctatgttctg gactactggg gtcaaggaac ctcagtcacc	720
gtctccagcg ctagcaccaa gggcccatcg gtcttcccc tggcaccctc ctccaagagc	780
acctctgggg gcacagcggc cctgggctgc ctgggtcaagg actacttccc cgaaccggtg	840
acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta	900
cagtcctcag gactctactc cctcagcagc gtgggtgaccg tgccctccag cagcttgggc	960
accagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa	1020
gttgagcca aatcttgtga caaaactcac acatgccac cgtgcccagc acctgaactc	1080
ctgggggggac cgtcagtctt cctcttcccc ccaaaacca aggacaccct catgatctcc	1140
cggacccctg aggtcacatg cgtgggtggtg gacgtgagcc acgaagaccc tgaggtcaag	1200
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag	1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg	1320
aatggcaagg agtacaagt caaggtctcc aacaaagccc tcccagcccc catcgagaaa	1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc	1440
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tgggtcaaagg cttctatccc	1500
agcgacatcg ccgtggagt ggagagcaat gggcagccgg agaacaacta caagaccacg	1560
cctcccgtgc tggactccga cggctccttc ttctctaca gcaagctcac cgtggacaag	1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac	1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa	1719

<210> 257

<211> 573

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-1P13 Heavy chain IgG1 N297G polypeptide sequence

<400> 257

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
 1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
 20 25 30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
 35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
 50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
 65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
 85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
 100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
 115 120 125

Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys
 130 135 140

Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Phe Met Asn Trp Val Lys
 145 150 155 160

Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Phe Asn Pro Phe

165

170

175

Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe Lys Gly Lys Ala Thr Leu
 180 185 190

Thr Val Asp Lys Ser Ser Ser Thr Ala His Met Glu Leu Arg Ser Leu
 195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Arg Gly Arg Tyr
 210 215 220

Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
 225 230 235 240

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 245 250 255

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 260 265 270

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 275 280 285

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 290 295 300

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 305 310 315 320

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 325 330 335

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 340 345 350

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 355 360 365

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu

370

375

380

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 385 390 395 400

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 405 410 415

Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
 420 425 430

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 435 440 445

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 450 455 460

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 465 470 475 480

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 485 490 495

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 500 505 510

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 515 520 525

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 530 535 540

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 545 550 555 560

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570

<210> 258

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<211> 1728

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polynucleotide sequence

<400> 258

aacccaattt gcaagggatg cttaaagctgt agcaaggaca acggatgttc acggtgccag	60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac	120
tcctgcccct cgggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc	180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc	240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag	300
gagactatgg aatgcgtgga ggggtggtggt ggctcgggat ccggaggctc cgggtggcgggt	360
ggcagcgagg tccaactcgt agaatcaggt ggtggtttg tcaaaccagg tggctctcgg	420
aagttgtcct gtgctgcctc tggatttaca ttcagtgact acggtatgca ctgggtccgt	480
caggctccag agaaggggct ggagtgggtt gcctacatta gtagtggcag tagtaccatc	540
tactatgcag acacagtga gggccgattc accatctcca gagacaatgc caagaacacc	600
ctgttcctac aaatgaccag tctaaggtct gaggacacag ccatgtatta ctgttcaagg	660
aagggagggt ttggtgacta cgagaaaagc tatgctatgg actactgggg tcaaggaacc	720
tcagtcaccg tctccagcgc tagcaccaag ggcccatcgg tcttccccct ggcaccctcc	780
tccaagagca cctctggggg cacagcggcc ctgggctgcc tgggtcaagga ctacttcccc	840
gaaccggtga cgggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccc	900
gctgtcctac agtcctcagg actctactcc ctacgcagcg tggtgaccgt gccctccagc	960
agcttgggca cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaagggtg	1020
gacaagaaag ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca	1080
cctgaactcc tgggggggacc gtcagtcttc ctcttcccc caaaacccaa ggacaccctc	1140
atgatctccc ggaccctga ggtcacatgc gtgggtggtg acgtgagcca cgaagaccct	1200
gagggtcaagt tcaactggta cgtggacggc gtggagggtgc ataatgcaa gacaaagccg	1260
cgggaggagc agtacggcag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag	1320

SRZN_010_03WO_ST25 (1).TXT

gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 1380
atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 1440
cccccatccc gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 1500
ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggagccgga gaacaactac 1560
aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctacag caagctcacc 1620
gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 1680
ctgcacaacc actacacgca gaagagcctc tcctgtctc cgggtaaa 1728

<210> 259

<211> 576

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polypeptide sequence

<400> 259

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser

100

105

110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
 115 120 125

Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Arg Lys Leu Ser Cys
 130 135 140

Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Gly Met His Trp Val Arg
 145 150 155 160

Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly
 165 170 175

Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile
 180 185 190

Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe Leu Gln Met Thr Ser Leu
 195 200 205

Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ser Arg Lys Gly Gly Phe
 210 215 220

Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
 225 230 235 240

Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 245 250 255

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 260 265 270

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 275 280 285

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 290 295 300

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser

305 310 315 320

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
325 330 335

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
340 345 350

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
355 360 365

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
370 375 380

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
385 390 395 400

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
405 410 415

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val
420 425 430

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
435 440 445

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
450 455 460

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
465 470 475 480

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
485 490 495

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
500 505 510

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

515

520

525

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 530 535 540

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 545 550 555 560

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570 575

<210> 260

<211> 1719

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-2I22 Heavy
 chain IgG1 N297G polynucleotide sequence

<400> 260

aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
 caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
 tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
 cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
 ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
 gagactatgg aatgcgtgga ggggtggtggt ggctcgggat ccggaggctc cgggtggcgg 360
 ggacgcgagg ttcaactgca gcagtctgga cctgaactgg tgaagcctgg ggcttcagt 420
 aagatatacct gcaaggcttc tggttactca tttactggct actttatgaa ctgggtgaag 480
 cagagccatg gaaagagcct tgagtggatt ggacgtttta atcctttcaa tgggtcaaact 540
 ttctacaatc aggagttcaa gggcaaggcc acattaactg ttgacaaatc ctctgacacc 600
 gccacatgg aactccggag cctgacatct gaggactctg cagtctatta ttgtgcaaga 660
 agaggaaggt acgacgttta ctatgctctg gactactggg gtcaaggaac ctcagtcacc 720
 gtctccagcg ctagcaccaa gggcccatcg gtcttcccc tggcaccctc ctccaagagc 780
 acctctgggg gcacagcggc cctgggctgc ctgggtcaagg actacttccc cgaaccggtg 840

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acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta      900
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc      960
accagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa     1020
gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc     1080
ctgggggggac cgtcagtctt cctcttcccc caaaaccca aggacaccct catgatctcc     1140
cggacccttg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgagggtcaag     1200
ttcaactggg acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag     1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg     1320
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa     1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc     1440
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tgggtcaaagg cttctatccc     1500
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg     1560
cctcccgtgc tggactccga cggctccttc ttctctaca gcaagctcac cgtggacaag     1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcattgaggc tctgcacaac     1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa                             1719

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<210> 261
 <211> 573
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-2I22 Heavy chain IgG1 N297G polypeptide sequence

<400> 261

Asn	Pro	Ile	Cys	Lys	Gly	Cys	Leu	Ser	Cys	Ser	Lys	Asp	Asn	Gly	Cys
1				5					10					15	

Ser	Arg	Cys	Gln	Gln	Lys	Leu	Phe	Phe	Phe	Leu	Arg	Arg	Glu	Gly	Met
			20					25					30		

Arg	Gln	Tyr	Gly	Glu	Cys	Leu	His	Ser	Cys	Pro	Ser	Gly	Tyr	Tyr	Gly

35

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125

Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys
130 135 140

Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Phe Met Asn Trp Val Lys
145 150 155 160

Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Phe Asn Pro Phe
165 170 175

Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe Lys Gly Lys Ala Thr Leu
180 185 190

Thr Val Asp Lys Ser Ser Asp Thr Ala His Met Glu Leu Arg Ser Leu
195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Arg Gly Arg Tyr
210 215 220

Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225 230 235 240

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro

245

250

255

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 260 265 270

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 275 280 285

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 290 295 300

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 305 310 315 320

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 325 330 335

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 340 345 350

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 355 360 365

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 370 375 380

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 385 390 395 400

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 405 410 415

Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
 420 425 430

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 435 440 445

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys

450

455

460

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 465 470 475 480

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 485 490 495

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 500 505 510

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 515 520 525

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 530 535 540

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 545 550 555 560

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570

<210> 262
 <211> 1695
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-3A24 Heavy
 chain IgG1 N297G polynucleotide sequence

<400> 262
 aaccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
 caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
 tcctgcccct cgggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
 cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
 ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
 gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cgggtggcgg 360

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ggcagcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagtg	420
aagatgtcct gtaaggcttc tggatacaca ttcactgact actacataaa ctgggtgagg	480
cagagtcatg gaaagagcct tgagtggatt ggacgtgtta ttcctagcaa tgggtgtagt	540
aactacaacc agaagttcaa gggcaaggcc acattgacag tagacaaatc cctcagtaca	600
gcctacatgc acctcaacag cctgacatct gaggactctg cggtctatta ctgtgcaacc	660
cagctgggac ggtggggcca agggactctg gtcactgtct ctgcagctag caccaagggc	720
ccatcggtct tccccctggc accctcctcc aagagcacct ctgggggcac agcggccctg	780
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctgaggcgcc	840
ctgaccagcg gcgtgcacac cttcccggt gtcctacagt cctcaggact ctactccctc	900
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg	960
aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaatc ttgtgacaaa	1020
actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc	1080
ttccccccaa aacccaagga caccctcatg atctcccga cccctgaggt cacatgcgtg	1140
gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg	1200
gaggtgcata atgccaagac aaagccgcgg gaggagcagt acggcagcac gtaccgtgtg	1260
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag	1320
gtctccaaca aagccctccc agccccatc gagaaaacca tctccaaagc caaagggcag	1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag	1440
gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag	1500
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc	1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc	1620
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc	1680
ctgtctccgg gtaaa	1695

<210> 263
 <211> 565
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-3A24 Heavy chain IgG1 N297G polypeptide sequence

<400> 263

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125

Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140

Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Ile Asn Trp Val Arg
145 150 155 160

Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Ile Pro Ser
165 170 175

Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu

180

185

190

Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met His Leu Asn Ser Leu
 195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Thr Gln Leu Gly Arg
 210 215 220

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly
 225 230 235 240

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
 245 250 255

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 260 265 270

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 275 280 285

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 290 295 300

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
 305 310 315 320

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
 325 330 335

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 340 345 350

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 355 360 365

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 370 375 380

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val

385 390 395 400

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser
405 410 415

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
420 425 430

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
435 440 445

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
450 455 460

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
465 470 475 480

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
485 490 495

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
500 505 510

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
515 520 525

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
530 535 540

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
545 550 555 560

Leu Ser Pro Gly Lys
565

<210>	264
<211>	1719
<212>	DNA
<213>	Artificial Sequence

SRZN_010_03WO_ST25 (1).TXT

<220>

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-3E20 Heavy chain IgG1 N297G polynucleotide sequence

<400> 264

aaccaattt gcaagggatg ctttaagctgt agcaaggaca acggatgttc acggtgccag	60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac	120
tcctgcccct cgggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc	180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc	240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag	300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cgggtggcgg	360
ggcagccagg tccaactgca gcagtctggg gctgaactgg caaaacctgg ggcctcagt	420
aagatgtcct gcaaggcttc tggctacacc tttagtagct actggataca ctgggtaaaa	480
cagaggcctg gacagggtct ggaatggatt ggatacatta atcctagcag tggttatgct	540
gagtacaatc agaagttcaa ggtcagggcc acattgactg cagacaaatc ctccagcaca	600
gcctacatgc aactaagcag cctgacatct gaggactctg cagtctatta ctgtgcaaga	660
gaaagttact atagtttcga ctatactatg gactactggg gtcaaggaac ctgagtcacc	720
gtctccagcg ctagcaccaa gggcccatcg gtcttcccc tggcaccctc ctccaagagc	780
acctctgggg gcacagcggc cctgggctgc ctgggtcaagg actacttccc cgaaccgggtg	840
acgggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta	900
cagtcctcag gactctactc cctcagcagc gtgggtgaccg tgccctccag cagcttgggc	960
accagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa	1020
gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc	1080
ctgggggggac cgtcagtctt cctcttcccc caaaaccca aggacaccct catgatctcc	1140
cggaccctg aggtcacatg cgtgggtggtg gacgtgagcc acgaagacc tgaggtcaag	1200
ttcaactggg acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag	1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg	1320
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa	1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc	1440

SRZN_010_03WO_ST25 (1).TXT

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cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtaaagg cttctatccc      1500
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg      1560
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag      1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcagtaggc tctgcacaac      1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa                               1719

```

<210> 265
 <211> 573
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-3E20 Heavy chain IgG1 N297G polypeptide sequence

<400> 265

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
 1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
 20 25 30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
 35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
 50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
 65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
 85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
 100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln

115

120

125

Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys
 130 135 140

Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Ile His Trp Val Lys
 145 150 155 160

Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
 165 170 175

Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe Lys Val Arg Ala Thr Leu
 180 185 190

Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
 195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Glu Ser Tyr Tyr
 210 215 220

Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
 225 230 235 240

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 245 250 255

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 260 265 270

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 275 280 285

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 290 295 300

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 305 310 315 320

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys

325

330

335

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 340 345 350

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 355 360 365

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 370 375 380

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 385 390 395 400

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 405 410 415

Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
 420 425 430

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 435 440 445

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 450 455 460

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 465 470 475 480

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 485 490 495

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 500 505 510

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 515 520 525

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln

530

535

540

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 545 550 555 560

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570

<210> 266
 <211> 1701
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-7B13 Heavy
 chain IgG1 N297G polynucleotide sequence

<400> 266
 aaccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
 caaaagctgt ttttcttcct cggcggggaa ggaatgcggc agtacggcga atgtctccac 120
 tcctgcccct cgggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
 cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
 ttctaccttc accggggcgag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
 gagactatgg aatgcgtgga ggggtggtgg ggctcgggat ccggaggctc cgggtggcggg 360
 ggtagcgagg tccagctgca acaatctgga cctgaggtgg tgaagcctgg ggcttcagt 420
 aagatgtcct gtaagacttc tggattcaca ttcactgact actacatgaa ctgggtgaag 480
 cagggtcatt gaaagagcct tgagtggatt ggacgtgtta atcctagcaa tgatgatact 540
 aggtacaatc agaagttcaa gggaaaggcc acattgacag tagacaagtc cctcagcaca 600
 gcctacatgc agctcaacag cctgacatct gaggactctg cggctctatta ctgtacaagg 660
 tggttctact ttgactactg gggccaaggc actactctca cagtctccag cgctagcacc 720
 aaggggcccat cggctcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 780
 gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca 840
 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 900
 tccctcagca gcgtgggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 960

SRZN_010_03WO_ST25 (1).TXT

```

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt      1020
gacaaaactc acacatgccc accgtgcccga gcacctgaac tcctggggggg accgtcagtc      1080
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca      1140
tgcgtggtgg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtacgtggac      1200
ggcgtggagg tgcataatgc caagacaaaag ccgcggggagg agcagtacgg cagcacgtac      1260
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag      1320
tgcaagggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa      1380
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag      1440
aaccagggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag      1500
tgggagagca atgggcagcc ggagaacaac tacaagacca cgctcccgt gctggactcc      1560
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagggtg gcagcagggg      1620
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc      1680
ctctccctgt ctccgggtaa a                                              1701

```

<210> 267
 <211> 567
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-7B13 Heavy chain IgG1 N297G polypeptide sequence

<400> 267

```

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1           5           10           15

```

```

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20           25           30

```

```

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35           40           45

```

```

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn

```

50

55

60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125

Ser Gly Pro Glu Val Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140

Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
145 150 155 160

Gln Gly His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Asn Pro Ser
165 170 175

Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180 185 190

Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu
195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg Trp Phe Tyr Phe
210 215 220

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
225 230 235 240

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
245 250 255

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu

260

265

270

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 275 280 285

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 290 295 300

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 305 310 315 320

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
 325 330 335

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 340 345 350

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 355 360 365

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 370 375 380

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 385 390 395 400

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 405 410 415

Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 420 425 430

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 435 440 445

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 450 455 460

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
500 505 510

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
515 520 525

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
530 535 540

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
545 550 555 560

Leu Ser Leu Ser Pro Gly Lys
565

```
<210> 268
<211> 708
<212> DNA
<213> Artificial Sequence
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<220>
<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-8M24 Heavy chain IgG1 N297G polynucleotide sequence

<400>	268						
caggttcagc	tgcagcagtc	tggagctgag	ctggcgaggc	ctggggcttc	agtgaagctg		60
tcctgcaagg	cttctggcta	caccttcaca	aattatggta	taaactgggt	gaagcagaga		120
actggacagg	gccttgagtg	gattggagag	atttttccta	gaagtgataa	tactttctac		180
aatgagaagt	tcaagggcaa	ggccacactg	actgcagaca	aatcctccac	cacagcgtac		240
atggagctcc	gcagcctgac	atctgaggac	tctgcggtct	atttctgtgc	aagaaaaggc		300
agggactacg	gtactagcca	ctactttgac	tactggggtc	aaggcaccac	tctcacagtc		360
tccagcgcta	gcaccaaggg	cccatcggtc	ttccccctgg	caccctcctc	caagagcacc		420
tctgggggca	cagcggccct	gggctgcctg	gtcaaggact	acttccccga	accggtgacg		480

SRZN_010_03WO_ST25 (1).TXT

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 540
tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 600
cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagaaagtt 660
gagcccaaat cttgtggatc cggctccgga catcatcatc accatcac 708

<210> 269
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in lab - synthesizedRSP02 (F105R/F109A), LP1-8M24 Heavy chain IgG1 N297G polypeptide sequence

<400> 269

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Ile Asn Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Lys Gly Arg Asp Tyr Gly Thr Ser His Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

SRZN_010_03WO_ST25 (1).TXT

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Gly Ser Gly Ser Gly His His His His His His
225 230 235

<210> 270
<211> 1698
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-9M16 Heavy
chain IgG1 N297G polynucleotide sequence

<400> 270
aacc caattt gcaagggatg ctt aagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cgggtggcgg 360
ggcagcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagt 420

SRZN_010_03WO_ST25 (1).TXT

aagatgtcct gtaaggcttc tggatacaca ttcactgact actacatgaa ctgggtgaag	480
cagagtcattg gaaagagcct tgagtggatt ggacgtgtta atcctaacaa tgggtggttct	540
aactacaacc agaaattcaa gggcaaggcc acattgacag tagacaaatc cctcagcaca	600
gcctacatgc agctcaacag cctgacatct gaggactctg cgggtctatta ctgtgcaagt	660
cgaaacttcg atgtctgggg cgaggggacc acggtcaccg tctccagcgc tagcaccaag	720
ggcccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc	780
ctgggctgcc tgggtcaagga ctacttcccc gaaccggtga cgggtgtcgtg gaactcaggc	840
gccctgacca gcggcgtgca caccttcccc gctgtcctac agtcctcagg actctactcc	900
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac	960
gtgaatcaca agcccagcaa caccaagggtg gacaagaaag ttgagcccaa atcttgtgac	1020
aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc	1080
ctcttcccc caaaaccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc	1140
gtgggtggtg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc	1200
gtggaggtgc ataatgcaa gacaaagccg cgggaggagc agtacggcag cacgtaccgt	1260
gtggtcagcg tcctcacctg cctgcaccag gactggctga atggcaagga gtacaagtgc	1320
aaggtctcca acaaagccct cccagcccc atcgagaaaa ccatctcaa agccaaaggg	1380
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac	1440
caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg	1500
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac	1560
ggctccttct tcctctacag caagctcacc gtggacaaga gcagggtggca gcaggggaac	1620
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc	1680
tccctgtctc cgggtaaa	1698

<210> 271
 <211> 566
 <212> PRT
 <213> Artificial Sequence

<220>

SRZN_010_03WO_ST25 (1).TXT

<223> Made in lab - synthesized RSP02 (F105R/F109A), LP1-9M16 Heavy chain IgG1 N297G polypeptide sequence

<400> 271

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15

Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30

Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45

His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60

Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95

Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110

Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125

Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140

Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
145 150 155 160

Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Asn Pro Asn
165 170 175

Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180 185 190

SRZN_010_03WO_ST25 (1).TXT

Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu
195 200 205

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Ser Arg Asn Phe Asp
210 215 220

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
225 230 235 240

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
245 250 255

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
260 265 270

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
275 280 285

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
290 295 300

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
305 310 315 320

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
325 330 335

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
340 345 350

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
355 360 365

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
370 375 380

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
385 390 395 400

SRZN_010_03WO_ST25 (1).TXT

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly
405 410 415

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
420 425 430

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
435 440 445

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
450 455 460

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
465 470 475 480

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
485 490 495

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
500 505 510

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
515 520 525

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
530 535 540

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
545 550 555 560

Ser Leu Ser Pro Gly Lys
565

<210> 272
<211> 1338
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in lab - synthesized Anti-ASGR1 heavy chain polynucleotide

SRZN_010_03WO_ST25 (1).TXT

sequence

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<400> 272
gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg      60
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cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac      180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac      240
ttgcaaataa actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc      300
agctcacgcc ggtggtacct tgagtactgg ggacaggga cccctgtcac cgtgtcagat      360
gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag      420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg      480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca      540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg caccagacc      600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc      660
aaatgttgtg tcgagtgcgc accgtgcca gcaccacctg tggcaggacc gtcagtcttc      720
ctcttcccc caaaaccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc      780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc      840
gtggaggtgc ataatgcaa gacaaagcca cgggaggagc agttcaacag cacgttccgt      900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc      960
aaggtctcca acaaaggcct ccagcccc atcgagaaaa ccatctcaa aaccaaagg      1020
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac      1080
caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg      1140
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac      1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac      1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc      1320
tccctgtctc cgggtaaa

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<210> 273

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in lab - synthesized Anti-ASGR1 heavy chain polypeptide sequence

<400> 273

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

SRZN_010_03WO_ST25 (1).TXT

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

SRZN_010_03WO_ST25 (1).TXT

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 274
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-1F8 VL polypeptide sequence

<400> 274

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
85 90 95

Ser Tyr Tyr Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

100

105

110

<210> 275
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-1F8 VH polypeptide sequence

<400> 275

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Ala Lys Arg Leu Glu Trp Val
 35 40 45

Ala Thr Ile Ser Ser Ile Gly Val Asn Thr Tyr Tyr Pro Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Ala Arg His Val Asp Tyr Tyr Asp Gly Ile Ser Phe Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser
 115 120

<210> 276
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-1N15 VL polypeptide sequence

<400> 276

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
 1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser His
 20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
 35 40 45

Ile Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Pro Glu Tyr
 65 70 75 80

Glu Glu Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 277

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-1N15 VH polypeptide sequence

<400> 277

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu Glu Trp Ile
 35 40 45

SRZN_010_03WO_ST25 (1).TXT

Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Met Asp Tyr Trp Gly Pro Gly Thr Ser Val Thr Val Ser
100 105 110

Ser

<210> 278
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-1P13 VL polypeptide sequence
<400> 278

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Gln Thr Val Ile Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Tyr Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Ser Thr Trp

85

90

95

Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
 100 105

<210> 279

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-1P13 VH polypeptide sequence

<400> 279

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
 20 25 30

Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
 35 40 45

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala His
 65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
 115 120

<210> 280

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-1P5 VL polypeptide sequence

<400> 280

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 281

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-1P5 VH polypeptide sequence

<400> 281

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Leu Thr Tyr
20 25 30

SRZN_010_03WO_ST25 (1).TXT

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser Glu Met Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Glu Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Ala Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 282

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-2E12 VL polypeptide sequence

<400> 282

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15

Asp Arg Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30

Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

<210> 284
 <211> 106
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-2I13 VL polypeptide sequence

<400> 284

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
 20 25 30

Leu Val Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
 35 40 45

Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His His Tyr Gly Thr Trp Thr
 85 90 95

Phe Gly Gly Gly Ile Lys Leu Glu Ile Lys
 100 105

<210> 285
 <211> 124
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-2I13 VH polypeptide sequence

<400> 285

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15

SRZN_010_03WO_ST25 (1).TXT

Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ser Arg Lys Gly Gly Phe Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 286
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-2I22 VL polypeptide sequence

<400> 286

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Ile Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val Thr Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asp Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Thr Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 287

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-2I22 VH polypeptide sequence

<400> 287

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asp Thr Ala His
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 288
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-3A24 VL polypeptide sequence

<400> 288

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ser Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 289
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-3A24 VH polypeptide sequence

<400> 289

SRZN_010_03WO_ST25 (1).TXT

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Ile Asn Trp Val Arg Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gln Leu Gly Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ala

<210> 290

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-3E20 VL polypeptide sequence

<400> 290

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile

35

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
 65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Trp Thr
 85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 291
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-3E20 VH polypeptide sequence
 <400> 291

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe
 50 55 60

Lys Val Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

SRZN_010_03WO_ST25 (1).TXT

Ala Arg Glu Ser Tyr Tyr Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 292

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-6H3 VL polypeptide sequence

<400> 292

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro His Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 293

<211> 115

<212> PRT

<213> Artificial Sequence

SRZN_010_03WO_ST25 (1).TXT

<220>

<223> Made in Lab - synthesized LP1-6H3 VH polypeptide sequence

<400> 293

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Phe
20 25 30

Asp Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Arg Asp Lys Ala Ser Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Ser Ser Tyr Tyr Gly Asn Pro Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 294

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-7B13 VL polypeptide sequence

<400> 294

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15

Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr

20

25

30

Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
 35 40 45

Lys Phe Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Thr
 65 70 75 80

Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Leu
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 100 105

<210> 295

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-7B13 VH polypeptide sequence

<400> 295

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30

Tyr Met Asn Trp Val Lys Gln Gly His Gly Lys Ser Leu Glu Trp Ile
 35 40 45

Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
 65 70 75 80

SRZN_010_03WO_ST25 (1).TXT

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Trp Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 296
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-7I20 VL polypeptide sequence

<400> 296

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Lys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Gly Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Asn Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 297

SRZN_010_03WO_ST25 (1).TXT

<211> 116
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Made in Lab - synthesized LP1-7I20 VH polypeptide sequence
 <400> 297

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30

Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
 35 40 45

Ala Leu Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
 50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ala Leu Arg Ala Glu Asp Ser Ala Thr Tyr
 85 90 95

Tyr Cys Ala Val Thr Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ala
 115

<210> 298
 <211> 107
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Made in Lab - synthesized LP1-8M24 VL polypeptide sequence
 <400> 298

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly

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1           5           10           15
Glu Thr Val Thr Ile Thr Cys Arg Ile Ser Glu Asn Ile Tyr Ser Asn
      20                25                30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro His Leu Leu Val
      35                40                45
Tyr Ala Ala Ile Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
      50                55                60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Ser
      65                70                75                80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Phe
      85                90                95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
      100                105

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<210> 299
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-7I20 VH polypeptide sequence

<400> 299

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Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1           5           10           15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
      20                25                30
Gly Ile Asn Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
      35                40                45
Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn Glu Lys Phe
      50                55                60

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SRZN_010_03WO_ST25 (1).TXT

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Lys Gly Arg Asp Tyr Gly Thr Ser His Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 300

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-9C3 VL polypeptide sequence

<400> 300

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15

Asp Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30

Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Thr Ile Lys Pro Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Ala
85 90 95

Thr His Gln Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

100

105

110

<210> 301
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-9C3 VH polypeptide sequence

<400> 301

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30

Tyr Met Gly Val Ser Trp Ile Arg Lys Pro Ser Gly Lys Gly Leu Glu
 35 40 45

Trp Leu Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
 65 70 75 80

Phe Leu Met Ile Thr Ser Val Glu Thr Ala Asp Thr Ala Thr Tyr Tyr
 85 90 95

Cys Gly Gly Pro Tyr Tyr Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ala
 115

<210> 302
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized LP1-9M16 VL polypeptide sequence

<400> 302

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
 1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
 20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
 35 40 45

Tyr Arg Ala Asn Arg Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Tyr
 65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 100 105

<210> 303

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-9M16 VH polypeptide sequence

<400> 303

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
 35 40 45

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Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Arg Asn Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
100 105 110

Ser Ser

<210> 304
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized LP1-10C22 VL polypeptide sequence

<400> 304

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Gly Ile Val His Ser
20 25 30

Asn Gly Asn Ile Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly

85

90

95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 305

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized LP1-10C22 VH polypeptide sequence

<400> 305

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
 1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
 35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Val Arg His Glu Glu Tyr Gly Lys Ser Gly Phe Ala Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Ile Thr Val Ser Ala
 115 120

<210> 306

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 306

Asp	Ser	Val	Ser	Ser	Asn	Ser	Ala	Ala	Trp	Tyr
1				5					10	

<210> 307

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 307

Asp	Thr	Phe	Thr	Gly	Tyr	Tyr	Ile	His
1				5				

<210> 308

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 308

Phe	Ala	Phe	Ser	Asn	Phe	Ala	Met	Ile
1				5				

<210> 309

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 309

Phe Ser Phe Ser Asn Tyr Ala Met Ser
1 5

<210> 310
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 310

Phe Thr Phe Asn Asn Phe Gly Met Ser
1 5

<210> 311
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 311

Phe Thr Phe Ser Asn Tyr Ala Met Gly
1 5

<210> 312
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 312

Phe Thr Phe Ser Ser Tyr Ala Met His
1 5

<210> 313
<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 313

Gly Phe Asn Ile Lys Asp Asp
1 5

<210> 314

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 314

Gly Phe Asn Ile Lys Asp Thr
1 5

<210> 315

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 315

Gly Phe Thr Phe Ser Asp Tyr
1 5

<210> 316

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 316

Gly Thr Phe Ser Gly Tyr Tyr Met His
1 5

<210> 317

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 317

Gly Thr Phe Ser Asn Thr Asp Ile Asn
1 5

<210> 318

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 318

Gly Thr Phe Ser Asn Tyr Ala Ile Ser
1 5

<210> 319

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 319

Gly Thr Phe Ser Asn Tyr Ser Leu Ser
1 5

<210> 320

<211> 9
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 320

Gly Thr Phe Ser Ser Tyr Ala Ile Ser
 1 5

<210> 321
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 321

Gly Thr Phe Ser Thr Ser Gly Ile Thr
 1 5

<210> 322
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 322

Tyr Arg Phe Thr Asn Tyr Tyr Met His
 1 5

<210> 323
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 323

Tyr Arg Phe Thr Ser Tyr Tyr Leu His
1 5

<210> 324

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 324

Tyr Thr Phe Ile Gly Tyr Tyr Met His
1 5

<210> 325

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 325

Tyr Thr Phe Arg Arg Tyr Pro Met His
1 5

<210> 326

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 326

Tyr Thr Phe Ser Arg Tyr Phe Met His
1 5

<210> 327
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

 <400> 327

Tyr Thr Phe Thr Ala Tyr Tyr Met His
 1 5

<210> 328
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

 <400> 328

Tyr Thr Phe Thr Glu Tyr Tyr Met His
 1 5

<210> 329
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

 <400> 329

Tyr Thr Phe Thr Gly Tyr Tyr Met His
 1 5

<210> 330
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against

hRNF43/ZNRF3

<400> 330

Tyr Thr Phe Thr Asn Tyr Gly Ile Ser
1 5

<210> 331

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 331

Tyr Thr Phe Thr Asn Tyr Lys Met His
1 5

<210> 332

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 332

Tyr Thr Phe Thr Asn Tyr Tyr Met His
1 5

<210> 333

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hRNF43/ZNRF3

<400> 333

Tyr Thr Phe Thr Arg His Tyr Met His
1 5

<210> 334
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

<400> 334

Tyr Thr Phe Thr Arg Tyr Tyr Met His
 1 5

<210> 335
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

<400> 335

Tyr Thr Phe Thr Ser Tyr Ala Met His
 1 5

<210> 336
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH1 sequence of binders against
 hRNF43/ZNRF3

<400> 336

Tyr Thr Phe Thr Ser Tyr Asp Ile Asn
 1 5

<210> 337
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 337

Tyr Thr Phe Thr Ser Tyr Gly Val Ser
1 5

<210> 338

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 338

Tyr Thr Phe Thr Ser Tyr Tyr Leu His
1 5

<210> 339

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hRNF43/ZNRF3

<400> 339

Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5

<210> 340

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 340

Asp Pro Ala Asn Gly Lys
1 5

<210> 341
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3

<400> 341

Asp Pro Glu Asn Gly Asp
 1 5

<210> 342
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3

<400> 342

Gly Gly Ile Ile Pro Ile Phe Asp Ala Ala Thr Tyr Ala
 1 5 10

<210> 343
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3

<400> 343

Gly Gly Ile Ile Pro Ile Phe Asp Ala Thr Asn Tyr Ala
 1 5 10

<210> 344
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 344

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala
1 5 10

<210> 345

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 345

Gly Ile Ile Asn Pro Asn Gly Gly Arg Thr Thr Tyr Ala
1 5 10

<210> 346

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 346

Gly Ile Ile Asn Pro Arg Gly Gly Ser Thr Ser Tyr Ala
1 5 10

<210> 347

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 347

Gly Ile Ile Asn Pro Arg Arg Gly Ser Thr Arg Tyr Ala

1 5 10

<210> 348
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 348

Gly Ile Ile Asn Pro Ser Gly Gly Ser Ala Asn Tyr Ala
1 5 10

<210> 349
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 349

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala
1 5 10

<210> 350
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 350

Gly Lys Ile Asn Pro Ser Ser Gly Ser Thr Ser Tyr Ala
1 5 10

<210> 351
<211> 13
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 351

Gly	Arg	Ile	Lys	Pro	Asn	Ser	Gly	Asn	Thr	Gly	Tyr	Ala
1				5					10			

<210> 352

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 352

Gly	Arg	Ile	Ser	Pro	Asn	Arg	Gly	Gly	Thr	Lys	Tyr	Ala
1				5					10			

<210> 353

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 353

Gly	Arg	Thr	Tyr	Tyr	Arg	Ser	Lys	Trp	Tyr	His	Asp	Tyr	Ala
1				5					10				

<210> 354

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 354

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Gly Val Ile Asn Pro Gly Gly Ser Asp Thr Thr Tyr Ala
1 5 10

<210> 355
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 355

Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser
1 5 10

<210> 356
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 356

Gly Trp Ile Asn Pro His Ser Gly Gly Thr Asn Tyr Ala
1 5 10

<210> 357
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 357

Gly Trp Ile Asn Pro Asn Arg Gly Gly Thr Ser Tyr Ala
1 5 10

<210> 358
<211> 13
<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 358

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala
1 5 10

<210> 359

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 359

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Arg Tyr Ala
1 5 10

<210> 360

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 360

Gly Trp Ile Asn Pro Asn Ser Gly Asn Thr Lys Tyr Ala
1 5 10

<210> 361

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 361

Gly Trp Ile Asn Pro Asn Thr Gly Gly Thr Lys Ser Ala
1 5 10

<210> 362
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 362

Gly Trp Ile Ser Ala Asp Asn Gly Asn Thr Asn Tyr Ala
1 5 10

<210> 363
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 363

Gly Trp Ile Ser Pro Asn Ser Gly Ala Thr Asn Tyr Ala
1 5 10

<210> 364
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 364

Gly Trp Met Asn Pro Lys Ser Gly Gly Thr Asn Tyr Ala
1 5 10

<210> 365
<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 365

Gly	Trp	Met	Asn	Pro	Asn	Ser	Gly	His	Ala	Gly	Ser	Ala
1				5					10			

<210> 366

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 366

Gly	Trp	Met	Asn	Pro	Asn	Ser	Gly	Asn	Thr	Gly	Tyr	Ala
1				5					10			

<210> 367

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 367

Gly	Trp	Met	Asn	Pro	Asn	Thr	Gly	Gly	Ile	Lys	Tyr	Ser
1				5					10			

<210> 368

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hRNF43/ZNRF3

<400> 368

Gly Trp Val Asn Pro Lys Asn Gly His Thr Gly Tyr Ala
1 5 10

<210> 369

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 369

Lys Ser Lys Thr Asp Gly Gly Ile
1 5

<210> 370

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 370

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10

<210> 371

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against
hRNF43/ZNRF3

<400> 371

Ser Ala Ile Ser Gly Ser Gly Arg Thr Thr Tyr Tyr Ala
1 5 10

<210> 372

<211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3
 <400> 372

Ser Ala Ile Ser Gly Ser Gly Thr Tyr Tyr Ala
 1 5 10

<210> 373
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3
 <400> 373

Ser Gly Ile Ser Ala Ser Gly Arg Asn Thr Tyr Tyr Ala
 1 5 10

<210> 374
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3
 <400> 374

Ala Ile Tyr Tyr Leu Glu Ala Phe Asp Val
 1 5 10

<210> 375
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 375

Cys Ala Lys Asp Leu Glu His Thr Gly Tyr Ser Ser Gly Trp Ala Gly
1 5 10 15

Phe Asp Tyr Trp
20

<210> 376

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
hRNF43/ZNRF3

<400> 376

Cys Ala Lys Asp Ser Gly Tyr Cys Ser Ser Thr Ser Cys Tyr Asp Gly
1 5 10 15

Gly Tyr Phe Asp Leu Trp
20

<210> 377

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
hRNF43/ZNRF3

<400> 377

Cys Ala Lys Ser Arg Ala Leu Lys Gly Ser Tyr Thr Ser Trp
1 5 10

<210> 378

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against

hRNF43/ZNRF3

<400> 378

Cys Ala Arg Asp Gly Leu Gly Val Asp Ala Phe Asp Ile Trp
 1 5 10

<210> 379

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 379

Cys Ala Arg Asp Gly Tyr Tyr Tyr Gly Met Asp Val Trp
 1 5 10

<210> 380

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 380

Cys Ala Arg Asp Lys Val Gly Ala Ile Asp Tyr Trp
 1 5 10

<210> 381

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 381

Cys Ala Arg Asp Leu Met Val Arg Gly Gly Pro Pro Phe Asp Tyr Trp
 1 5 10 15

<210> 382
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 382

Cys Ala Arg Asp Pro Val Arg Gly Ile Ser Ala Phe Asp Tyr Trp
 1 5 10 15

<210> 383
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 383

Cys Ala Arg Asp Gln Gly His Asp Tyr Gly Asp Tyr Glu Ile Asp Tyr
 1 5 10 15

Trp

<210> 384
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 384

Cys Ala Arg Asp Gln Lys Gly Lys Ser Ser Ser Trp Phe Arg Phe Asp
 1 5 10 15

Pro Trp

<210> 385
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 385

Cys Ala Arg Asp Ser Trp Leu Arg Gly Ala Trp Gly Tyr Trp
 1 5 10

<210> 386
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 386

Cys Ala Arg Glu Asp Tyr Asn Trp Asn Asp Gly Trp Phe Asp Pro Trp
 1 5 10 15

<210> 387
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 387

Cys Ala Arg Glu Thr Arg His Gly Ser Asp Tyr Trp
 1 5 10

<210> 388
 <211> 23
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 388

Cys	Ala	Arg	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Tyr	Pro	Tyr	Tyr	Tyr	Tyr
1				5					10					15	

Tyr	Tyr	Gly	Met	Asp	Val	Trp
			20			

<210> 389

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 389

Cys	Ala	Arg	Gly	Gly	Arg	Ser	Tyr	Gly	Tyr	Trp	Tyr	Phe	Asp	Leu	Trp
1				5					10					15	

<210> 390

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 390

Cys	Ala	Arg	Gly	Gly	Arg	Thr	Thr	Val	Thr	Thr	Met	Ala	Tyr	Trp
1				5					10					15

<210> 391

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 391

Cys Ala Arg Gly Gly Ser Gly Trp Leu Asp Tyr Trp
1 5 10

<210> 392

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 392

Cys Ala Arg Gly Met Tyr Ser Ser Ser Trp Leu Arg Tyr Trp
1 5 10

<210> 393

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 393

Cys Ala Arg Gly Arg Gln Gly Val Trp Asp Tyr Trp
1 5 10

<210> 394

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 394

Cys Ala Arg Gly Arg Arg Ser Gly Leu Ser Pro Pro Ala Tyr Trp
1 5 10 15

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<210> 395
 <211> 22
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 395

Cys Ala Arg Gly Arg Arg Ser Arg Gly Ser Ser Ser Leu Gly Tyr Tyr
 1 5 10 15

Tyr Tyr Met Asp Val Trp
 20

<210> 396
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 396

Cys Ala Arg Gly Arg Ser Gly Asn Trp Lys Phe Trp
 1 5 10

<210> 397
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 397

Cys Ala Arg Gly Arg Val Val Arg Gly Val Ile Ile Ser Tyr Gly Met
 1 5 10 15

Asp Val Trp

<210> 398
 <211> 12
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

 <400> 398

Cys	Ala	Arg	Gly	Ser	Leu	Gly	Tyr	Phe	Asp	Leu	Trp
1				5						10	

<210> 399
 <211> 11
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

 <400> 399

Cys	Ala	Arg	Gly	Ser	Asn	Gly	Met	Asp	Val	Trp
1				5						10

<210> 400
 <211> 13
 <212> PRT
 <213> Artificial Sequence

 <220>
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 hRNF43/ZNRF3

 <400> 400

Cys	Ala	Arg	Leu	Arg	Ala	Asn	Tyr	Gly	Met	Asp	Val	Trp
1				5								10

<210> 401
 <211> 16
 <212> PRT
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 <220>

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<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 401

Cys	Ala	Arg	Arg	Gln	Tyr	Ser	Gly	Tyr	Asp	Thr	His	Phe	Asp	Tyr	Trp
1				5					10					15	

<210> 402

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 402

Cys	Ala	Arg	Arg	Arg	Asp	Gly	Tyr	Asn	Trp	Gly	Tyr	Trp
1				5					10			

<210> 403

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 403

Cys	Ala	Arg	Arg	Thr	Ser	Ser	Phe	Ser	Leu	Trp
1				5					10	

<210> 404

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 404

Cys	Ala	Arg	Ser	Phe	Gly	Val	Ala	Gly	Thr	Leu	Asp	Tyr	Trp
1				5					10				

<210> 405
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 405

Cys Ala Arg Ser Gly Ala Gly Met Trp Tyr Phe Asp Leu Trp
 1 5 10

<210> 406
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 406

Cys Ala Arg Val Leu Arg Gly Ser Leu Gly Phe Asp Tyr Trp
 1 5 10

<210> 407
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hRNF43/ZNRF3

<400> 407

Cys Ala Arg Val Val Arg Ala Val Asp Ala Phe Asp Ile Trp
 1 5 10

<210> 408
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 408

Cys	Ala	Arg	Tyr	Ser	Ser	Ser	Trp	Ser	Trp	Pro	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 409

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 409

Cys	Thr	Arg	Ala	Arg	Gly	Gln	Arg	Ser	Gly	Tyr	Ser	Tyr	Phe	Asp	Leu
1				5					10					15	

Trp

<210> 410

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 410

Cys	Val	Gly	Gly	Arg	Ser	Gly	Trp	Ile	Trp	Tyr	Phe	Asp	Leu	Trp
1				5					10					15

<210> 411

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 411

Gly Gly Gly Tyr Tyr Gly Met Asp Tyr
1 5

<210> 412

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hRNF43/ZNRF3

<400> 412

Ser Arg Thr Thr Ala Leu Asp Tyr
1 5

<210> 413

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 413

Lys Ala Ser Gln Ser Val Arg Pro Ala Val Ala
1 5 10

<210> 414

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 414

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 415
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRL1 sequence of binders against
 hRNF43/ZNRF3

<400> 415

Gln	Ala	Ser	Gln	Asp	Ile	Ser	Arg	Tyr	Leu	Asn
1				5					10	

<210> 416
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRL1 sequence of binders against
 hRNF43/ZNRF3

<400> 416

Arg	Ala	Gly	Gln	Ser	Ile	Ser	Arg	Phe	Leu	Asn
1				5					10	

<210> 417
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
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 hRNF43/ZNRF3

<400> 417

Arg	Ala	Ser	Glu	Asn	Ile	His	Lys	Tyr	Leu	Asn
1				5					10	

<210> 418
 <211> 15
 <212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 418

Arg	Ala	Ser	Glu	Ser	Val	Asp	Ser	Tyr	Gly	Asn	Ser	Phe	Met	His
1				5					10				15	

<210> 419

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 419

Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Ser	Leu	Asn
1				5					10	

<210> 420

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 420

Arg	Ala	Ser	Gln	Asp	Ile	Ser	Arg	Tyr	Leu	Ala
1				5					10	

<210> 421

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 421

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Arg Ala Ser Gln Asp Ile Tyr Arg Tyr Leu Asn
1 5 10

<210> 422
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 422

Arg Ala Ser Gln Phe Ile Ser Thr Tyr Leu Asn
1 5 10

<210> 423
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 423

Arg Ala Ser Gln Gly Ile Ser Asn Asn Leu Asn
1 5 10

<210> 424
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 424

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 425
<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 425

Arg	Ala	Ser	Gln	Asn	Ile	Arg	Ser	Trp	Leu	Ala
1				5					10	

<210> 426

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 426

Arg	Ala	Ser	Gln	Asn	Ile	Tyr	Asp	Trp	Leu	Ala
1				5					10	

<210> 427

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 427

Arg	Ala	Ser	Gln	Ser	Ile	Asn	Asn	Trp	Leu	Ala
1				5					10	

<210> 428

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 428

Arg Ala Ser Gln Ser Ile Arg Ser Tyr Leu Asn
1 5 10

<210> 429

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 429

Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala
1 5 10

<210> 430

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 430

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> 431

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 431

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 432

<211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 432

Arg	Ala	Ser	Gln	Ser	Ile	Ser	Thr	Trp	Leu	Ala
1				5					10	

<210> 433
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 433

Arg	Ala	Ser	Gln	Ser	Val	Asp	Ser	Ser	Tyr	Leu	Ala
1				5					10		

<210> 434
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 434

Arg	Ala	Ser	Gln	Ser	Val	Asn	Ser	Arg	Tyr	Leu	Ala
1				5					10		

<210> 435
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 435

Arg Ala Ser Gln Ser Val Ser Ala Ser Leu Ala
1 5 10

<210> 436

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 436

Arg Ala Ser Gln Ser Val Ser Ser Ser Asn Leu Ala
1 5 10

<210> 437

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 437

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 438

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 438

Arg Ala Ser Gln Tyr Ile Gly Ser Tyr Leu Asn
1 5 10

<210> 439

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 439

Arg Ser Ser Gln Ser Ile Arg Thr Tyr Leu Asn
1 5 10

<210> 440

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 440

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
1 5 10 15

<210> 441

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hRNF43/ZNRF3

<400> 441

Arg Val Ser Gln Gly Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 442

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against

hRNF43/ZNRF3

<400> 442

Ser Gly Asp Ser Leu Gly Ser Tyr Tyr Val His
1 5 10

<210> 443

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hRNF43/ZNRF3

<400> 443

Thr Ser Ser Gln Ser Val Leu His Ser Ser Asn Lys Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 444

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 444

Ala Ala Ser Ala Arg Ala Ala
1 5

<210> 445

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 445

Ala Ala Ser Ser Leu His Ser
1 5

<210> 446
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 446

Ala Ala Ser Ser Leu Gln Arg
1 5

<210> 447
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 447

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 448
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 448

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 449
<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 449

Ala Ala Ser Thr Val Glu Ser
1 5

<210> 450

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 450

Ala Thr Ser Thr Arg Ala Thr
1 5

<210> 451

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 451

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 452

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 452

Asp Ala Ser Ser Leu Glu Thr
1 5

<210> 453

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 453

Asp Ala Ser Ser Leu Pro Ser
1 5

<210> 454

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 454

Asp Ala Ser Ser Leu Gln Arg
1 5

<210> 455

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against
hRNF43/ZNRF3

<400> 455

Gly Ala Ser Ser Leu Gln Ser
1 5

<210> 456

<211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 456

Gly Ala Ser Ser Arg Ala Thr
 1 5

<210> 457
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 457

Gly Ala Ser Thr Arg Ala Thr
 1 5

<210> 458
 <211> 7
 <212> PRT
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<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 458

Lys Ala Ser Ser Leu Glu Ser
 1 5

<210> 459
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 459

Leu Ala Ser Asn Leu Glu Ser
1 5

<210> 460

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 460

Leu Ala Ser Asn Arg His Thr
1 5

<210> 461

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 461

Leu Gly Ser Asn Arg Ala Ser
1 5

<210> 462

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hRNF43/ZNRF3

<400> 462

Leu Gly Ser Tyr Arg Ala Ser
1 5

<210> 463
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
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 hRNF43/ZNRF3

 <400> 463

Arg Asn Lys Gln Arg Pro Ser
 1 5

<210> 464
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRL2 sequence of binders against
 hRNF43/ZNRF3

 <400> 464

Trp Ala Ser Thr Arg Ala Ser
 1 5

<210> 465
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRL2 sequence of binders against
 hRNF43/ZNRF3

 <400> 465

Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 466
 <211> 11
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Made in Lab - synthesized CDRL3 sequence of binders against

hRNF43/ZNRF3

<400> 466

Cys	His	Gln	Tyr	Phe	Ser	Pro	Pro	Met	Thr	Phe
1				5					10	

<210> 467

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hRNF43/ZNRF3

<400> 467

Cys	Leu	Gln	Asp	Tyr	Asp	Tyr	Pro	Leu	Thr	Phe
1				5					10	

<210> 468

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hRNF43/ZNRF3

<400> 468

Cys	Met	Gln	Ala	Leu	Gln	Thr	Pro	Leu	Thr	Phe
1				5					10	

<210> 469

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hRNF43/ZNRF3

<400> 469

Cys	Met	Gln	Gly	Thr	His	Trp	Pro	Arg	Thr	Phe
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 hRNF43/ZNRF3

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1				5					10	

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Cys	Gln	Gln	Gly	Tyr	Ser	Thr	Pro	Tyr	Thr	Phe
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1				5					10	

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<400> 479

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Cys Gln Gln Ser Tyr Ser Arg Pro Phe Thr Phe
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<400> 491

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Cys Gln Gln Thr Tyr Ser Thr Pro Phe Thr Phe
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<400> 493

Cys Gln Gln Tyr Gly Ser Ser Pro Ile Thr Phe
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<400> 494

Cys	Gln	Gln	Tyr	Gly	Ser	Ser	Pro	Arg	Thr	Phe
1				5					10	

<210> 495

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<400> 495

Cys	Gln	Gln	Tyr	Gly	Ser	Ser	Arg	Leu	Thr	Phe
1				5					10	

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<400> 496

Cys	Gln	Gln	Tyr	His	Ser	Thr	Pro	Tyr	Thr	Phe
1				5					10	

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<400> 498

Cys Gln Gln Tyr Tyr Ser Asp Pro Ile Thr Phe
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<400> 499

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<212> PRT

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Leu Gln His Trp Asn Tyr Pro Tyr Thr
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<210> 502

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<400> 502

Gln Gln Asn Asn Glu Asp Pro Leu Thr
1 5

<210> 503

<211> 11

<212> PRT

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<400> 503

Gln Thr Tyr Asp Trp Met Tyr Ser Ser Arg Val
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<210> 504

<211> 11

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<223> Made in Lab - synthesized CDRH1 sequence of binders against hASGR1/2

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Ala Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
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<213> Artificial Sequence

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<223> Made in Lab - synthesized CDRH1 sequence of binders against
hASGR1/2

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Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
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<210> 506

<211> 11

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against
hASGR1/2

<400> 506

Phe Ser Leu Ser Thr Ser Tyr Met Gly Val Ser
1 5 10

<210> 507

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hASGR1/2

<400> 507

Phe Thr Phe Ser Asp Tyr Gly Met His
1 5

<210> 508

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<400> 508

Phe Thr Phe Ser Ser Tyr Ala Met Ser
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<210> 509
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<400> 509

Phe Thr Phe Ser Ser Tyr Ala Met Ser
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<210> 510
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<400> 510

Phe Thr Phe Ser Ser Tyr Gly Met Ser
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<400> 511

Phe Thr Phe Ser Thr Tyr Thr Met Ser
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<210> 512

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<400> 512

Phe Thr Phe Thr Asp Tyr Tyr Met Asn
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<210> 513

<211> 9

<212> PRT

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hASGR1/2

<400> 513

Phe Thr Phe Thr Asp Tyr Tyr Met Ser
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<210> 514

<211> 9

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Gly Phe Ser Phe Asn Thr Tyr
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<210> 516
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 <212> PRT
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Gly Phe Thr Phe Ser Ser Tyr
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 <400> 517

Gly Thr Phe Ser Ser Tyr Ala Ile Ser
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hASGR1/2

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His Thr Phe Ser Ser Tyr Ala Met Gly
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<210> 519

<211> 9

<212> PRT

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<400> 519

Tyr Ser Phe Thr Asp Tyr Phe Met Asn
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<210> 520

<211> 9

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Tyr Ser Phe Thr Gly Asn Tyr Met His
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<400> 521

Tyr Ser Phe Thr Gly Tyr Phe Met Asn
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 hASGR1/2

<400> 522

Tyr Ser Ile Thr Ser Gly Tyr Tyr Trp Asn
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<400> 523

Tyr Thr Phe Leu Thr Tyr Trp Met Asn
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<400> 524

Tyr Thr Phe Ser Asp Tyr Tyr Val His
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<210> 525
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hASGR1/2

<400> 525

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<210> 526

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hASGR1/2

<400> 526

Tyr Thr Phe Ser Arg Phe Asp Met His
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hASGR1/2

<400> 527

Tyr Thr Phe Thr Asp Tyr Asn Met His
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<400> 528

Tyr Thr Phe Thr Asp Tyr Tyr Ile Asn
1 5

<210> 529
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<400> 529

Tyr Thr Phe Thr Asp Tyr Tyr Met Asn
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<400> 530

Tyr Thr Phe Thr Gly Tyr His Met His
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<210> 531
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<400> 531

Tyr Thr Phe Thr Gly Tyr Tyr Met His
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<210> 532
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<400> 532

Tyr Thr Phe Thr Asn Tyr Gly Ile Asn
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<210> 533

<211> 9

<212> PRT

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<220>

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<400> 533

Tyr Thr Phe Thr Ser Tyr Gly Ile Ser
1 5

<210> 534

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hASGR1/2

<400> 534

Tyr Thr Phe Thr Ser Tyr Trp Ile His
1 5

<210> 535

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH1 sequence of binders against hASGR1/2

<400> 535

Tyr Thr Phe Thr Thr Tyr Tyr Met His

1 5

<210> 536
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<212> PRT
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<220>
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hASGR1/2

<400> 536

Ala Ala Ile Ser Gln Ser Gly Tyr Val Arg Tyr Tyr Ala
1 5 10

<210> 537
<211> 12
<212> PRT
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<220>
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hASGR1/2

<400> 537

Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn
1 5 10

<210> 538
<211> 12
<212> PRT
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<220>
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hASGR1/2

<400> 538

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10

<210> 539
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<400> 539

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<400> 540

Ala	Ser	Ile	Ser	Ser	Gly	Gly	Ser	Tyr	Thr	Tyr	Tyr	Pro
1				5				10				

<210> 541

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<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hASGR1/2

<400> 541

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<400> 542

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Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala
1 5 10

<210> 543
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hASGR1/2

<400> 543

Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn
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<210> 544
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hASGR1/2

<400> 544

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala
1 5 10

<210> 545
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hASGR1/2

<400> 545

Gly Gly Ile Ile Pro Met Phe Gly Thr Val Lys Tyr Ala
1 5 10

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<223> Made in Lab - synthesized CDRH2 sequence of binders against hASGR1/2

<400> 546

Gly Gly Ile Ile Pro Val Phe Gly Ala Pro Asn Tyr Ala
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<210> 547

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<400> 547

Gly Ile Ile Asn Pro Arg Asn Gly Arg Thr Ser Tyr Ala
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<400> 548

Gly Ile Ile Asn Pro Ser Gly Gly Gly Thr Ser Tyr Ala
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<400> 549

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Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser
1 5 10

<210> 550
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<400> 550

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn
1 5 10

<210> 551
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<400> 551

Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
1 5 10

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<400> 552

Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Tyr Asp Tyr Ala
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Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn
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 hASGR1/2
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Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn
 1 5 10

<210> 555
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Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn
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<400> 556

Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn
1 5 10

<210> 557

<211> 12

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<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hASGR1/2

<400> 557

Gly Ser Ile Gly Tyr Asp Asp Thr Asn His Tyr Asn
1 5 10

<210> 558

<211> 13

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<400> 558

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<210> 559

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<212> PRT

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<223> Made in Lab - synthesized CDRH2 sequence of binders against hASGR1/2

<400> 559

Gly Trp Ile Asn Pro Lys Ser Gly Gly Thr Lys Tyr Ala
1 5 10

<210> 560

<211> 13
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 <213> Artificial Sequence

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 hASGR1/2

<400> 560

Gly Trp Ile Asn Pro Asn Gly Gly Gly Thr Asn Tyr Ala
 1 5 10

<210> 561
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<220>
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 hASGR1/2

<400> 561

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala
 1 5 10

<210> 562
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 hASGR1/2

<400> 562

Gly Trp Met Asn Pro Asn Thr Gly Asn Thr Ala Tyr Ala
 1 5 10

<210> 563
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 <212> PRT
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<220>
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 hASGR1/2

<400> 563

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn
1 5 10

<210> 564

<211> 8

<212> PRT

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<220>

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<400> 564

Arg Ser Lys Ser Asn Asn Tyr Ala
1 5

<210> 565

<211> 13

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRH2 sequence of binders against hASGR1/2

<400> 565

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10

<210> 566

<211> 6

<212> PRT

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<220>

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<400> 566

Ser Gly Ser Gly Gly Ser
1 5

<210> 567
 <211> 6
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 hASGR1/2

 <400> 567

Ser Ser Gly Gly Asp Tyr
 1 5

<210> 568
 <211> 13
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 <220>
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 hASGR1/2

 <400> 568

Ser Tyr Ile Ser Ser Tyr Asn Ser His Thr Asn Asp Ala
 1 5 10

<210> 569
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 <212> PRT
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 <220>
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 hASGR1/2

 <400> 569

Cys Ala Gly Asp Tyr Pro Phe Ala Phe Trp
 1 5 10

<210> 570
 <211> 14
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hASGR1/2

<400> 570

Cys Ala Lys Asp Arg Gly Tyr Arg Phe Asp Phe Asp Leu Trp
 1 5 10

<210> 571

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
 hASGR1/2

<400> 571

Cys Ala Lys Asp Arg Thr Ala Met Ala Pro Glu Gly Ala Phe Asp Ile
 1 5 10 15

Trp

<210> 572

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against
 hASGR1/2

<400> 572

Cys Ala Lys Asp Ser Pro Ile Val Arg Arg Gly Glu Arg Gly Arg Tyr
 1 5 10 15

Tyr Gly Met Asp Val Trp
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<210> 573

<211> 15

<212> PRT

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<400> 573

Cys	Ala	Lys	Ser	Ser	Phe	Ser	Tyr	Leu	Arg	Ala	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 574

<211> 15

<212> PRT

<213> Artificial Sequence

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<400> 574

Cys	Ala	Lys	Ser	Ser	Phe	Thr	Phe	Gly	Arg	Tyr	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 575

<211> 15

<212> PRT

<213> Artificial Sequence

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<400> 575

Cys	Ala	Lys	Ser	Trp	Tyr	Leu	Pro	Gly	Arg	Gly	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 576

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 576

Cys	Ala	Arg	Asp	Gly	Gly	Tyr	Gly	Met	Asp	Val	Trp
1				5					10		

<210> 577
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 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 577

Cys Ala Arg Asp His Leu Tyr Gly Met Asp Val Trp
 1 5 10

<210> 578
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 <212> PRT
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<220>
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 hASGR1/2

<400> 578

Cys Ala Arg Asp Lys Asn Tyr Tyr Gly Met Asp Val Trp
 1 5 10

<210> 579
 <211> 17
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<220>
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 hASGR1/2

<400> 579

Cys Ala Arg Asp Arg Gly Ile Thr Met Val Arg Gly Val Met Asp Tyr
 1 5 10 15

Trp

<210> 580

<211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 580

Cys	Ala	Arg	Asp	Thr	Gly	Ala	Thr	Ala	Glu	Tyr	Phe	Gln	His	Trp
1				5					10					15

<210> 581
 <211> 16
 <212> PRT
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<220>
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 hASGR1/2

<400> 581

Cys	Ala	Arg	Glu	Ser	Tyr	Tyr	Ser	Phe	Asp	Tyr	Thr	Met	Asp	Tyr	Trp
1				5					10					15	

<210> 582
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hASGR1/2

<400> 582

Cys	Ala	Arg	Gly	Met	Asp	Tyr	Trp
1				5			

<210> 583
 <211> 16
 <212> PRT
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<220>
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 hASGR1/2

<400> 583

Cys	Ala	Arg	His	Val	Asp	Tyr	Tyr	Asp	Gly	Ile	Ser	Phe	Asp	Tyr	Trp
1				5					10					15	

<210> 584

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

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<400> 584

Cys	Ala	Arg	Lys	Gly	Arg	Asp	Tyr	Gly	Thr	Ser	His	Tyr	Phe	Asp	Tyr
1				5					10					15	

Trp

<210> 585

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 585

Cys	Ala	Arg	Arg	Gly	Arg	Tyr	Asp	Val	Tyr	Tyr	Ala	Leu	Asp	Tyr	Trp
1				5					10					15	

<210> 586

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 586

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Cys Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp
1 5 10 15

<210> 587
<211> 15
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<220>
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<400> 587

Cys Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp
1 5 10 15

<210> 588
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 588

Cys Ala Arg Trp Ala Val Ala Ala Gly Gly Gln Tyr Tyr Tyr Met Asp
1 5 10 15

Val Trp

<210> 589
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 589

Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp
1 5 10

<210> 590
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hASGR1/2

<400> 590

Cys Ala Ser Ala Gly Gly Gly Tyr Trp
 1 5

<210> 591
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH3 sequence of binders against
 hASGR1/2

<400> 591

Cys Ala Ser Phe Gly Val Gly Ala Pro Asp Tyr Trp
 1 5 10

<210> 592
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 592

Cys Ala Ser Arg Asn Phe Asp Val Trp
 1 5

<210> 593
 <211> 10
 <212> PRT
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<220>

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<400> 593

Cys Ala Ser Ser Tyr Tyr Gly Asn Pro Trp
1 5 10

<210> 594

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

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<400> 594

Cys Ala Ser Trp Thr Arg Gly Ala Phe Asp Ile Trp
1 5 10

<210> 595

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 595

Cys Ala Thr Gln Leu Gly Arg Trp
1 5

<210> 596

<211> 12

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 596

Cys Ala Val Ser Asp Gly Tyr Asp Leu Asp Tyr Trp
1 5 10

<210> 597
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 597

Cys Ala Val Thr Tyr Gly Ala Tyr Trp
 1 5

<210> 598
 <211> 11
 <212> PRT
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<220>
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 hASGR1/2

<400> 598

Cys Gly Gly Pro Tyr Tyr Pro Phe Thr Tyr Trp
 1 5 10

<210> 599
 <211> 14
 <212> PRT
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<220>
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 hASGR1/2

<400> 599

Cys Asn Ala Arg Trp Gly Ala Gly Ser Leu Phe Ala Ser Trp
 1 5 10

<210> 600
 <211> 19
 <212> PRT
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<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 600

Cys	Ser	Arg	Lys	Gly	Gly	Phe	Gly	Asp	Tyr	Glu	Lys	Ser	Tyr	Ala	Met
1				5				10						15	

Asp Tyr Trp

<210> 601

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 601

Cys	Thr	Arg	Trp	Phe	Tyr	Phe	Asp	Tyr	Trp
1				5				10	

<210> 602

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 602

Cys	Val	Arg	His	Glu	Glu	Tyr	Gly	Lys	Ser	Gly	Phe	Ala	Tyr	Trp
1				5				10					15	

<210> 603

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 603

Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr
1 5 10

<210> 604

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 604

Glu Gly Thr Gly Gly Met Asp Tyr
1 5

<210> 605

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRH3 sequence of binders against hASGR1/2

<400> 605

Pro Arg Tyr Asp Tyr Trp Tyr Phe Asp Val
1 5 10

<210> 606

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 606

Lys Ala Ser Gln Asp Ile Asn Ser His Leu Ser
1 5 10

<210> 607
 <211> 11
 <212> PRT
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<220>
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 hASGR1/2

<400> 607

Lys Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser
 1 5 10

<210> 608
 <211> 11
 <212> PRT
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<220>
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 hASGR1/2

<400> 608

Lys Ala Ser Gln Asn Val Gly Ser Asn Val Ala
 1 5 10

<210> 609
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 609

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
 1 5 10

<210> 610
 <211> 17
 <212> PRT
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<220>
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hASGR1/2

<400> 610

Lys	Ser	Ser	Gln	Ser	Leu	Phe	Asn	Ser	Arg	Thr	Arg	Lys	Asn	Tyr	Leu
1				5					10					15	

Ala

<210> 611

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 611

Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asp	Ser	Asp	Gly	Lys	Thr	Tyr	Leu	Asn
1				5					10					15	

<210> 612

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 612

Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asp	Ser	Asp	Gly	Lys	Thr	Tyr	Leu	Asn
1				5					10					15	

<210> 613

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 613

Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
1 5 10

<210> 614
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 614

Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1 5 10

<210> 615
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 615

Arg Ala Ser Glu Asn Ile Tyr Ser Tyr Leu Val
1 5 10

<210> 616
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 616

Arg Ala Ser Gln Gly Ile Ala Thr Trp Leu Ala
1 5 10

<210> 617
<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 617

Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp	Leu	Ala
1				5					10	

<210> 618

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 618

Arg	Ala	Ser	Gln	Asn	Ile	Tyr	Thr	Tyr	Leu	Asn
1				5					10	

<210> 619

<211> 11

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 619

Arg	Ala	Ser	Gln	Ser	Ile	Asn	Asn	Tyr	Leu	Asn
1				5					10	

<210> 620

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 620

Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala
1 5 10

<210> 621

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hASGR1/2

<400> 621

Arg Ala Ser Gln Ser Ile Ser Asn Tyr Leu His
1 5 10

<210> 622

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hASGR1/2

<400> 622

Arg Ala Ser Gln Ser Ile Ser Arg Tyr Leu Asn
1 5 10

<210> 623

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
hASGR1/2

<400> 623

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> 624

<211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
 hASGR1/2

<400> 624

Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	Leu	Asn
1				5					10	

<210> 625
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
 hASGR1/2

<400> 625

Arg	Ala	Ser	Gln	Ser	Val	Gly	Ser	Tyr	Leu	Ala
1				5					10	

<210> 626
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
 hASGR1/2

<400> 626

Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Tyr	Leu	Ala
1				5					10	

<210> 627
 <211> 11
 <212> PRT
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<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against
 hASGR1/2

<400> 627

Arg	Ile	Ser	Glu	Asn	Ile	Tyr	Ser	Asn	Leu	Ala
1				5					10	

<210> 628

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 628

Arg	Ser	Ser	Gln	Gly	Ile	Val	His	Ser	Asn	Gly	Asn	Ile	Tyr	Leu	Glu
1				5					10					15	

<210> 629

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 629

Arg	Ser	Ser	Gln	Ser	Leu	Ala	Asn	Ser	Tyr	Gly	Asn	Thr	Tyr	Leu	Ser
1				5					10					15	

<210> 630

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL1 sequence of binders against hASGR1/2

<400> 630

Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser	Asp	Gly	His	Asn	Tyr	Leu	Gln
1				5					10					15	

<210> 631
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<220>
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 hASGR1/2

<400> 631

Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser	Asn	Gly	Tyr	Asn	Tyr	Leu	Asp
1				5					10					15	

<210> 632
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 <212> PRT
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<220>
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 hASGR1/2

<400> 632

Arg	Thr	Ser	Glu	Asn	Ile	Tyr	Ser	Asn	Leu	Ala
1				5					10	

<210> 633
 <211> 11
 <212> PRT
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<220>
 <223> Made in Lab - synthesized CDRL1 sequence of binders against
 hASGR1/2

<400> 633

Arg	Thr	Ser	Glu	Asn	Ile	Tyr	Ser	Tyr	Leu	Ala
1				5					10	

<210> 634
 <211> 12
 <212> PRT
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<220>
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hASGR1/2

<400> 634

Ser Ala Ser Ser Ser Val Ser Ser Ser Phe Leu His
1 5 10

<210> 635

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 635

Ala Ala Ile Asn Leu Ala Asp
1 5

<210> 636

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 636

Ala Ala Ser Asn Leu Gln Ser
1 5

<210> 637

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 637

Ala Ala Ser Arg Leu Gln Ser
1 5

<210> 638
 <211> 7
 <212> PRT
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 <220>
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 hASGR1/2

<400> 638

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> 639
 <211> 7
 <212> PRT
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 <220>
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 hASGR1/2

<400> 639

Ala Ala Thr Asn Leu Ala Asp
 1 5

<210> 640
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
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 hASGR1/2

<400> 640

Ala Ala Thr Thr Leu Gln Ser
 1 5

<210> 641
 <211> 7
 <212> PRT
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<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 641

Asp Ala Ser Asn Leu Gln Ser
1 5

<210> 642

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 642

Asp Ala Ser Asn Leu Arg Ser
1 5

<210> 643

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 643

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 644

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 644

Asp Ala Thr Asn Arg Ala Thr
1 5

<210> 645
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
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 hASGR1/2

<400> 645

Phe Ala Ser Gln Ser Ile Ser
 1 5

<210> 646
 <211> 7
 <212> PRT
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 <223> Made in Lab - synthesized CDRL2 sequence of binders against
 hASGR1/2

<400> 646

Gly Ala Thr Asn Leu Ala Asp
 1 5

<210> 647
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRL2 sequence of binders against
 hASGR1/2

<400> 647

Gly Ile Ser Asn Arg Phe Ser
 1 5

<210> 648
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 648

Gly Lys Asn Asn Arg Pro Ser
1 5

<210> 649

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 649

Gly Arg Asn Asn Arg Pro Ser
1 5

<210> 650

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 650

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 651

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 651

Leu Gly Ser Tyr Arg Ala Ser

1 5

<210> 652
<211> 7
<212> PRT
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<220>
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hASGR1/2

<400> 652

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 653
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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hASGR1/2

<400> 653

Asn Ala Lys Thr Leu Ala Glu
1 5

<210> 654
<211> 7
<212> PRT
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<220>
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hASGR1/2

<400> 654

Asn Ala Lys Thr Leu Ala Lys
1 5

<210> 655
<211> 7
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<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 655

Gln Ala Ser Asn Lys Asp Thr
1 5

<210> 656

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 656

Arg Ala Asn Arg Leu Ala Asp
1 5

<210> 657

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 657

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 658

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in Lab - synthesized CDRL2 sequence of binders against hASGR1/2

<400> 658

Arg Thr Ser Asn Leu Ala Ser
1 5

<210> 659
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hASGR1/2

<400> 659

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 660
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hASGR1/2

<400> 660

Ser Ser Ser Tyr Arg Tyr Ser
1 5

<210> 661
<211> 7
<212> PRT
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<220>
<223> Made in Lab - synthesized CDRL2 sequence of binders against
hASGR1/2

<400> 661

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 662
<211> 11
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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 662

Cys	Phe	Gln	Gly	Ser	His	Val	Pro	Pro	Thr	Phe
1				5					10	

<210> 663

<211> 10

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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 663

Cys	Lys	Gln	Ser	Tyr	Tyr	Leu	Leu	Thr	Phe
1				5					10

<210> 664

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 664

Cys	Leu	Gln	Ala	Thr	His	Gln	Pro	Trp	Thr	Phe
1				5					10	

<210> 665

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 665

Cys Leu Gln Gly Thr His Gln Pro Leu Thr Phe
1 5 10

<210> 666
<211> 10
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<220>
<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 666

Cys Leu Gln Tyr Asp Asp Leu Trp Thr Phe
1 5 10

<210> 667
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 667

Cys Leu Gln Tyr Asp Glu Phe Pro Phe Thr Phe
1 5 10

<210> 668
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 668

Cys Leu Gln Tyr Asp Glu Phe Pro Leu Thr Phe
1 5 10

<210> 669
<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 669

Cys	Met	Gln	Ala	Leu	Gln	Thr	Pro	Leu	Thr	Phe
1				5					10	

<210> 670

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 670

Cys	Met	Gln	Ala	Thr	His	Trp	Pro	Pro	Thr	Phe
1				5					10	

<210> 671

<211> 12

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 671

Cys	Asn	Ser	Arg	Asp	Arg	Arg	Gly	Tyr	Ser	Val	Phe
1				5						10	

<210> 672

<211> 13

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 672

Cys Asn Ser Arg Lys Ser Ser Ser Lys Asn Val Val Phe
1 5 10

<210> 673

<211> 13

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 673

Cys Asn Ser Arg Leu Arg Ser Gly Lys Met Val Val Phe
1 5 10

<210> 674

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 674

Cys Gln His Phe Trp Gly Ser Thr Trp Thr Phe
1 5 10

<210> 675

<211> 11

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<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 675

Cys Gln His Phe Trp Gly Thr Pro Phe Thr Phe
1 5 10

<210> 676

<211> 11
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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 676

Cys Gln His Phe Trp Gly Thr Thr Trp Thr Phe
1 5 10

<210> 677
<211> 11
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<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 677

Cys Gln His His Tyr Gly Thr Pro Tyr Thr Phe
1 5 10

<210> 678
<211> 10
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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 678

Cys Gln His His Tyr Gly Thr Trp Thr Phe
1 5 10

<210> 679
<211> 7
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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against
hASGR1/2

<400> 679

Cys Gln His Arg Arg Thr Phe
1 5

<210> 680

<211> 11

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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 680

Cys Gln Gln Ala Asn Ser Phe Pro Leu Thr Phe
1 5 10

<210> 681

<211> 11

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<400> 681

Cys Gln Gln Ala Asn Ser Phe Pro Val Thr Phe
1 5 10

<210> 682

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 682

Cys Gln Gln Ala Tyr Asp Phe Pro Leu Thr Phe
1 5 10

<210> 683
 <211> 11
 <212> PRT
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<220>
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 hASGR1/2

<400> 683

Cys Gln Gln Gly Tyr Ser Thr Pro Leu Thr Phe
 1 5 10

<210> 684
 <211> 11
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<220>
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 hASGR1/2

<400> 684

Cys Gln Gln Gly Tyr Thr Ile Pro Ile Thr Phe
 1 5 10

<210> 685
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRL3 sequence of binders against
 hASGR1/2

<400> 685

Cys Gln Gln Arg Ser Asn Trp Pro Leu Thr Phe
 1 5 10

<210> 686
 <211> 11
 <212> PRT
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<220>
 <223> Made in Lab - synthesized CDRL3 sequence of binders against

hASGR1/2

<400> 686

Cys	Gln	Gln	Arg	Ser	Asn	Trp	Pro	Val	Thr	Phe
1				5					10	

<210> 687

<211> 11

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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 687

Cys	Gln	Gln	Ser	Asn	Ser	Trp	Pro	Leu	Thr	Phe
1				5					10	

<210> 688

<211> 11

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 688

Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Leu	Thr	Phe
1				5					10	

<210> 689

<211> 11

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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 689

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 <211> 11
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 hASGR1/2

<400> 690

Cys Gln Gln Tyr Asn Ser Phe Pro Leu Thr Phe
 1 5 10

<210> 691
 <211> 11
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 hASGR1/2

<400> 691

Cys Gln Gln Tyr Asn Ser Tyr Pro Leu Thr Phe
 1 5 10

<210> 692
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 hASGR1/2

<400> 692

Cys Gln Gln Tyr Tyr Asn Tyr Pro Ile Thr Phe
 1 5 10

<210> 693
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<400> 693

Cys Trp Gln Gly Thr His Phe Pro His Thr Phe
1 5 10

<210> 694

<211> 12

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 694

Asn Ser Leu Glu Arg Ile Gly Tyr Leu Ser Tyr Val
1 5 10

<210> 695

<211> 9

<212> PRT

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<220>

<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 695

Gln Gln Trp Ser Gly Tyr Pro Tyr Thr
1 5

<210> 696

<211> 9

<212> PRT

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<223> Made in Lab - synthesized CDRL3 sequence of binders against hASGR1/2

<400> 696

Trp Gln Gly Thr His Phe Pro Tyr Thr
1 5

<210> 697
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in Lab - synthesized CDRH2 sequence of binders against
 hRNF43/ZNRF3

<400> 697

Ser Tyr Ile Ser Arg Ser Ser Ser Thr Ile Tyr Tyr Ala
 1 5 10

<210> 698
 <211> 4
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<400> 698

Gly Gly Gly Gly
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<210> 699
 <211> 5
 <212> PRT
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<400> 699

Gly Gly Gly Gly Gly
 1 5

<210> 700
 <211> 7
 <212> PRT
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<220>
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<400> 700

Gly Gly Gly Gly Gly Gly Gly
1 5

<210> 701

<211> 5

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<400> 701

Gly Gly Gly Gly Ser
1 5

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Gly Gly Gly Gly Gly Lys
1 5

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<211> 7

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Gly Gly Gly Gly Gly Lys Arg
1 5

<210> 704

<211> 8

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Gly Gly Gly Lys Gly Gly Gly Gly
1 5

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<223> Made in Lab - CDRH1

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Gly Phe Thr Phe Ser His Tyr Thr Leu
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<210> 706

<211> 17

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<220>

<223> Made in Lab - CDRH2

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Val Ile Ser Gly Asp Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 707

<211> 9

<212> PRT

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<223> MAde in Lab - CDRH3

<400> 707

Asn Phe Ile Lys Tyr Val Phe Ala Asn
1 5

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<211> 11
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<220>
<223> Made in Lab - CDRL1

<400> 708

Ser Gly Asp Lys Leu Gly Lys Lys Tyr Ala Ser
1 5 10

<210> 709
<211> 11
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<400> 709

Ser Gly Asp Asn Ile Gly Ser Phe Tyr Val His
1 5 10

<210> 710
<211> 8
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<400> 710

Glu Lys Asp Asn Arg Pro Ser Gly
1 5

<210> 711
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<223> MAdE in Lab - CDRL2

<400> 711

Asp Lys Ser Asn Arg Pro Ser Gly
1 5

<210> 712

<211> 8

<212> PRT

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<223> MAdE in Lab - CDRL3

<400> 712

Ser Ser Phe Ala Gly Asn Ser Leu
1 5

<210> 713

<211> 8

<212> PRT

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<220>

<223> MAdE in Lab - CDRL3

<400> 713

Gln Ser Tyr Ala Asn Thr Leu Ser
1 5

<210> 714

<211> 90

<212> PRT

<213> Homo sapiens

<400> 714

Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
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Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
20 25 30

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Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
35 40 45

Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
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Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
65 70 75 80

Ser Ser Arg Leu His Thr Cys Gln Arg His
85 90

<210> 715
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<400> 715

Lys Met Ser His Ile Lys Gly His Glu Gly Asp Pro Cys Leu Arg Ser
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Ser Asp Cys Ile Glu Gly Phe Cys Cys Ala Arg His Phe Trp Thr Lys
20 25 30

Ile Cys Lys Pro Val Leu His Gln Gly Glu Val Cys Thr Lys Gln Arg
35 40 45

Lys Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Asp Cys Ala
50 55 60

Lys Gly Leu Ser Cys Lys Val Trp Lys Asp Ala Thr Tyr Ser Ser Lys
65 70 75 80

Ala Arg Leu His Val Cys Gln Lys
85