



(51) International Patent Classification:

C07K 16/28 (2006.01) A61K 39/00 (2006.01)

C07K 16/30 (2006.01)

(21) International Application Number:

PCT/US2018/066616

(22) International Filing Date:

19 December 2018 (19.12.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/607,875 19 December 2017 (19.12.2017) US

62/641,217 09 March 2018 (09.03.2018) US

62/680,522 04 June 2018 (04.06.2018) US

(71) Applicant: **SURROZEN, INC.**, [US/US]; 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US).

(72) Inventors: **LI, Yang**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **YUAN, Tom Zhiye**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **SATO, Aaron Ken**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, Califor-

nia 94080 (US). **YEH, Wen-Chen**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **JANDA, Claudia Yvonne**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **FOWLER, Tristan William**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **BARIBAUT, Helene**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **LAI, Kuo-Pao**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **XIE, Liqin**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **BREZSKI, Randall J.**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US). **LU, Cheng-gang**; c/o Surrozen, Inc., 171 Oyster Point Blvd., Suite 400, South San Francisco, California 94080 (US).

(74) Agent: **LAHERTY, Carol D.** et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, District of Columbia 20004-2400 (US).

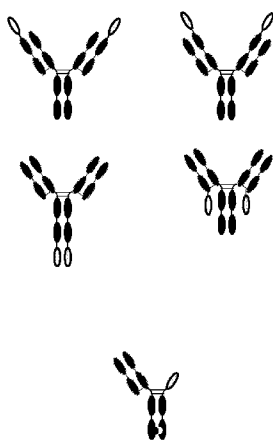
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

(54) Title: WNT SURROGATE MOLECULES AND USES THEREOF

FIG. 1

A.

Formats for Fab+Nab (or scFv)



□ Denote Nab or scFv

(57) Abstract: The present invention provides Wnt pathway agonists and related compositions, which may be used in any of a variety of therapeutic methods for the treatment of diseases.



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

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

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

WNT SURROGATE MOLECULES AND USES THEREOF

Cross Reference to Related Applications

This application claims priority to U.S. Provisional Application No. 62/607,875, filed December 19, 2017, US Provisional Application No. 62/641,217, filed March 9, 2018, and U.S. Provisional Application No. 62/680,522, filed June 4, 2018, each of which is incorporated by reference herein in its entirety.

Statement Regarding Sequence Listing

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_006_03WO_ST25.txt. The text file is 1.2 MB, was created on December 19, 2018, and is being submitted electronically via EFS-Web.

BACKGROUND

Technical Field

The present invention relates generally to Wnt signaling pathway agonist molecules, compositions, and methods of using the same. Such molecules are useful, for example, in modulating Wnt signaling pathways.

Description of the Related Art

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, 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.

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. Accordingly, there is clearly a need in the art for binding moieties that specifically bind to one or more Fzd, LRP5, or LRP6 to modulate Wnt signaling pathways. The present invention addresses this need.

BRIEF SUMMARY

In various embodiments, the present invention provides WNT surrogate molecules and related uses thereof.

In one embodiment, the disclosure provides a soluble, bivalent, bispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises: (i) one or more regions that specifically binds to one or more Frizzled (Fzd) receptor (a Fzd binding region); and (ii) one or more regions that specifically binds to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) (a LRP5/6 binding region).

In particular embodiments, the Wnt surrogate molecule comprises two or more Fzd binding regions and two or more LRP5/6 binding regions. In particular embodiments, one or more Fzd binding regions comprise one or more antigen-binding fragments of an antibody. In particular embodiments, one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and VHH or sdAb

In particular embodiments, any of the Fzd antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Tables 1A or 1B; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Tables 1A or 1B, or a variant of said Fzd binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid

substitutions in said CDR sequences. In particular embodiments, any of the Fzd binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:1-65 or 129-132, or an antigen-binding fragment thereof.

In particular embodiments, any of the Fzd binding regions bind to one or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10). In particular embodiments, any of the Fzd binding region binds to two or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10). In particular embodiments, any of the Fzd binding region binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii) Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8.

In particular embodiments, any of the surrogate molecules comprise one or more LRP5/6 binding regions comprise one or more antigen-binding fragments of an antibody. In particular embodiments, the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and VHH or sdAb. In particular embodiments, any of the one or more LRP5/6 binding regions or antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2, or a variant of said LRP5/6 binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, any of the one or more LRP5/6 binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:66-88 or 133, or an antigen-binding fragment thereof.

In particular embodiments of any of the Wnt surrogate molecules, the Fzd binding region comprising a Fab, and the LRP5/6 binding region

comprising a VHH or sdAb. In particular embodiments, the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In particular embodiments, the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain. In particular embodiments, the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the light chain. In certain embodiments, the LRP5/6 binding region is fused to the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig. In certain embodiments, the LRP5/6 binding region is fused to the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig. In certain embodiments, the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig. In certain embodiments, the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable light chain region of the full IgG. In particular embodiments, any of the LRP5/6 binding region is fused to the heavy chain or the light chain via one or more linker moiety.

In certain embodiments of any of the Wnt surrogate molecules, the Fzd binding region comprises a VHH or sdAb and the LRP5/6 binding region comprises a Fab. In particular embodiments, the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In certain embodiments, the Fzd binding region is fused to the N-terminus or the C-terminus of the heavy chain. In certain embodiments, the Fzd binding region is fused to the N-terminus or the C-terminus of the light chain. In some embodiment, the Fzd binding region is fused to the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig. In some embodiments, the Fzd binding region is fused to the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig. In some embodiments, the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig. In some embodiments, the variable light chain region of the Fzd binding Fab is fused to

the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fab is fused to the N-terminus of the variable light chain region of the full IgG. In certain embodiments, any of the the Fzd binding region is fused to the heavy chain or the light chain via one or more linker moiety.

In another embodiment, any of the Fzd binding region comprises a Fab or Fv, and the LRP5/6 binding region comprises a Fab or Fv. In particular embodiments, the Fab of the Fzd binding region or the Fab or Fv of the LRP5/6 binding region is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In particular embodiments, only one of the Fab of the Fzd binding region or the Fab of the LRPp5/6 binding region is present within the full immunoglobulin (Ig). In particular embodiments, the Fab or Fv of the Fzd binding region is present within the full Ig. In particular embodiments, the Fab or Fv of the LRP5/6 binding region is fused to the N-terminus of the Ig. In particular embodiments, the Fab of the LRP5/6 binding region is fused to the C-terminus of the Ig. In a further embodiment, the Fab of the LRP5/6 binding region is present within the full Ig. In particular embodiments, the Fab of the Fzd binding region is fused to the N-terminus of the Ig. In particular embodiments, the Fab of the Fzd binding region is fused to the C-terminus of the Ig. In some embodiments, the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fab is fused to the N-terminus of the variable light chain region of the full IgG. In some embodiments, the variable light chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable light chain region of the full IgG. In some embodiments, the variable heavy chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable light chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable light chain region of the full IgG. In some embodiments, variable light chain region of the Fzd binding Fv is fused to the N-terminus of the variable heavy chain

region of the full Ig, and the variable heavy chain region of the Fzd binding Fv is fused to the N-terminus of the variable light chain region of the full IgG. In some embodiments, the variable heavy chain region of the Fzd binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable light chain region of the Fzd binding Fv is fused to the N-terminus of the variable light chain region of the full IgG.

In another embodiment, any of the Fzd binding regions comprises a VHH or sdAb, and the LRP5/6 binding region comprises a VHH or sdAb. In particular embodiments, the Fzd binding region is fused to the Lrp5/6 binding region, and wherein the Fzd binding region or the LRP5/6 binding region is fused to an Fc region. In particular embodiments, the Fzd binding region is fused to the N-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the C-terminus of an Fc region. In particular embodiments, the Fzd binding region is fused to the C-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the N-terminus of an Fc region.

In a further embodiment, any of the antibodies or one or more antigen-binding fragment thereof, is humanized. In a further embodiment, any of the Wnt surrogate molecules binds to one or more Fzd receptor with a K_D of 50 μ M or lower. In further embodiments, any of the Wnt surrogate molecules binds to LRP5 and/or LRP6 with a K_D of 50 μ M or lower.

In a further embodiment, any of the Wnt surrogate molecule modulates a Wnt signaling pathway in a cell, optionally a mammalian cell. In particular embodiments, the Wnt surrogate molecule increases signaling via the Wnt signaling pathway in the cell. In particular embodiments, the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway.

In a related embodiment, the present disclosure provides an isolated polynucleotide encoding a polypeptide sequence comprising one or more of the Fzd binding regions and/or one or more of the LRP5/6 binding regions of a Wnt surrogate molecule. In particular embodiments, the present disclosure provides an expression vector comprising the isolated

polynucleotide. In further particular embodiments, the present disclosure provides an isolated host cell comprising the expression vector.

In a related embodiment, the present disclosure provides a pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of any of the Wnt surrogate molecules disclosed herein.

In related embodiments, the present disclosure provides a method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell any of the Wnt surrogate molecules, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

In particular embodiments, the present disclosure provides 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 the pharmaceutical composition, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway. In particular embodiments, the disease or disorder is selected from the group consisting of: bone fractures, osteoporosis (e.g., post-menopausal osteoporosis), osteoporotic fractures, spinal fusion, vertebral compression fracture, pre-operative spinal surgery optimization, osseointegration of orthopedic devices, tendon-bone integration, tooth growth and regeneration, dental implantation, periodontal diseases, maxillofacial reconstruction, osteonecrosis of the jaw, osteoarthritis (OA), muscular dystrophy, muscle atrophy resulting from sarcopenia or cachexia, alopecia, hearing loss, including regeneration of inner and outer auditory hair cells, vestibular hypofunction, macular degeneration, vitreoretinopathy, diseases of retinal degeneration, including diabetic retinopathy, diseases/disorders affecting the integrity of the blood brain barrier, Fuchs' dystrophy, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, spinal cord injuries, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), in particular IBD with fistula formation, metabolic syndrome, diabetes, dyslipidemia, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, coronary artery disease,

acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), pulmonary fibrosis, including idiopathic pulmonary fibrosis, acute liver failure, acute alcoholic liver injuries, chronic liver diseases with hepatitis C virus (HCV), HCV subjects post-antiviral drug therapies, chronic liver diseases with hepatitis B virus (HBV), fibrosis, HBV subjects post-antiviral drug therapies, chronic alcoholic liver diseases, alcoholic hepatitis, non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis (NASH), cirrhosis, and chronic liver insufficiencies of all causes. In certain embodiments, the disease or disorder is a bone disease or disorder. In particular embodiments, the disease or disorder is a bone disease or disorder, and the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6. In certain embodiments, the disease or disorder is a bone disease or disorder, and the Wnt surrogate molecule binds Fzd1, Fzd2, FZD7, Fzd5 and Fzd8, and also binds LRP5 and/or LRP6.

In another related embodiment, the present disclosure provides a method for increasing bone mineral density, increasing bone volume, increasing bone cortical thickness, increasing bone mineral apposition rate, increasing bone stiffness, increasing bone biomechanical strength, increasing resistance to bone fracture, decreasing bone resorption, or decreasing bone loss associated with osteoporosis, in a subject in need thereof, comprising providing to the subject an effective amount of a pharmaceutical composition comprising a Wnt surrogate molecule, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway. In certain embodiments, the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6. In certain embodiments, the Wnt surrogate molecule binds Fzd1, Fzd2, FZD7, Fzd5 and Fzd8, and also binds LRP5 and/or LRP6.

In particular embodiments, methods of the invention, including those related to treating or preventing a bone disease or disorder, such as osteoporosis (e.g., post-menopausal osteoporosis), further comprise providing the subject an antiresorptive agent (in combination with a Wnt surrogate molecule). Examples of anti-resorptive agents include, but are not limited to, bisphosphonates or selective estrogen receptor modulators. Antiresorptive

agents are used to increase bone strength in individuals with osteoporosis and include five principal classes of agents: bisphosphonates, estrogens, selective estrogen receptor modulators (SERMs), calcitonin and monoclonal antibodies such as denosumab, any of which may be used. Illustrative examples of antiresorptive agents include, but are not limited to: bisphosphonates, e.g., alendronate -generic medication (Brand name: Fosamax™, Fosamax™ Plus D), risedronate (Brand name: Actonel™, Actonel™ with Calcium), ibandronate (Brand name: Boniva™), and zoledronic acid (Brand name: Reclast™); other antiresorptives, e.g., estrogen therapy or hormone therapy, raloxifene (Brand name: Evista™), and denosumab (Prolial™); and anabolic medication, e.g., teriparatide (Forteo™).

In a further related embodiment, the present 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, in a subject in need thereof, comprising providing to the subject an effective amount of a pharmaceutical composition comprising a Wnt surrogate molecule, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-D. Schematic diagrams of illustrative formats of Wnt surrogate molecules.

FIGS. 2A-2D. Characterization of a Wnt surrogate molecule, R2M3-26.

FIGS. 3A-3D. Characterization of a Wnt surrogate molecule,, R2M3-32.

FIGS. 4A-4B. Graphs showing that R2M3-26 and R2M3-32 activities can be inhibited by soluble Fzd ECD and by R2M3 IgG alone without the Lrp binding arm.

FIG. 5. Characterization of illustrative R2M3-Lrp6 binder fusions in 293, Huh7, A375, and BNL.CL2 Wnt dependent reporter assays.

FIG. 6. Characterization of illustrative 18R5-Lrp6 binder fusions in 293, A375, and BNL.CL2 Wnt dependent reporter assays.

FIG. 7. Characterization of illustrative 18R5-Lrp5 binder fusions in 293 Wnt dependent reporter assays.

FIG. 8A-8B. Characterization of illustrative Fzd binders-Lrp6 binder 26 fusions in 293 Wnt dependent reporter assays.

FIG. 9. SAR analysis of illustrative Wnt surrogate molecules in the IgG-Nab fusion format.

FIG. 10A-10B. Characterization of R2M3-26 in the Fab format in 293 Wnt dependent reporter assays.

FIG. 11A-11B. Characterization of R2M3-32 in the Fab format in 293 Wnt dependent reporter assays.

FIG. 12A-12B. Characterization of R2M3-26 in the Hetero-Ig format in 293 Wnt dependent reporter assays.

FIG. 13. Characterization of 26-17SB9 in the VHH/sdAb-VHH/sdAb format, in different tandem formats, and on different ends of the Fc fragment in 293 Wnt dependent reporter assays.

FIG. 14A-14H. Characterization of 18R5-LRP6 Binder Fusions in tandem scFv formats in 293 Wnt dependent reporter assays.

FIG. 15A-15G. Characterization of various Wnt Surrogate molecules in the Fab-IgG format in 293 Wnt dependent reporter assays.

FIG. 16A-16C. Characterization of R2M3-26 in the F(ab')₂ format in 293 Wnt dependent reporter assays.

FIG. 17A-17H. Characterization of additional Wnt surrogate molecules in 293 Wnt dependent reporter assays

FIG. 18A-18C. A. Schematic diagram of the 2Fv-Ig format. B-C. Characterization of the Wnt surrogate molecule, 10SG11-1RC07.

FIG. 19. Sequences of polypeptide chains of illustrative Wnt surrogates molecules.

FIG. 20A-20B. In vivo PK/PD characterization of R2M3-26

FIGS. 21A-21E. Images and graphs showing that systemic expression of 18R5-DKK1c for 14 days results in increased bone mineral density. *P value <0.05; ** P value <0.0001. For each time point, the bars from left to right are as follows: vehicle (diamond), romosozumab (square), AAV CAG-GFP (triangle), AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His (inverted triangle), and AAV 18R5-DKK1c-FLagHis (circle).

FIGS. 22A-22D. Images and graphs showing that systemic expression of 18R5-DKK1c for 14 days or 28 days results in increased bone volume. For each time point, the bars from left to right are as follows: vehicle, romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FLagHis. *P value <0.05; ** P value <0.0001, **** P value <0.0001.

FIGS.23A-23B. Graphs showing the dynamic parameters of bone formation based on fluorochrome labelling. For each time point, the bars from left to right are as follows: vehicle, romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FlagHis.

FIGS. 24A-24D. Graphs and images showing that systemic expression of 18R5-DKK1c results in increased osteoblast and reduced osteoclast on bone surface. For each time point, the bars from left to right are as follows: vehicle, romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FlagHis. ** P value <0.05.

FIGS. 25A-25C. Diagram of assay for bone stiffness and fracture and graphs showing ultimate load to failure and stiffness in mice treated as indicated.

FIGS. 26A-26D. Graphs and images showing that systemic treatment with R2M3-26 results in rapid and sustained increase in bone after

one week. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom. **** indicates P value <0.0001.

FIGS. 27A-27C. Images and graphs showing that R2M3-26 treatment rapidly reverses the bone loss associated with ovariectomy-induced osteoporosis. For each time point, the bars from left to right correspond to the treatments indicated from top to bottom.

FIGS. 28A-28C. Images and graphs showing that a single injection of R2M3-26 rapidly increases bone volume.

FIGS. 29A-29D. Graphs showing that high doses of R2M3-26 and 1R-C07-26 significantly and rapidly increase bone formation in naïve mice. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom.

FIG. 30. Graphs showing that R2M3-26 and 1R-C07-3 increase bone mineral density in naïve mice. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom.

FIG. 31. Graph showing changes in whole body bone mineral density (BMD) measured weekly in ovariectomized mice as compared with naïve and sham surgery operated mice.

FIG 32. Changes in vertebral mineral density (image shown) and changes the vertebral resistance to compression fracture in vertebra isolated from mice after various treatments (bar graph) as measured in newton units of force (N) after 4 weeks of treatment.

FIGS. 33A-D. Test of Wnt surrogate molecules in an Einhorn fracture model. Radiographs of the callus after 1 week (A) and 6 weeks (B) of treatment with Wnt surrogate molecules are shown. Graphs of changes in whole body bone mineral density (BMD) in contralateral femur are shown (C). Scatter plots showing changes in callus tissue volume, callus bone volume, bone volume/tissue volume ratio (BV/TV), and bone mineral content per millimeter (BMC/mm) as shown in (D) along with representative images of bone slices are shown.

FIG. 34. Graph with changes in whole body bone mineral density (BMD) measured weekly with different Wnt surrogate molecule dosing schedules is shown.

FIG 35. Graph with changes in whole body bone mineral density (BMD) measured weekly from mice treated with different Wnt surrogate molecule alone and in combination with Romosozumab is shown.

FIG 36. Levels of therapeutic molecules in serum as measured by ELISA. These data accompany gene expression data presented in Table 4.

FIGS. 37A-37C. Liver (A), small intestine (B) and colon (C) to body weight ratio after treatment with AAV-delivered Wnt surrogates. (**) $p < 0.01$. For each graph, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 38A-38B. Body weight (A) and liver to body weight (B) ratio after treatment with recombinantly produced Wnt surrogate proteins. (*) $p < 0.05$. For each time point, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 39A-39D. Induction of proliferation markers in response to R2M3-26 and Rspo2 recombinant proteins. Liver Ki67 (A) and cyclinD1 (B) mRNA expression. Average count of PCNA (C) or phospho-histone H3 (D) positive nuclei per 10x field after immunohistochemistry staining with PCNA and phospho-histone H3 antibodies respectively. (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, (****) $p < 0.0001$. For each time point, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 40A-40H. Efficacy of AAV-delivered Wnt surrogate and R-Spondin in a thioacetamide-induced chronic liver disease model. Design for study 1 (A) and study 2 (B). Liver to body weight ratio (C-D), liver weight (E-F), liver collagen A1 mRNA expression (G) and percentage red area in liver histological sections stained with Sirius red (H) in response to AAV-delivered wnt surrogate and R-spondin in study 1 (C, E, G and H) and study 2 (D, F, H). (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, (****) $p < 0.0001$. For each graph, the

treatments shown from left to right correspond to those in the legend from top to bottom (not including baseline).

FIGS. 41A-41N. Efficacy of recombinantly produced Wnt surrogate and R-Spondin in a thioacetamide-induced chronic liver disease model. Study design (A). D-2, D0, D3, D7, D10, D14 represents days relative to the start of treatment with recombinant proteins. Liver to body weight ratio (B, C), liver axin2 mRNA (D, E), cyclinD1 mRNA (F, G) and Ki67 mRNA (H, I) expression, average count of PCNA (J, K) or phospho-histone H3 (L, M) positive nuclei per 10x field after immunohistochemistry staining with PCNA and phospho-histone H3 antibodies respectively, in a study using Rspo2 mono treatment (B, D, F, H, J, L) or R2M3-26/Rspo2 combination treatment (C, E, G, I, K, M). Pro-thrombin time ratio relative to the average pro-thrombin time in plasma collected from control naïve mice without TAA exposure (N). (*) $p < 0.05$, (**) $p < 0.01$, (****) $p < 0.0001$. No TAA treatment is indicated by the dashed line. For each bar graph timepoint, the treatments shown from left to right correspond to those in the legend shown above from top to bottom.

FIGS. 42A-42C. Efficacy of recombinantly produced Wnt surrogate and R-Spondin in a CCl₄-induced chronic liver disease model. Study design (A). Liver to body weight ratio (B) pro-thrombin time (C) and sirius red staining (D) in response to CCl₄ treatment, R2M3-26 and Rspo2. (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, (****) $p < 0.0001$. For each graph, the treatments shown from left to right correspond to those in the legend from top to bottom (not including baseline).

FIGS. 43A-43D. Induction of proliferation markers in response to recombinantly produced Wnt surrogate in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24 and 48 hours after treatment with acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (*) $p < 0.05$, (***) $p < 0.001$, (****) $p < 0.0001$.

FIGS. 44A-44D. Induction of proliferation markers in response to R-Spondin in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24 and 48 hours after treatment with

acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (**) $p < 0.01$, (***) $p < 0.001$, (****) $p < 0.0001$.

FIGS. 45A-45D. Induction of proliferation markers in response to Wnt surrogate and R-Spondin in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24, 36, 48 and 60 hours after treatment with acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (*) $p < 0.05$, (****) $p < 0.0001$. For each time point, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 46A-46D. Efficacy of recombinantly produced Wnt surrogate and R-Spondin on the survival of mice after acetaminophen-induced liver injury. Study design (A). Survival curve of mice treated with the control anti-eGFP control protein or R2M3-26 (B), Rspo2 (C) or a combination of R2M3-26 and Rspo2 (D) recombinant proteins.

DETAILED DESCRIPTION

The present disclosure relates to Wnt surrogate molecules that bind to one or more Fzd receptor and one or more LRP5 or LRP6 receptor and modulate a downstream Wnt signaling pathway. In particular embodiments, the

5 Wnt surrogate molecules activate a Wnt signaling pathway or increase signaling via a Wnt signaling pathway. In particular embodiments, the Wnt surrogate molecules disclosed herein comprise: (i) one or more antibodies or antigen-binding fragments thereof that specifically bind to one or more Fzd receptor, including antibodies or antigen-binding fragments thereof having

10 particular Fzd receptor specificity and/or functional properties; and (ii) one or more antibodies or antigen-binding fragments thereof that specifically bind to LRP5 and/or LRP6. Certain embodiments encompass specific structural formats or arrangements of the Fzd binding region(s) and LRP5/6 binding region(s) of Wnt surrogate molecules advantageous in increasing downstream

15 Wnt pathway signaling and related biological effects.

Embodiments of the invention pertain to the use of Wnt surrogate molecules for the diagnosis, assessment and treatment of diseases and disorders associated with Wnt signaling pathways. In certain embodiments, the subject Wnt surrogate molecules are used to modulate a Wnt signaling pathway

20 in a cell or tissue. In certain embodiments, the subject Wnt surrogate molecules are used in the treatment or prevention of diseases and disorders associated with aberrant or deregulated (e.g., reduced) Wnt signaling, or for which modulating, e.g., increasing, Wnt signaling would provide a therapeutic benefit.

25 The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., *Current*

30 *Protocols in Molecular Biology* or *Current Protocols in Immunology*, John Wiley

& Sons, New York, N.Y.(2009); Ausubel *et al.*, *Short Protocols in Molecular Biology*, 3rd ed., Wiley & Sons, 1995; Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); Maniatis *et al.* *Molecular Cloning: A Laboratory Manual* (1982); *DNA Cloning: A Practical Approach*, vol. I
5 & II (D. Glover, ed.); *Oligonucleotide Synthesis* (N. Gait, ed., 1984); *Nucleic Acid Hybridization* (B. Hames & S. Higgins, eds., 1985); *Transcription and Translation* (B. Hames & S. Higgins, eds., 1984); *Animal Cell Culture* (R. Freshney, ed., 1986); Perbal, *A Practical Guide to Molecular Cloning* (1984) and other like references.

10 As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the content clearly dictates otherwise.

 Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or
15 "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

 Each embodiment in this specification is to be applied *mutatis mutandis* to every other embodiment unless expressly stated otherwise.

20 Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. These and related techniques
25 and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of, molecular
30 biology, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and

commonly used in the art. Standard techniques may be used for recombinant technology, molecular biological, microbiological, chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of subjects.

5 Embodiments of the present invention relate to antibodies and antigen-binding fragments thereof that bind to one or more Fzd receptor. Sequences of illustrative antibodies, or antigen-binding fragments, or complementarity determining regions (CDRs) thereof, are set forth in SEQ ID NOs:1-65 or 129-132, Tables 1A and 1B, and Table 3. Anti-Fzd antibodies and
10 antigen-binding fragments there that may be used or present in the Wnt surrogate molecules disclosed herein include, but are not limited to, those described in the U.S. provisional application no. 62/607,877, titled Anti-Frizzled Antibodies and Methods of Use, Attorney docket no. SRZN-004/00US, filed on December 19, 2017.

15 Embodiments of the present invention relate to antibodies and antigen-binding fragments thereof that bind to LRP5 and/or LRP6. Sequences of illustrative antibodies, or antigen-binding fragments, or complementarity determining regions (CDRs) thereof, are set forth in SEQ ID NOs:66-88 or 133, Tables 2A and 2B, and Table 3. Anti-LRP5/6 antibodies and antigen-binding
20 fragments there that may be used or present in the Wnt surrogate molecules disclosed herein include, but are not limited to, those described in the U.S. provisional application no. 62/607,879, titled Anti-LRP5/6 Antibodies and Methods of Use, Attorney docket no. SRZN-005/00US, filed on December 19, 2017.

25 As is well known in the art, an antibody is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one epitope recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal
30 antibodies, but also fragments thereof (such as dAb, Fab, Fab', F(ab')₂, Fv), single chain (scFv), VHH or sdAb, synthetic variants thereof, naturally occurring

variants, fusion proteins comprising an antibody or an antigen-binding fragment thereof, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment (epitope recognition site) of the required specificity.

5 "Diabodies" or 2scFV-Ig antibodies, are multivalent or multispecific fragments constructed by gene fusion (WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993) are also a particular form of antibody contemplated herein. Minibodies comprising a scFv joined to a CH3 domain are also included herein (S. Hu et al., Cancer Res., 56, 3055-3061, 1996). See
10 e.g., Ward, E. S. *et al.*, Nature 341, 544-546 (1989); Bird et al., Science, 242, 423-426, 1988; Huston et al., PNAS USA, 85, 5879-5883, 1988); PCT/US92/09965; WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993; Y. Reiter et al., Nature Biotech, 14, 1239-1245, 1996; S. Hu et al., Cancer Res., 56, 3055-3061, 1996.

15 The term "antigen-binding fragment" as used herein refers to a polypeptide fragment that contains at least one CDR of an immunoglobulin heavy and/or light chain, or of a VHH or sdAb, that binds to the antigen of interest, in particular to one or more Fzd receptor or LRP5 or LRP6 receptor. In this regard, an antigen-binding fragment of the herein described antibodies may
20 comprise 1, 2, 3, 4, 5, or all 6 CDRs of a VH and VL sequence set forth herein from antibodies that bind one or more Fzd receptor or LRP5 and/or LRP6. In particular embodiments, an antigen-binding fragment may comprise all three VH CDRs or all three VL CDRs. Similarly, an antigen binding fragment thereof may comprise all three CDRs of a VHH or sdAb. An antigen-binding fragment of
25 a Fzd-specific antibody is capable of binding to a Fzd receptor. An antigen-binding fragment of a LRP5/6-specific antibody is capable of binding to a LRP5 and/or LRP6 receptor. As used herein, the term encompasses not only isolated fragments but also polypeptides comprising an antigen-binding fragment of an antibody disclosed herein, such as, for example, fusion proteins comprising an
30 antigen-binding fragment of an antibody disclosed herein, such as, e.g., a

fusion protein comprising a VHH or sdAb that binds one or more Fzd receptors and a VHH or sdAb that binds LRP5 and/or LRP6.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. In certain embodiments, a binding agent (e.g., a Wnt surrogate molecule or binding region thereof) is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In certain embodiments, a Wnt surrogate molecule or binding region thereof (e.g., an antibody or antigen-binding fragment thereof) is said to specifically bind an antigen when the equilibrium dissociation constant is $\leq 10^{-7}$ or $\leq 10^{-8}$ M. In some embodiments, the equilibrium dissociation constant may be $\leq 10^{-9}$ M or $\leq 10^{-10}$ M.

In certain embodiments, antibodies and antigen-binding fragments thereof as described herein include a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain framework region (FR) set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V

region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

The structures and locations of immunoglobulin CDRs and variable domains may be determined by reference to Kabat, E. A. et al., Sequences of Proteins of Immunological Interest. 4th Edition. US Department of Health and Human Services. 1987, and updates thereof, now available on the Internet (immuno.bme.nwu.edu). Alternatively, CDRs may be determined by using "IMGT®, the international ImMunoGeneTics information system® available at <http://www.imgt.org> (see, e.g., Lefranc, M.-P. et al. (1999) *Nucleic Acids Res.*, 27:209-212; Ruiz, M. et al. (2000) *Nucleic Acids Res.*, 28:219-221; Lefranc, M.-P. (2001) *Nucleic Acids Res.*, 29:207-209; Lefranc, M.-P. (2003) *Nucleic Acids Res.*, 31:307-310; Lefranc, M.-P. et al. (2004) *In Silico Biol.*, 5, 0006 [Epub], 5:45-60 (2005)]; Lefranc, M.-P. et al. (2005) *Nucleic Acids Res.*, 33:D593-597; Lefranc, M.-P. et al. (2009) *Nucleic Acids Res.*, 37:D1006-1012; Lefranc, M.-P. et al. (2015) *Nucleic Acids Res.*, 43:D413-422).

A "monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an epitope. Monoclonal antibodies are highly specific, being directed against a single epitope. The term "monoclonal antibody"

encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain (scFv), VHH or sdAb, variants thereof, fusion proteins comprising an antigen-binding fragment of a monoclonal antibody, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding fragment (epitope recognition site) of the required specificity and the ability to bind to an epitope, including Wnt surrogate molecules disclosed herein. It is not intended to be limited as regards the source of the antibody or the manner in which it is made (e.g., by hybridoma, phage selection, recombinant expression, transgenic animals, etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the F(ab) fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the F(ab')₂ fragment which comprises both antigen-binding sites. An Fv fragment for use according to certain embodiments of the present invention can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions of an IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H:V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar *et al.* (1972) *Proc. Nat. Acad. Sci. USA* 69:2659-2662; Hochman *et al.* (1976) *Biochem* 15:2706-2710; and Ehrlich *et al.* (1980) *Biochem* 19:4091-4096.

In certain embodiments, single chain Fv or scFV antibodies are contemplated. For example, Kappa bodies (Ill *et al.*, *Prot. Eng.* 10: 949-57 (1997); minibodies (Martin *et al.*, *EMBO J* 13: 5305-9 (1994); diabodies (Holliger *et al.*, *PNAS* 90: 6444-8 (1993); or Janusins (Traunecker *et al.*, *EMBO*

J 10: 3655-59 (1991) and Traunecker *et al.*, *Int. J. Cancer Suppl.* 7: 51-52 (1992), may be prepared using standard molecular biology techniques following the teachings of the present application with regard to selecting antibodies having the desired specificity. In still other embodiments, bispecific or chimeric
5 antibodies may be made that encompass the ligands of the present disclosure. For example, a chimeric antibody may comprise CDRs and framework regions from different antibodies, while bispecific antibodies may be generated that bind specifically to one or more Fzd receptor through one binding domain and to a second molecule through a second binding domain. These antibodies may be
10 produced through recombinant molecular biological techniques or may be physically conjugated together.

A single chain Fv (scFv) polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston *et al.* (1988) *Proc.*
15 *Nat. Acad. Sci. USA* 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an scFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding
20 site. See, e.g., U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston *et al.*; and U.S. Pat. No. 4,946,778, to Ladner *et al.*

In certain embodiments, an antibody as described herein is in the form of a diabody. Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin
25 light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (e.g. by a peptide linker) but unable to associate with each other to form an antigen binding site: antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide
30 within the multimer (WO94/13804).

A dAb fragment of an antibody consists of a VH domain (Ward, E. S. *et al.*, Nature 341, 544-546 (1989)).

Where bispecific antibodies are to be used, these may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. *Current Opinion Biotechnol.* 4, 446-449 (1993)), e.g. prepared chemically or from hybrid hybridomas, or may be any of the bispecific antibody fragments mentioned above. Diabodies and scFv can be constructed without an Fc region, using only variable domains, potentially reducing the effects of anti-idiotypic reaction.

10 Bispecific diabodies, as opposed to bispecific whole antibodies, may also be particularly useful because they can be readily constructed and expressed in *E. coli*. Diabodies (and many other polypeptides such as antibody fragments) of appropriate binding specificities can be readily selected using phage display (WO94/13804) from libraries. If one arm of the diabody is to be
15 kept constant, for instance, with a specificity directed against antigen X, then a library can be made where the other arm is varied and an antibody of appropriate specificity selected. Bispecific whole antibodies may be made by knobs-into-holes engineering (J. B. B. Ridgeway *et al.*, *Protein Eng.*, 9, 616-621, 1996).

20 In certain embodiments, the antibodies described herein may be provided in the form of a UniBody®. A UniBody® is an IgG4 antibody with the hinge region removed (see GenMab Utrecht, The Netherlands; see also, e.g., US20090226421). This proprietary antibody technology creates a stable, smaller antibody format with an anticipated longer therapeutic window than
25 current small antibody formats. IgG4 antibodies are considered inert and thus do not interact with the immune system. Fully human IgG4 antibodies may be modified by eliminating the hinge region of the antibody to obtain half-molecule fragments having distinct stability properties relative to the corresponding intact IgG4 (GenMab, Utrecht). Halving the IgG4 molecule leaves only one area on
30 the UniBody® that can bind to cognate antigens (e.g., disease targets) and the UniBody® therefore binds univalently to only one site on target cells.

In certain embodiments, the antibodies of the present disclosure may take the form of a VHH or sdAb. VHH or sdAb technology was originally developed following the discovery and identification that *camelidae* (e.g., camels and llamas) possess fully functional antibodies that consist of heavy chains only and therefore lack light chains. These heavy-chain only antibodies contain a single variable domain (V_{HH}) and two constant domains (C_{H2} , C_{H3}). The cloned and isolated single variable domains have full antigen binding capacity and are very stable. These single variable domains, with their unique structural and functional properties, form the basis of "VHH or sdAb". VHH or sdAb are encoded by single genes and are efficiently produced in almost all prokaryotic and eukaryotic hosts e.g. *E. coli* (see e.g. U.S. Pat. No. 6,765,087), molds (for example *Aspergillus* or *Trichoderma*) and yeast (for example *Saccharomyces*, *Kluyvermyces*, *Hansenula* or *Pichia* (see e.g. U.S. Pat. No. 6,838,254). The production process is scalable and multi-kilogram quantities of VHH or sdAb have been produced. VHH or sdAb may be formulated as a ready-to-use solution having a long shelf life. The VHH or sdAb method (see, e.g., WO 06/079372) is a proprietary method for generating VHH or sdAb against a desired target, based on automated high-throughput selection of B-cells. VHH or sdAb are single-domain antigen-binding fragments of camelid-specific heavy-chain only antibodies. VHH antibodies or sdAb, typically have a small size of around 15 kDa.

In certain embodiments, the antibodies or antigen-binding fragments thereof as disclosed herein are humanized. This refers to a chimeric molecule, generally prepared using recombinant techniques, having an antigen-binding site derived from an immunoglobulin from a non-human species and the remaining immunoglobulin structure of the molecule based upon the structure and/or sequence of a human immunoglobulin. The antigen-binding site may comprise either complete variable domains fused onto constant domains or only the CDRs grafted onto appropriate framework regions in the variable domains. Epitope binding sites may be wild type or modified by one or more amino acid substitutions. This eliminates the constant region as an immunogen

in human individuals, but the possibility of an immune response to the foreign variable region remains (LoBuglio, A. F. *et al.*, (1989) *Proc Natl Acad Sci USA* 86:4220-4224; Queen *et al.*, *PNAS* (1988) 86:10029-10033; Riechmann *et al.*, *Nature* (1988) 332:323-327). Illustrative methods for humanization of the anti-
5 Fzd antibodies disclosed herein include the methods described in U.S. patent no. 7,462,697.

Another approach focuses not only on providing human-derived constant regions, but modifying the variable regions as well so as to reshape them as closely as possible to human form. It is known that the variable
10 regions of both heavy and light chains contain three complementarity-determining regions (CDRs) which vary in response to the epitopes in question and determine binding capability, flanked by four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When nonhuman antibodies are prepared with
15 respect to a particular epitope, the variable regions can be "reshaped" or "humanized" by grafting CDRs derived from nonhuman antibody on the FRs present in the human antibody to be modified. Application of this approach to various antibodies has been reported by Sato, K., *et al.*, (1993) *Cancer Res* 53:851-856. Riechmann, L., *et al.*, (1988) *Nature* 332:323-327; Verhoeyen, M.,
20 *et al.*, (1988) *Science* 239:1534-1536; Kettleborough, C. A., *et al.*, (1991) *Protein Engineering* 4:773-3783; Maeda, H., *et al.*, (1991) *Human Antibodies Hybridoma* 2:124-134; Gorman, S. D., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:4181-4185; Tempest, P. R., *et al.*, (1991) *Bio/Technology* 9:266-271; Co, M. S., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:2869-2873; Carter, P., *et al.*,
25 (1992) *Proc Natl Acad Sci USA* 89:4285-4289; and Co, M. S. *et al.*, (1992) *J Immunol* 148:1149-1154. In some embodiments, humanized antibodies preserve all CDR sequences (for example, a humanized mouse antibody which contains all six CDRs from the mouse antibodies). In other embodiments, humanized antibodies have one or more CDRs (one, two, three, four, five, six)
30 which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

In certain embodiments, the antibodies of the present disclosure may be chimeric antibodies. In this regard, a chimeric antibody is comprised of an antigen-binding fragment of an antibody operably linked or otherwise fused to a heterologous Fc portion of a different antibody. In certain embodiments, the heterologous Fc domain is of human origin. In other embodiments, the heterologous Fc domain may be from a different Ig class from the parent antibody, including IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG (including subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. In further embodiments, the heterologous Fc domain may be comprised of CH2 and CH3 domains from one or more of the different Ig classes. As noted above with regard to humanized antibodies, the antigen-binding fragment of a chimeric antibody may comprise only one or more of the CDRs of the antibodies described herein (e.g., 1, 2, 3, 4, 5, or 6 CDRs of the antibodies described herein), or may comprise an entire variable domain (VL, VH or both).

Wnt Surrogates

The disclosure provides, in certain aspects, Wnt surrogate molecules that bind both one or more Fzd receptors and one or both of LRP5 and/or LRP6. Wnt surrogate molecules may also be referred to as "Wnt surrogates" or "Wnt mimetics." In particular embodiments, the Wnt surrogate molecules bind one or more human Fzd receptors and one or both of a human LRP5 and/or a human LRP6.

In certain embodiments, a Wnt surrogate molecule is capable of modulating or modulates Wnt signaling events in a cell contacted with the Wnt surrogate molecule. In certain embodiments, the Wnt surrogate molecule increases Wnt signaling, e.g., via the canonical Wnt/ β -catenin pathway. In certain embodiments, the Wnt surrogate molecule specifically modulates the biological activity of a human Wnt signaling pathway.

Wnt surrogate molecules of the present invention are biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist. The term "Wnt agonist activity" refers to the ability of an agonist to

mimic the effect or activity of a Wnt protein binding to a frizzled protein and/or LRP5 or LRP6. The ability of the Wnt surrogate molecules and other Wnt agonists disclosed herein to mimic the activity of Wnt can be confirmed by a number of assays. Wnt agonists typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the Wnt agonists disclosed herein activate, enhance or increase the canonical Wnt/ β -catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/ β -catenin signaling compared with the level in the absence of a Wnt agonist, e.g., a Wnt surrogate molecule disclosed herein. In particular embodiments, the increase in the level of Wnt/ β -catenin signaling is at least 10%, at least 20%, at least 50%, 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 level of Wnt/ β -catenin signaling in the absence of the Wnt agonist, e.g., in the same cell type. Methods of measuring Wnt/ β -catenin signaling are known in the art and include those described herein.

In particular embodiments, Wnt surrogate molecules disclosed herein are bispecific, i.e., they specifically bind to two or more different epitopes, e.g., one or more Fzd receptor, and LRP5 and/or LRP6.

In particular embodiments, Wnt surrogate molecules disclosed herein are multivalent, e.g., they comprise two or more regions that each specifically bind to the same epitope, e.g., two or more regions that bind to an epitope within one or more Fzd receptor and/or two or more regions that bind to an epitope within LRP5 and/or LRP6. In particular embodiments, they comprise two or more regions that bind to an epitope within one or more Fzd receptor and two or more regions that bind to an epitope within LRP5 and/or LRP6. In certain embodiments, Wnt surrogate molecules comprise a ratio of the number of regions that bind one or more Fzd receptor to the number of regions that bind LRP5 and/or LRP6 of or about: 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 2:3, 2:5, 2:7, 7:2, 5:2, 3:2, 3:4, 3:5, 3:7, 3:8, 8:3, 7:3, 5:3, 4:3, 4:5, 4:7, 4:9, 9:4, 7:4, 5:4, 6:7, 7:6, 1:2,

1:3, 1:4, 1:5, or 1:6. In certain embodiments, Wnt surrogate molecules are bispecific and multivalent.

Wnt surrogate molecules disclosed herein may have any of a variety of different structural formats or configurations. Wnt surrogate molecules may comprise polypeptides and/or non-polypeptide binding moieties, e.g., small molecules. In particular embodiments, Wnt surrogate molecules comprise both a polypeptide region and a non-polypeptide binding moiety. In certain embodiments, Wnt surrogate molecules may comprise a single polypeptide, or they may comprise two or more, three or more, or four or more polypeptides. In certain embodiments, one or more polypeptides of a Wnt surrogate molecule are antibodies or antigen-binding fragments thereof. In certain embodiments, Wnt surrogates comprise two antibodies or antigen binding fragments thereof, one that binds one or more Fzd and one that binds LRP5 and/or LRP6. In certain embodiments, the Wnt surrogates comprises one, two, three, or four polypeptides, e.g., linked or bound to each other or fused to each other.

When the Wnt surrogate molecules comprise a single polypeptide, they may be a fusion protein comprising one or more Fzd binding domain and one or more LRP5/6 binding domain. The binding domains may be directly fused or they may be connected via a linker, e.g., a polypeptide linker, including but not limited to any of those disclosed herein.

When the Wnt surrogate molecules comprise two or more polypeptides, the polypeptides may be linked via covalent bonds, such as, e.g., disulfide bonds, and/or noncovalent interactions. For example, heavy chains of human immunoglobulin IgG interact at the level of their CH3 domains directly, whereas, at the level of their CH2 domains, they interact via the carbohydrate attached to the asparagine (Asn) N84.4 in the DE turn. In particular embodiments, the Wnt surrogate molecules comprise one or more regions derived from an antibody or antigen-binding fragment thereof, e.g., antibody heavy chains or antibody light chains or fragments thereof. In certain embodiments, a Wnt surrogate polypeptide comprises two antibody heavy chain regions (e.g., hinge regions) bound together via one or more disulfide

bond. In certain embodiments, a Wnt surrogate polypeptide comprises an antibody light chain region (e.g., a C_L region) and an antibody heavy chain region (e.g., a C_{H1} region) bound together via one or more disulfide bond.

Wnt surrogate polypeptides may be engineered to facilitate binding between two polypeptides. For example, Knob-into-holes amino acid modifications may be introduced into two different polypeptides to facilitate their binding. Knobs-into-holes amino acid (AA) changes is a rational design strategy developed in antibody engineering, used for heterodimerization of the heavy chains, in the production of bispecific IgG antibodies. AA changes are engineered in order to create a knob on the CH3 of the heavy chains from a first antibody and a hole on the CH3 of the heavy chains of a second antibody. The knob may be represented by a tyrosine (Y) that belongs to the 'very large' IMGT volume class of AA, whereas the hole may be represented by a threonine (T) that belongs to the 'small' IMGT volume class. Other means of introducing modifications into polypeptides to facilitate their binding are known and available in the art. For example, specific amino acids may be introduced and used for cross-linking, such as Cysteine to form an intermolecular disulfide bond.

Wnt surrogate molecules may have a variety of different structural formats, including but not limited to those shown in FIG. 1.

In one embodiment, a Wnt surrogate molecule comprises an scFv or antigen-binding fragment thereof fused to a VHH or sdAb or antigen-binding fragment thereof. In certain embodiments, the scFv specifically binds one or more Fzd receptor, and the VHH or sdAb specifically binds LRP5 and/or LRP6. In certain embodiments, the scFv specifically binds LRP5 and/or LRP6, and the VHH or sdAb specifically binds one or more Fzd receptor. In particular embodiments, the scFv or antigen-binding fragment thereof is fused directly to the VHH or sdAb or antigen-binding fragment thereof, whereas in other embodiments, the two binding regions are fused via a linker moiety. In particular embodiments, the VHH or sdAb is fused to the N-terminus of the scFv, while in other embodiments, the VHH or sdAb is fused to the C-terminus

of the scFv. In particular embodiments, the scFv is described herein or comprises any of the CDR sets described herein. In particular embodiments, the VHH or sdAb is described herein or comprises any of the CDR sets disclosed herein.

5 In various embodiments, including but not limited to those depicted in FIG. 1A, a Wnt surrogate molecule comprises one or more Fab or antigen-binding fragment thereof and one or more VHH or sdAb or antigen-binding fragment thereof (or alternatively, one or more scFv or antigen-binding fragment thereof). In certain embodiments, the Fab specifically binds one or
10 more Fzd receptor, and the VHH or sdAb (or scFv) specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds LRP5 and/or LRP6, and the VHH or sdAb (or scFv) specifically binds one or more Fzd receptor. In certain embodiments, the VHH or sdAb (or scFv) is fused to the N-terminus of the Fab, while in some embodiments, the VHH or sdAb (or scFv) is
15 fused to the C-terminus of the Fab. In particular embodiments, the Fab is present in a full IgG format, and the VHH or sdAb (or scFv) is fused to the N-terminus and/or C-terminus of the IgG light chain. In particular embodiments, the Fab is present in a full IgG format, and the VHH or sdAb (or scFv) is fused to the N-terminus and/or C-terminus of the IgG heavy chain. In particular
20 embodiments, two or more VHH or sdAb (or scFvs) are fused to the IgG at any combination of these locations.

 Fabs may be converted into a full IgG format that includes both the Fab and Fc fragments, for example, using genetic engineering to generate a fusion polypeptide comprising the Fab fused to an Fc region, i.e., the Fab is
25 present in a full IgG format. The Fc region for the full IgG format may be derived from any of a variety of different Fcs, including but not limited to, a wild-type or modified IgG1, IgG2, IgG3, IgG4 or other isotype, e.g., wild-type or modified human IgG1, human IgG2, human IgG3, human IgG4, human IgG4Pro (comprising a mutation in core hinge region that prevents the
30 formation of IgG4 half molecules), human IgA, human IgE, human IgM, or the modified IgG1 referred to as IgG1 LALAPG. The L235A, P329G (LALA-PG)

variant has been shown to eliminate complement binding and fixation as well as Fc- γ dependent antibody-dependent cell-mediated cytotoxicity (ADCC) in both murine IgG2a and human IgG1. These LALA-PG substitutions allow a more accurate translation of results generated with an

5 “effectorless” antibody framework scaffold between mice and primates. In particular embodiments of any of the IgG disclosed herein, the IgG comprises one or more of the following amino acid substitutions: N297G, N297A, N297E, L234A, L235A, or P236G.

Non-limiting examples of bivalent and bispecific Wnt surrogate

10 molecules that are bivalent towards both the one or more Fzd receptor and the LRP5 and/or LRP6 are provided as the top four structures depicted in FIG. 1A, where the VHH or sdAb or scFv is depicted in white, and the Fab or IgG is depicted in black. As shown, the VHH or sdAb (or scFvs) may be fused to the N-termini of both light chains, to the N-termini of both heavy chains, to the C-

15 termini of both light chains, or to the C-termini of both heavy chains. It is further contemplated, e.g., that VHH or sdAb (or scFvs) could be fused to both the N-termini and C-termini of the heavy and/or light chains, to the N-termini of the light chains and the heavy chains, to the C-termini of the heavy and light chains, to the N-termini of the heavy chains and C-termini of the light chains, or

20 to the C-termini of the heavy chains and the N-termini of the light chains. In other related embodiments, two or more VHH or sdAb (or scFvs) may be fused together, optionally via a linker moiety, and fused to the Fab or IgG at one or more of these locations. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas the Fab is present as a half antibody, and

25 one or more VHH or sdAb (or scFv) is fused to one or more of the N-terminus of the Fc, the N-terminus of the Fab, the C-terminus of the Fc, or the C-terminus of the Fab. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1A. In certain embodiments, the Fab or antigen-binding fragment (or IgG) thereof is fused directly to the VHH or sdAb

30 (or scFv) or antigen-binding fragment thereof, whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments,

the Fab is described herein or comprises any of the CDR sets described herein. In particular embodiments, the VHH or sdAb or scFv is described herein or comprises any of the CDR sets disclosed herein.

In various embodiments, including but not limited to those depicted in FIG. 1B, a Wnt surrogate molecule comprises one or more Fab or antigen-binding fragment thereof that binds one or more Fzd receptor and one or more Fab or antigen-binding fragment thereof that binds LRP5 and/or LRP6. In certain embodiments, it comprises two Fab or antigen-binding fragments thereof that bind one or more Fzd receptor and/or two Fab or antigen-binding fragments thereof that bind LRP5 and/or LRP6. In particular embodiments, one or more of the Fab is present in a full IgG format, and in certain embodiments, both Fab are present in a full IgG format. In certain embodiments, the Fab in full IgG format specifically binds one or more Fzd receptor, and the other Fab specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds one or more Fzd receptor, and the Fab in full IgG format specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds LRP5 and/or LRP6, and the Fab in full IgG format specifically binds one or more Fzd receptor. In certain embodiments, the Fab is fused to the N-terminus of the IgG, e.g., to the heavy chain or light chain N-terminus, optionally via a linker. In certain embodiments, the Fab is fused to the N-terminus of the heavy chain of the IgG and not fused to the light chain. In particular embodiments, the two heavy chains can be fused together directly or via a linker. An example of such a bispecific and bivalent with respect to both receptors is shown at the top of FIG. 1B. In other related embodiments, two or more VHH or sdAb may be fused together, optionally via a linker moiety, and fused to the Fab or IgG at one or more of these locations. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas one of the Fab is present as a half antibody, and the other Fab is fused to one or more of the N-terminus of the Fc, the N-terminus of the Fab, or the C-terminus of the Fc. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1B. In certain embodiments, the Fab or

antigen-binding fragment thereof is fused directly to the other Fab or IgG or antigen-binding fragment thereof, whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments, the one or both of the two Fabs are described herein or comprise any of the CDR sets
5 described herein.

In certain embodiments, Wnt surrogate molecules have a format as described in PCT Application Publication No. WO2017/136820, e.g., a Fabs-in-tandem IgG (FIT-IG) format. Shiyong Gong, Fang Ren, Danqing Wu, Xuan Wu & Chengbin Wu (2017). FIT-IG also include the formats disclosed in “Fabs-in-tandem immunoglobulin is a novel and versatile bispecific design for
10 engaging multiple therapeutic targets” mAbs, 9:7, 1118-1128, DOI: 10.1080/19420862.2017.1345401. In certain embodiments, FIT-IGs combine the functions of two antibodies into one molecule by re-arranging the DNA sequences of two parental monoclonal antibodies into two or three constructs and co-expressing them in mammalian cells. Examples of FIT-IG formats and
15 constructs are provided in FIGS. 1A and 1B and FIGS. 2A and 2B of PCT Application Publication No. WO2017/136820. In certain embodiments, FIT-IGs require no Fc mutation; no scFv elements; and no linker or peptide connector. The Fab-domains in each arm work “in tandem” forming a tetravalent bi-specific
20 antibody with four active and independent antigen binding sites that retain the biological function of their parental antibodies. In particular embodiments, Wnt surrogates comprises a Fab and an IgG. In certain embodiments, the Fab binder LC is fused to the HC of the IgG, e.g., by a linker of various length in between. In various embodiment, the Fab binder HC can be fused or unfused to
25 the LC of the IgG. A variation of this format has been called Fabs-in-tandem IgG (or FIT-Ig).

In particular embodiments, Wnt surrogate molecules comprise two or more VHH or sdAb (or scFvs), including at least one that binds one or more Fzd receptor and at least one that binds LRP5 and/or LRP6. In certain
30 embodiments, one of the binding regions is a VHH or sdAb and the other is an scFv. Wnt memetic molecules comprising two or more VHH or sdAb (or scFvs)

may be formatted in a variety of configurations, including but not limited to those depicted in FIG. 1C. In certain bispecific, bivalent formats, two or more VHH or sdAb (or scFvs) are fused in tandem or fused to two different ends of an Fc, optionally via one or more linkers. Where linkers are present, the linker and its length may be the same or different between the VHH or sdAb (or scFv) and the other VHH or sdAb (or scFv), or between the VHH or sdAb and Fc. For example, in certain embodiments, the VHH or sdAb is fused to the N-terminus and/or C-terminus of the IgG heavy chain. In particular embodiments, two or more VHH or sdAb are fused to the IgG at any combination of these locations.

Non-limiting examples of bivalent and bispecific Wnt surrogate molecules of this format are depicted as the top seven structures depicted in FIG. 1C, where the first VHH or sdAb is depicted in white, the Fc or IgG is depicted in black, and the second VHH or sdAb is depicted as light gray. In various embodiments, both VHH or sdAb may be fused to the N-termini of the Fc, to the C-termini of the Fc, or one or more VHH or sdAb may be fused to either or both of an N-terminus or C-terminus of the Fc. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas one VHH or sdAb is present as a half antibody, and the other is fused to the N-terminus of the Fc or the C-terminus of the Fc. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1C. In certain embodiments, the VHH or sdAb is fused directly to the other VHH or sdAb whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments, the VHH or sdAb are described herein or comprises any of the CDR sets described herein. In various embodiments, any of these formats may comprise one or more scFvs in place of one or more VHH or sdAb.

In certain embodiments, a Wnt surrogate molecule is formatted as a diabody. As shown in Fig. 1D, the binders against Fzd and LRP can also be linked together in a diabody (or DART) configuration. The diabody can also be in a single chain configuration. If the diabody is fused to an Fc, this will create a bivalent bispecific format. Without fusion to Fc, this would be a monovalent bispecific format. In certain embodiments, a diabody is a noncovalent dimer

scFv fragment that consists of the heavy-chain variable (VH) and light-chain variable (VL) regions connected by a small peptide linker. Another form of diabody is a single-chain (Fv)₂ in which two scFv fragments are covalently linked to each other.

5 As discussed, Wnt surrogate molecules, in various embodiments, comprise one or more antibodies or antigen-binding fragments thereof disclosed herein. Thus, in particular embodiments, a Wnt surrogate comprises two polypeptides, wherein each polypeptide comprises an Nab or scFv that binds LRP5/6 and an Nab or scFv that binds one or more Wnts, optionally
10 wherein one of the binding domains is an scFv and the other is an Nab. In certain embodiments, a Wnt surrogate comprises three polypeptides, wherein the first polypeptide comprises an antibody heavy chain and the second polypeptide comprises an antibody light chain, wherein the antibody heavy chain and light chain bind LRP5/6 or one or more Fzds, and wherein the third
15 polypeptide comprises a VHH or sdAb fused to a heavy chain Fc region, wherein the VHH or sdAb binds to either LRP5/6 or one or more Fzds. In other embodiments, Wnt polypeptides comprise four polypeptides, including two heavy chain polypeptides and two light chain polypeptides, wherein the two heavy chains and two light chains bind LRP5/6 or one or more Fzds, and
20 further comprise one or more Nab or scFv fused to one or more of the heavy chains and/or light chains, wherein the Nab or scFv binds to LRP5/6 or one or more Fzds. In another illustrative embodiment, a Wnt surrogate comprises at least four polypeptides, including two heavy chain polypeptides and two light chain polypeptides that bind either LRP5/6 or one or more Fzds, wherein the
25 Wnt surrogate further comprises a Fab that binds either LRP5/6 or one or more Fzds. For example, the Fab may comprise two polypeptides, each fused to one of the two heavy chain polypeptides, and two polypeptides, each fused to one of the two light chain polypeptides, or it may comprise two polypeptides each fused to one of the two heavy chain polypeptides and two additional
30 polypeptides, each bound to one of the two polypeptides fused to the heavy

chain polypeptides, thus making a second Fab. Other configurations may be used to produce the Wnt surrogates disclosed herein.

In particular embodiments, a Wnt surrogate molecule comprises a Fzd binding region, e.g., an anti-Fzd antibody, or antigen-binding fragment thereof, fused or bound to a polypeptide that specifically binds to one or more Fzd receptor. In particular embodiments, the polypeptide that specifically binds to one or more Fzd receptor is an antibody or antigen-binding fragment thereof. In certain embodiments, it is an antibody or antigen-binding fragment thereof disclosed herein or in the U.S. provisional patent application no. 62/607,877, titled, "Anti-Frizzled antibodies and Methods of Use," Attorney docket number SRZN-004/00US, filed on December 19, 2017, which is incorporated herein by reference in its entirety. In particular embodiments, the Fzd binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1A. In particular embodiments, the Fzd binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1A, wherein the CDRs collectively comprise one, two, three, four, five, six, seven, or eight amino acid modifications, e.g., substitutions, deletions, or additions. In certain embodiments, the Fzd binding domain is a VHH or sdAb or was derived from a VHH or sdAb, so Table 1A only includes the three heavy chain CDRs. In particular embodiments, the Fzd binding domain comprises the three CDR HC sequences provided in Table 1A or variants wherein the CDRs collectively comprise one, two, three, four, five, six, seven or eight amino acid modifications. In particular embodiments, the Fzd binding domain comprises the heavy chain fragment and/or light chain fragment of any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1B or SEQ ID NOs:1-65 or 129-132 (or an antigen-binding fragment or variant of either). In certain embodiments, the Fzd binding domain is an Fab or was derived from an Fab, so the heavy chain of Table 1B includes VH and CH1

sequence, but not CH2 or CH3 sequences. In certain embodiments, the Fzd binding domain is a VHH or sdAb or was derived from a VHH or sdAb, so Table 1B includes the VHH domain. In certain embodiments, the Fzd binding region is a polypeptide, e.g., an antibody or antigen-binding fragment thereof, that

5 competes with any of these antibodies for binding to one or more Fzd receptor.

Table 1A: Anti-Fzd Antibody Clone IDs and CDR sequences

Clone ID	Initial Binding	CDRH 1	CDRH 1 SEQ ID	CDRH 2	CDRH 2 SEQ ID	CDRH3	CDR H3 SEQ ID	CDRL1	CDRL 1 SEQ ID	CDR L2	CDRL 2 SEQ ID	CDRL3	CDRL 3 SEQ ID
001S-A01	Fzd 1	YTFTSYGIS	391	GWISAYNGNTNYA	570	CARASAWTPYGAFDIW	752	SGSSSNI GSHTVS	1156	SNYQRP S	1256	CAAWDGS LFGHWVF	1265
001S-B01	Fzd 1	GSISSGGYSWS	283	GSIIHSGSTY YN	547	CARFYDILTGYSYFDY W	818	RSSRSLLD TDDGN TYLD	1142	TLSHRA S	1259	CMQSIQLP WTF	1295
001S-E01	Fzd 1	GSISNYYWS	282	GEIDRSGDTNYN	488	CARVRARRFLVSDRS AFDIW	945	SGNTLGS HYVS	1155	QDSKRP S	1246	CQVWDSSTV VF	1431
001S-F01	Fzd 1	GSISGNNYYZG	281	GSIIYFTGGT YYN	546	CARVMLITDAFDIW	942	RSSQSLLHSNGYN YLD	1138	LGSNRA S	1237	CMQGT HWPYTF	1289
001S-G01	Fzd 1	GSISSSYW WG	285	GYIYSGSTY YN	589	CARATYGGDAFDIW	760	TRSSSNI GAGYDV H	1161	GNSIRPS	1220	CGTWDS SLSAWVF	1267
001S-H01	Fzd 1	GSISSGGYWS	284	GYIYSGSTY YN	589	CARHAGFYGLADYFDY W	875	RSSQSLLHSNGYN YLD	1138	LGSKRA S	1236	CMQALQIPP TF	1280
001S-A02	Fzd 1	GSISSGGYWS	284	GYIYSGSTY YN	589	CARGKGYSYGYGKDW FDPW	845	QASQDI GKYL N	1041	DASNLE T	1185	CQQNDYLP LTF	1332
001S-E02	Fzd 1	GSISGNNYYW G	280	GSIIYFTGGT YYN	546	CARVMLITDAFDIW	942	RSSQSLLHSNGYN YLD	1138	LGSNRA S	1237	CMQGT HWPYTF	1289
001S-G02	Fzd 1	GAISGTSYF W G	266	GSIIYTGNT YYN	548	CARIGIAVAAPVDHW	882	RASQSV GTYLT	1110	DASNRA T	1188	CMQATQFPL TF	1284
001S-H02	Fzd 1	GSISSSYW WG	285	GYIYSGSTY YN	589	CARATYGGDAFDIW	760	TRSSSNI GAGYDV H	1161	GNSIRPS	1220	CGTWDS SLSAWVF	1267
001S-	Fzd 1	GSISSGGYWS	284	GYIYSGSTY YN	589	CARVRDYYDSSGYYYD YFDYW	946	RASRSISS YFN	1128	AASLQ S	1175	CQQA DTFPP TF	1314

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
A03													
001S - B03	Fzd 1	ASFS GHY WT	15 8	GEID HTGS TNYE	48 7	CARGGQG GYDWGHY HGLDVW	835	SGDKVG HKYAS	11 54	EDS QRP S	11 99	CQAW DSSTD VVF	13 01
001S - H08	Fzd 5	RAFT DNV MA	32 9	ATISG GGGS TFDD	46 6	CAAASSLTS TPYDLW	678						
001S - A09	Fzd 5	RSFRT NALG	33 3	AAIS WTG GSTY YA	42 2	CNTVITYTG GSYKNYW	100 5						
001S - B09	Fzd 5	SIDSI NAM A	35 6	AALTS GGITY HA	42 8	CNVITIVRG MGPRAYW	100 6						
001S - C09	Fzd 5	SIFSIN AMG	35 7	ATIQS GGRT NYA	46 5	CNVITIVRG MGPRAYW	100 6						
001S - C07	Fzd 8	YTFTS YGIS	39 1	GWIS AYNG NTNY A	57 0	CARDGTPF YSGSYGS W	772	QGDSLRT YYAS	10 52	GKN NRP S	12 19	CNSRD NSGK HKVF	13 00
001S - D07	Fzd 8	GTFSS YAIS	29 5	GRIIPI LGIAN YA	52 9	CARVPTSP YDILTGPF YW	944	RSSQSLL HSNGFN YVD	11 36	FGS YRA S	12 06	CMQN LQTP WTF	12 91
001S - E07	Fzd 8	ASVSS NSAA WN	15 9	GRTY YRSK WYN DYA	54 2	CARWKNY FDPW	953	RASQGIR SDLA	10 70	AAS TLES	11 77	CLQDY SYPRT F	12 73
001S - H07	Fzd 8	FTFSS YAMS	22 8	STISG GGGS TYA	64 6	CAKDLVP WGSSAFNI W	704	RASQSVS SYLA	11 21	GAS SRA T	12 13	CQQY GSSPP TF	14 10
004S - E05	Fzd 5	FTFST YEMN	24 3	SGVS WNG SRTH YV	61 8	CARGQSEK WWSGLYG MDVW	856	RASQGIS SALA	10 76	AAS ALQ S	11 65	CQQT YSTPR TF	13 94
004S -	Fzd 5	GTFST YAIS	29 8	GWIN SGNG	56 5	CWTGLLW FGESTDAF DIW	103 1	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E03				NTKYS									
004S - G06	Fzd5	GTFTY RYLH	307	GGIPI FGTG NYA	501	CASSMVR VPYYGMDVW	964	RASQSI SYLN	1098	AAS SLQS	1175	CQQS YSTPL TF	1372
001S - D09	Fzd8	GPFN LFAM G	272	AGISR TGGN TGYA	445	CASKTTINS GWSREYH YW	958						
001S - E09	Fzd8	GPFN LFAM G	272	AGISR TGGN TGYA	445	CASKTTINS GWSREYH YW	958						
001S - F09	Fzd8	GFFSS FTMG	268	AAISR NGVY TRFA	409	CNALAPGV RGSW	987						
001S - G09	Fzd8	SLFRL NGM G	360	ATIST RGTT HYA	467	CTDEESW	1011						
001S - H09	Fzd8	GPFN LLAM G	273	AGISR TGGN TGYA	445	CASKTTINS GWSREYH YW	958						
001S - A10	Fzd8	SVVN FVVM G	364	AAITS GGST NYA	425	CNRVGSRE YSYW	1001						
001S - B10	Fzd8	RTSDL YTMG	352	AAIG YKVK WNG ERTYY L	404	CNAVTYN GYTIW	994						
001S - G12	Fzd1	SIFSS NTIY	359	ALITT SGNT NYA	455	CNAGAPA WYRMGT YYPQFGS W	986						
002S - A01	Fzd1	STFST YAM G	362	AAISG SGEN TYA	408	CVKFGMN LGYSYDY W	1028						
002S -	Fzd1	STFSN YAM G	361	AAIS WGG	411	CAAGPIAR WYRGDM DYW	681						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
B0 1				GSTFY S									
00 2S - C0 1	Fzd 1	RMFS NYA MG	33 1	AAISS GGSG TYYS	41 0	CAAGPIAR WYRGDM DYW	681						
00 2S - D0 1	Fzd 1	RTDG GYVM G	33 7	ATVT WRTG TTY A	46 9	CAAGPIAR WYRGDM DYW	681						
00 2S - E0 1	Fzd 1	RTFSS AAM G	34 5	AAIS WSGS TAY A	42 1	CATLTPYG TVASY	974						
00 2S - F0 1	Fzd 1	RTFSS YAM G	34 7	AAVN WSG GSTY YA	43 0	CAAVFLSR NYEIQEY RYQ	689						
00 2S - G 01	Fzd 1	RTFSS YAM G	34 7	AAIS WSG GSTY YA	41 8	CAAGPIAR WYRGDM DYW	681						
00 2S - H0 1	Fzd 1	RSFST YPMG	33 6	TVISG SGGS TYYS	67 6	CAAGPIAR WYRGDM DYW	681						
00 2S - A0 2	Fzd 1	RRFTT YGM G	33 2	AAVT WRSG STYYA	43 6	CYLEGPLD VYW	103 2						
00 2S - B0 2	Fzd 1	RTFN RHV MG	34 1	AAIS WSG DSTY YA	41 5	CAKLGGS WLREYDY W	724						
00 2S - C0 2	Fzd 1	RTFR AYAM G	34 2	SAIS WSG GSTY YA	60 3	CAAGPIAR WYRGDM DYW	681						
00 2S - D0 2	Fzd 1	RTFSE YAM G	34 3	AAIS WSG GSTH YA	41 7	CNADSLRG IDYW	984						
00 2S -	Fzd 1	FTFRE YAMT	19 9	SGISR DGGR TSYS	61 3	CAPRVLVT APSGGMD YW	734						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E0 2													
00 2S - F0 2	Fzd 1	GDFT NYA MA	26 7	AAVN WRG DGT YS	42 9	CAAVFLSR NYEIQEYY RYQ	689						
00 2S - G 02	Fzd 1	RTFG TWA MG	34 0	AAISY NGFS TYYS	42 4	CAAGPIAR WYRGDM DYW	681						
00 2S - H0 2	Fzd 1	RTFSS YAM G	34 7	AAIS WSG GSTY YA	41 8	CAAGPIAR WYRGDM DYW	681						
00 2S - D0 3	Fzd 1	RTFGS YAM G	33 9	AAIS WSG GSTY YA	41 8	CAAGPIAR WYRGDM DYW	681						
00 2S - E0 3	Fzd 1	SIFSIY AMG	35 8	AVVA TGGA TNYA	48 1	CNMRGN WYREGRP AEFLSW	100 0						
00 2S - F0 3	Fzd 1	RTSSS YAM G	35 3	AAIS WSG GSTY YA	41 8	CAAGPIAR WYRGDM DYW	681						
00 2S - G 03	Fzd 1	RTFGS YAM G	33 9	AAIS WSG GSTY YA	41 8	CAAGPIAR WYRGDM DYW	681						
00 2S - H0 3	Fzd 1	QTFT AYAM G	32 7	AAIS WSGS ATHY A	42 0	CNAWVLV AGSRGTSA DYW	996						
00 2S - A0 4	Fzd 1	RTFSS YAM G	34 7	AAIS WSGR STYYA	41 9	CAAGPIAR WYRGDM DYW	681						
00 2S - B0 4	Fzd 1	RTFSS YAM G	34 7	AAIS WSG GSTY YA	41 8	CAAGPNYS WFMPSSS RLIW	682						
00 2S -	Fzd 1	RRFTT YGM G	33 2	AAVT WRA	43 5	CSADKLDY LDDQPFKT WDYW	101 0						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
C0 4				GSTY YA									
00 2S - D0 4	Fzd 1	GTSST YAM G	30 9	AAIN RSGG STYYA	40 5	CAAVFLSR NYEIQEYY RYQ	689						
00 2S - E0 4	Fzd 1	GTFST YAM G	30 0	AAIS WSG DSTY YL	41 6	CAAGPIAR WYRGDM DYW	681						
00 4S - H0 4	Fzd 5	GTFSS YAIS	29 5	GWIS TYNG ATNY A	57 7	CARGGAG RFGEGMD VW	826	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 1S - A0 4	Fzd 5	YTFTS YGIS	39 1	GWIS AYNG NTNY A	57 0	CASSKEKA TYYYGMD VW	963	GLSSGSV STNYYP	10 35	YTN TRS S	12 63	CLLYL GRGI WVF	12 71
00 1S - D0 3	Fzd 5	GTFSS YAIS	29 5	GRIIPI LGIAN YA	52 9	CARLDPGY YYGMDVW	886	TGTSSDV GGYNSV S	11 59	DVT KRP S	11 96	CFSYA GSRF	12 66
00 1S - F0 3	Fzd 5	GTFSS YAIS	29 5	GRIIPI FGTA NYA	49 9	CARVIFSTV TTTNDIW	939	TRSSGSI ASNYVQ	11 60	END KRP S	12 02	CQSYD YDHR WVF	14 30
00 4S - E0 4	Fzd 5	YTFSG YYLH	37 4	GTVT PILGT ANYA	54 9	CARVDGSG YYGIDYW	933	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - A0 6	Fzd 5	GSFS NYAIS	27 8	GRIIPI LGSA NYA	53 0	CARTYLKA FDIW	930	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - F0 4	Fzd 5	YTFTN NFMH	38 3	GRIN PNSG GTNY A	53 7	CARDRFDN WFDPW	788	RASQGI SALA	10 76	AAS TLQ S	11 79	CQQS YNT WTF	13 51
00 1S - C0 3	Fzd 5	GTFSS YAIS	29 5	GRIIPI LGIAN YA	52 9	CAREGRSR VYGGNSFD YW	808	RSSQSLL RRNGHN YVD	11 39	MG SNR AP	12 38	CMHG LHPP TF	12 79
00 3S -	Fzd 1	YIFTD YYMH	36 8	GRIIPI FGTA NYA	49 9	CARMSSDY YDSSGYR RGMDVW	895	RASQGI NNLN	10 72	GAS TLQ S	12 15	CQQA DSFPP TF	13 12

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
A0 1													
00 3S - E0 1	Fzd 1	YIFTD YYMH	36 8	GGIPI FGTA NYA	49 9	CARAWKG LWFGEGTF DYW	761	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - F0 1	Fzd 1	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARLAFDI W	885	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - A0 2	Fzd 1	YTFTG YYMH	37 9	GWIN AGNG NTTY A	55 8	CAKDRGN YGDYLDY W	707	RASQSIG NYLA	10 74	EVS SVQ G	12 04	CQQS YSTPL AF	13 70
00 3S - C0 2	Fzd 1	FTFSN SDM N	21 4	ALISY DGSH TYA	45 4	CTGRSRIG WFDPW	101 5	RASQSIG RWLA	10 84	AAS RLQ S	11 71	CQQG FNFP LTF	13 25
00 3S - E0 2	Fzd 1	GTFSS YTIS	29 6	GGIPI SGKT DYA	50 5	CARARGG DSPLSL	749	RASQSIG NNLN	10 72	TAS SLQ S	12 58	CLQDY SYPY TF	12 74
00 3S - F0 2	Fzd 1	GTFRS YAIN	29 2	GGIPI FGTA NYA	49 9	CARGGWR PDYYGSGS YYSFDYW	840	RASQSVS SDLA	11 15	GAS TRA T	12 17	CQQY ETWP VLTF	14 05
00 3S - G 02	Fzd 1	FTFGT YWVT	19 6	SGITG SGGR TFYA	61 6	CARMKDW FGAFDIW	894	RASESVS SSSFA	10 56	GAS TRA T	12 17	CQQY NNWP PNYTF	14 20
00 3S - C0 3	Fzd 1	FTFSR YAMS	22 0	SYISG DSGY TNYA	65 8	CARGLVIA TNWFDPW	849	QANQDI SNYLN	10 38	AAS SLQ S	11 75	CQQT YNPP R TF	13 89
00 3S - D0 3	Fzd 1	YTFTS YYMH	39 2	GWIN TYNG NTNY P	56 7	CAESLTSTA DW	691	RASQSIG NNLN	10 72	AAS SLQ R	11 74	CQQS YSTP LTF	13 68
00 3S - E0 3	Fzd 1	YIFTD YYMH	36 8	GWV NPTT GNTG YA	58 6	CARNVEGA TSFPEFDY W	898	RASQSIG NNLN	10 72	SAS NLQ S	12 52	CQQS YSPPP YTF	13 64
00 3S -	Fzd 1	GTFSS YAIS	29 5	GGIPI FGTA NYA	49 9	CAKDIGSS WYYYMDV W	701	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
H03													
003S-A04	Fzd1	FTFGTYWVT	196	SGITGSGGRTFYA	616	CARMKDWFGAFDIW	894	RTSERSSISSFA	1148	GAS TRAT	1217	CQQYNNWPRNYTF	1420
003S-C04	Fzd1	FAVSSSYMS	168	ASIWFDSNQDYA	463	CAPNESGNVDYW	733	RASQGISNNLN	1072	KAS SLE N	1225	CQQSYSTPH TF	1369
003S-D04	Fzd1	FTFSSYAMH	227	SAISGSGGSTYYA	600	CARDHGSSWYQNTDAFDIW	774	QASQDIGNYLN	1042	DVS NLE R	1195	CQHLNSYPPGDTF	1304
003S-G04	Fzd1	FRFISHPIH	177	GRVIPILGVTNYA	545	CASSSDYGDYLKEPNYGMDVW	966	RASQGIS SYLN	1098	AAS SLQ S	1175	CQQSYSTPL TF	1372
003S-D05	Fzd2	FTFSNYAMT	216	SAIGTGGGTYYA	595	CATAYRRPGGLDVW	969	RSSQSLLHSDGKTYLY	1134	LGS NRA S	1237	CMQNTHWPLTR	1293
003S-E05	Fzd2	FTFSSYTMS	236	GRIKSKANGTTDYA	535	CARGSSSWYDW	863	KSSQSLLHSDGKTYLY	1036	LGS NRA S	1237	CMQNTHWPLTR	1293
003S-A06	Fzd2	FTFADYGMH	188	SYISSGSYTIYYS	659	CARGTFDWLLSPSYDYW	865	RASQGISNNLN	1072	AAS RLES	1170	CQQSYSTPL TF	1372
003S-C06	Fzd2	FTFSNYGMH	217	SAISNSGGSTYYA	601	CTSSFLTGSQPSGYW	1018	RASQDIS SYLA	1065	AAS SLQ S	1175	CQQSYRTPL TF	1353
003S-G06	Fzd2	FTFSDYGMH	207	SSTSGSGGN SKYS	642	CARHNPGYMGYYYGMDVW	877	RASQSVS SNLA	1116	DAS NRA T	1188	CQHR TSWPL TF	1307
003S-H06	Fzd2	GTFSSYTIS	296	GLVDPEDGETIYA	520	CTILPAAAA GTYYYYGMDVW	1012	RASQRV GNNLA	1083	DAS IRAT	1184	CQQYKDWP TF	1415
003S-	Fzd2	FTFSDHYMS	205	SSITRTPSG	639	CARDGGYW	768	RASQSVGSYLA	1109	GSS NRA A	1221	CQQYGTSLL TF	1414

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
B07				GTTE YA									
00 3S - D0 7	Fzd 2	YTFTN NFMH	38 3	GIINP SGGS TSYA	51 3	CARATSLG RRYCSSTSC YPRDAFDI W	759	QASQGIS NNLN	10 49	LGS DRA S	12 33	CQQS YSTPF TF	13 68
00 3S - E0 7	Fzd 2	YTFTN NFMH	38 3	GWIN PNSG GTKY A	56 3	CARSVGEV GATMLGIG VWYWFDP W	926	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPF TF	13 68
00 3S - A0 8	Fzd 2	FTFSN YAMT	21 6	SAIGT GGGT YYA	59 5	CATAYRRP GGLDVW	969	RSSQSLL HSDGKTY LY	11 34	LGF NRA S	12 32	CMQN THWP LTR	12 93
00 3S - C0 8	Fzd 2	LTVST NFMH	32 4	AGIG WDST NIGY A	44 0	CARDLVAA RPSNWDY W	782	RASQGIR NDLG	10 69	GAS TLQ R	12 14	CQQS YSTPR VTF	13 74
00 3S - E0 8	Fzd 2	FTFR NSAM H	20 1	STISG SGGS TYYS	64 7	CARGGGYS SSW	829	RSSRSLL HSDGKTY LY	11 43	LGS NRA S	12 37	CMQS SHWP KTF	12 98
00 3S - G 09	Fzd 4	FTFD HNP MIN	19 4	SAIGA GGGT YYA	59 3	CASPTVTR R	960	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - C1 0	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYGGS GSYPDW	880	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - D1 0	Fzd 4	FNFGI YSMT	17 2	SYISG DSGY TNYA	65 8	CARVGPG GWFDPW	936	RASQGIS SYLA	10 76	AAS NLL G	11 67	CQQT YSTP WTF	13 96
00 3S - E1 0	Fzd 4	FTFSS YAM H	22 7	AGISA SGGS TYA	44 2	CARPSTTG TKAFDIW	901	RASQSIG SNLD	10 85	AAS TLET	11 78	CQQS YSVPD TF	13 80
00 3S - A1 1	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYGGS GSYPDW	880	RASQSIG ZYZN	11 03	ZAS SLQ S	12 64	CQQS YSTPL TF	13 72
00 3S -	Fzd 4	GTFSS YAIS	29 5	GRIIPI FGTV NYA	52 8	CARGARLD YW	820	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
G 11													
00 3S - H1 1	Fzd 4	YTFTG YMH	37 9	GGIPI FGTP HYA	50 2	CASTDPSS GLDYW	967	RASQSIG SNLD	10 85	DAS SLES	11 89	CQQSF IMPLT F	13 41
00 3S - C1 2	Fzd 4	GTFSS YAIS	29 5	GWIN PNSG GTNY A	56 4	CARGGSSD VR	838	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - F1 2	Fzd 4	FTFSS YAM H	22 7	SVIST SGDT VLYT	65 2	CARGGSSD VR	838	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - B0 1	Fzd 4	GTFSS YAIS	29 5	GIINP SGGS TSYA	51 3	CAKDGVV R	698	RAIQSISS YLN	10 54	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - C0 1	Fzd 4	FTFSN HYTS	21 3	STISS SGGR TFYA	65 0	CARASRID GGWPIIDH L	754	RASQDIR DELA	10 62	AAS TLQ S	11 79	CQQA DSFPL TF	13 11
00 4S - D0 1	Fzd 4	FTFTN YAMS	24 8	SAISG SGGS TYA	60 0	CARATGFG TVVFDYW	757	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - E0 1	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYGGS GSYPDW	880	ZACLRIS YLN	11 63	FAS SLQ S	12 05	CQQS YSTPL TF	13 72
00 4S - F0 1	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARDGVE	773	RASQGIS NWLA	10 73	DAS SLQ S	11 90	CQQS HITPY TF	13 44
00 4S - H0 1	Fzd 4	FTFSN YAM H	21 5	ALMS PDGTI IYYA	45 6	CAKGIVGD YGAFDIW	717	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - B0 2	Fzd 4	FTFSS YGM H	23 0	SSINN SSRTV FYA	63 0	CAKDHLAV ADAHGR	700	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S -	Fzd 4	FTFSS YAM H	22 7	AVISY DGSN EYYA	47 4	CAGGEVYE L	692	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E0 2													
00 4S - F0 2	Fzd 4	FTFST YAM H	24 2	AVISS DGNN KYYT	47 3	CAAPDVVV TADGYVW	685	RASQGIS SALA	10 76	AAS TLQ S	11 79	CQQA NTVPF TF	13 22
00 4S - G 02	Fzd 4	FTFA NYA MN	19 0	ALISY DGGT KYYA	45 3	CAKTLVTS HALHIW	728	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - H0 2	Fzd 4	FTFA NYA MH	18 9	ALISY DGGN KYYA	45 2	CAKTLVTS HALHIW	728	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 1S - E0 3	Fzd 5	GSFS GYVW H	27 6	GEIN HSGS TNYN	48 9	CARGRRLV RFTVTSF DIW	858	TGSSSNI GAGFGV H	11 58	SDR NRP S	12 55	CQSYD SSLRA SVF	14 29
00 1S - B0 5	Fzd 5	GTFSS YAIS	29 5	GGIPI LGIAN YA	50 4	CARIPKPR GYSYGDN GSW	883	RSSQSLL HSNGNT YLD	11 37	LGS DRT S	12 34	CMQS LQTPY TF	12 97
00 4S - A0 7	Fzd 6	GNFK NYGIT	27 1	GRIIP ALGT ANYA	52 5	CARQYCSG GSCYPDAF DIR	908	RASQDIR SALA	10 63	QAS SLIS	12 45	CQQS YSMP QTF	13 61
00 4S - B0 7	Fzd 6	FTFSS YSMN	23 3	GVISK DGDN KYYA	55 3	CASSRDGY NRLAFDIW	965	QASQDIR NYLN	10 43	AAS SLQ S	11 75	CQQSS RFTW F	13 47
00 4S - A0 8	Fzd 6	GTFSS YAIS	29 5	GRIPI LGIAN YA	52 9	CARDGGD YGMDVW	767	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - B0 8	Fzd 6	YTFTN NFMH	38 3	GRIN PNSG GTNY A	53 7	CASQNYG SGSYPGFD YW	961	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - D0 8	Fzd 6	YTFTY RYLH	39 4	GGIPI FGTA NYA	49 9	CATHDSSG YYSFDYW	973	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S -	Fzd 6	FSVSS NYM N	18 7	SAIGT GGGT YYA	59 5	CTTRTYDSS GYETQNY YMDVW	102 4	RSSRSL HSNGNT YLQ	11 44	LGS NRA S	12 37	CVQTT QSPLT F	14 34

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E08													
004S - G08	Fzd 6	FTFSD YYMS	208	AAISY DESN KFYA	423	CARSAVAG AFDIW	916	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - A09	Fzd 6	FTFRD YAMN	198	SGIS WNS GSIGY A	615	CARRSGYS GSVYYYG MDVW	913	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - B09	Fzd 6	FTFSS FGMH	221	AGIN WNG GSVV YA	441	CARGPSHQ HTFDIW	854	RASQGI SALA	1076	AAS SLQ S	1175	CQQS YSHTA FTF	1357
004S - C09	Fzd 6	YTFTN NFMH	383	GGFD PEDG ETIYA	492	CARVGRGY SFDYW	937	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - E09	Fzd 6	DTFS NYVIS	163	GRISA YNGY KSYA	538	CARSSGYV GWFDPW	924	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - F09	Fzd 6	FTFSN YYTS	218	SYISG AGGS TEYA	657	CARLPRRS GKGSAFDI W	888	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - H09	Fzd 6	GTFSS YTIS	296	GWM NPNS GNTG YA	583	CARVGATS AGGMDV W	935	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - C10	Fzd 6	YIFTD YYMH	368	GLVD PEDG ETIYA	520	CAHSDDFFS GLSFGDW	693	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S - D10	Fzd 6	FTFSN SDMN	214	SSIST SGGS TYYA	637	CARGSYW	864	RASQNIN NYLA	1081	RAS TLQ S	1249	CQQY SSYPY TI	1425
004S - E10	Fzd 6	TTLNK YAIS	365	GRITP VVG VNYA	539	CALSSSWY GGFDYW	731	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
004S -	Fzd 6	GTFFS DHY	269	ALVG YDGS	458	CNTGIPML YW	1003	RASQSI SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
F10				QQFY G									
00 4S - G 10	Fzd 6	FTFSD YYMS	20 8	SAISG SGFTY YA	59 9	CARVSRGF AFDYW	948	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - A1 1	Fzd 6	GTFSS YAIS	29 5	GRIIPI LGIAN YA	52 9	CARESVNN YYMDVW	813	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - C1 1	Fzd 6	FTFSS YAMH	22 7	ALTSY DGSK KFYA	45 7	CAKTGRGY AFDIW	726	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - E1 1	Fzd 6	FTFSS YNM N	23 2	GRIKS KANG GTTD YA	53 5	CAKAGQQ LDW	696	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - H1 1	Fzd 6	FTFSS SAM Q	24 9	GIIPI FGTA NYA	49 9	CATVQTN YDSSGRF S YRAHYFDY W	977	RASQSI RWLA	10 94	AAS SLQ S	11 75	CQQY VSYPL TF	14 26
00 4S - A1 2	Fzd 6	YTFTN NFMH	38 3	GRIN PNSG GTNY A	53 7	CARGQGYS SGWYRGD AFDIW	855	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - D1 2	Fzd 6	FAFD DYA MH	16 5	GFIRS KAYG GTTE YA	49 0	CAKDRGYS SGWYLDY W	708	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - H0 1	Fzd 7	FNFS YTMR	17 3	SVIYG GGNT NYA	65 3	CARGGSG GNLSYW	836	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - A0 2	Fzd 7	GTFSS YAIS	29 5	GMIIP FLGIT NYA	52 1	CTRPYDAF DIW	101 6	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - C0 2	Fzd 8	YTFAS YGM H	37 3	GWIN AGNG NTTY A	55 8	CARLSVWK WEQVTN WFDPW	890	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S -	Fzd 8	GTFTS YAIS	30 5	GWIN AGNG	55 7	CTTGLFPY RYNWNND AFDIW	102 2	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E0 2				NTKY S									
00 5S - A0 3	Fzd 8	GTFSS YAIS	29 5	GWM NPNS GNTG YA	58 3	CAKWHIG ATGNWFD PW	729	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - H0 3	Fzd 8	YTFTN NFMH	38 3	GGIFP IYGIS TYA	49 4	CARDRPTS SWYAFDY W	792	RASQGI NNLN	10 72	DAS TLQ T	11 93	CQQSF SAPITF	13 42
00 5S - F0 4	Fzd 8	FSFSS TAMS	18 1	SYISS SGSIT HYA	67 0	CARYGDY DYW	954	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - H0 4	Fzd 8	YTFTN NFMH	38 3	GWIN AGNG NTTY A	55 8	CARVATGN AFDIW	932	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - B0 5	Fzd 8	FTFSS YWM H	23 9	AGISG SGKT TFYA	44 4	CARGGLF DYW	831	QASQDI NYLN	10 46	KAS SLES	12 26	CQQS YSTPR TF	13 73
00 5S - F0 5	Fzd 8	FTFTS SAVQ	25 1	GWM NPNS GNTG YA	58 3	CARRTAVA GTIDYW	914	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - G 05	Fzd 8	GTFSS YAIS	29 5	GWIS PYNG NTNY A	57 3	CARGGWT NYGGNLDY W	841	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - H0 5	Fzd 8	YTFTS YYMH	39 2	GRIN PNSG GTNY A	53 7	CARVPDF WSGYLDY W	943	RASQGI RTLZ	10 75	AAS SLQ S	11 75	CQQT YSMPI TF	13 92
00 5S - D0 6	Fzd 8	YTFTY RYLH	39 4	GGIPI FGTA NYA	49 9	CARDSYPY GMDVW	800	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - F0 6	Fzd 8	GTFSS YAIS	29 5	GRVIP ILGVT NYA	54 5	CAREYLG SFDIW	815	RASQSV GSNLA	11 08	GAS SRA T	12 13	CQQY GSSPP FTF	14 09
00 5S -	Fzd 9	FTFTG SAVQ	24 7	GGILP IYGTT KYA	50 9	CARGARLY GFDYW	822	RASQSV RNLA	11 14	GAS TRA T	12 17	CQQR SNWPI TF	13 35

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
A07													
0055-BO7	Fzd9	FTFTS SAVQ	251	GWM NPNS GNTG YA	583	CARGRGQ QWLTGY GMDVW	857	RASQGIS SALA	1076	GAS TLQ S	1215	CLQDY NYPFT F	1272
0055-CO7	Fzd9	FTFSS YSMN	233	SYIEN DGSIT TYA	654	CARAPYYY GSGSLFRL DYW	748	RASQGIS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
0055-DO7	Fzd9	GTFN SYAIA	291	GGIPI FGTA NYA	499	CARAGSGY YNFDYW	740	RASQSIN RWLA	1090	AAS SLQ S	1175	CQQT YNIPIT F	1388
0055-FO7	Fzd9	FSFSS YGMH	182	AYINS RGS L MYA	483	CAKTKLPI W	727	RASQSIN RNYLG	1089	AAS SRV T	1176	CQQY DSWP PTF	1402
0055-GO7	Fzd9	GSFS GYAI N	274	GGIPI FGTA NYA	499	CATGYYD YFDYW	972	RASQGIS NNLN	1072	AAS SLQ S	1175	CQHY YNLPL TF	1309
0055-HO7	Fzd9	GTFT NNF MH	303	GLVD PEDG ETIYA	520	CARTYRIV GATPRYYY YGMDVW	931	RASQTIN NQLA	1125	KAS NLE T	1224	CQQA NSFPV TF	1318
0055-BO8	Fzd9	YIFTD YYMH	368	GWIN PNSG GTIYA	562	CARGPRDS GYPPGAF DIW	853	RASQGIS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
0055-DO8	Fzd9	FAFSS HWM H	166	SAIDG SGGS TYA	592	CARDRQLG WAHWYFD LW	794	RASQGIS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
0055-GO8	Fzd9	YTFTG YYMH	379	GWIN AGNG NTTY A	558	CARDRDY W	787	QTSQDIN NNLN	1053	KAS SLES	1226	CQQS YSSPP TF	1366
0055-CO9	Fzd9	FTFSS YGMH	230	SAIGT GGGT YYA	595	CALLVGAA RGISYYYY GMDVW	730	QASQDIS NYLN	1046	AAS TLQ S	1179	CLQHK SFPTF	1276
0055-	Fzd9	YTFTS YAM H	389	GWIN AGNG	558	CARDRPYS SGWYYPAF DIW	793	RASQSVS SNQLA	1117	GAS TRA T	1217	CQQR YNWP PSITF	1339

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
D09				NTTYA									
005S-E09	Fzd9	FNLR RYNM N	175	SRISN SGSLV YYA	627	CARDADSS GYRYDAF DIW	762	RASQSVS SNLA	1116	DAS NRA T	1188	CQQR NNWL YTF	1334
005S-A10	Fzd9	YTFTD YYMH	376	GIINP SGGS TSYA	513	CARHVGYS GTNNWF DPW	878	RASQSVS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
005S-D10	Fzd9	YTFTS YYMH	392	GWM SPNS ANTG YA	583	CARGGPIH YYYYYMD VW	834	RASQGIS NNLN	1072	AAS TLQ S	1179	CQQT NLFPY TF	1385
005S-H10	Fzd9	GAFS TSSIS	265	GRIIP VLGT ANYA	534	CAKGGWR SSFDPW	715	RASQSVS SNLA	1116	GAS TRA T	1217	CQQY NSWP LTF	1421
005S-B11	Fzd9	YTFTS YDIN	390	GGFD PEDG ETIYA	492	CAKAGDW GLYGM DVW	695	RASQSVS RWLA	1094	AAS SLQ S	1175	CQQT NTFPF TF	1386
005S-C11	Fzd9	FTFTG SAVQ	247	GGILP IYGT KYA	509	CARGARLY GFDYW	822	RASQSVS RKLA	1113	GAS TRA T	1217	CQQR SNWPI TF	1335
005S-D11	Fzd9	YTFTN NFMH	383	GWIN PNSG DTKF A	561	CAREANYD ILTG YIRPD AFDIW	806	RASQSLR SKLA	1106	GAS TRA T	1217	CQQY ANSP WTF	1401
005S-E11	Fzd9	GTFSS YAIS	295	GWIN AGNG NTKY S	557	CTTTEYSSS PDYYYGM DVW	1025	QASQDIS NYLN	1046	GAS TLQ S	1215	CQQLS RYP SLF	1331
005S-G11	Fzd9	GTFT RNSIS	304	GGIPI FGTA NYA	499	CARSSDLRI FDYW	922	RASQSVS SNLA	1116	GAS NRP T	1209	CQQY GSSPY TF	1413
005S-H11	Fzd10	YTFAS YDIH	372	GWIN AGNG NTTY A	558	CARDGIW DIFDYW	769	RASQSVS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
005S-	Fzd10	YIFTD YYMH	368	GVIFP VYPT PDYA	551	CARGGSTG YGM DVW	839	RASQSV GRWMA	1107	AAS SLQ S	1175	CQQA NTFPF TF	1321

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E1 2													
00 5S - F1 2	Fzd 10	GTFSS YAIS	29 5	GRIVP IVDV VKYA	54 1	CARDTCSS TSCSPDYW	801	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 6S - A0 1	Fzd 10	FTFSS YSMN	23 3	SAIGT GGGT YYA	59 5	CAREGW GESPF GM DVW	810	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 6S - F0 1	Fzd 10	YTFTR YAVH	38 5	GWIS TFND NTNY A	57 6	CASPTG MT TNFDYW	959	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 6S - H0 1	Fzd 10	YIFTD YMH	36 8	GGIPI FGTA NYA	49 9	CAKGS YYY DSSGY W DAFDIW	723	RASQGI NNLN	10 72	AAS NLE T	11 66	CQQT SSTPL TF	13 87
00 6S - A0 2	Fzd 10	YIFTD YMH	36 8	GGIIP LFGTT DYA	50 7	CARDIT GA DGMDVW	775	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 6S - D0 2	Fzd 10	GTFSS YAIS	29 5	GRIIP TVGT ANYA	53 3	CARDVCS G GSCSPD V W	802	RASQGI NNLN	10 72	DAS SLES	11 89	CQQT YNTPR TF	13 90
00 6S - E0 2	Fzd 10	FTFTS SATQ	25 0	GGIPI FGTA NYA	49 9	CARDGSS G WYSPNA F DIW	770	RASQGI NNLN	10 72	AAS SLQ S	11 75	CLQH NGYPI TF	12 77
00 6S - H0 2	Fzd 10	FTFR MYG MH	20 0	SRISP DGRT TTYA	62 8	CARSPRW YDAFDIW	920	RSSQSLL HSNGYN YLD	11 38	RVS SRF S	12 51	CMQG THWP PTF	12 88
00 6S - A0 3	Fzd 10	YIFTD YMH	36 8	GWIN AGNG NTTY A	55 8	CARDPIM F GDQPGW F DPW	784	RASESV S SNLA	10 55	GAS SRA T	12 13	CQQY NKSPS F	14 19
00 6S - B0 3	Fzd 10	GTFSS YAIS	29 5	GWIN AGNG NTKY A	55 6	CAREGYD F WSGPYAF DIW	811	RASQTIS RYLN	11 26	EVS SLQ G	12 03	CQQS YSTP WTF	13 78
00 6S -	Fzd 10	GTFSS NVIS	29 3	GGIPI FGTA NYA	49 9	CARGGY Y GMDVW	843	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
C03													
014S - B01	Fzd 1	YIFTD YYMH	36 8	GGIPI FGTA NYA	49 9	CARMSSDY YDSSGYR RGMDVW	895	RASQGIS NNLN	10 72	GAS TLQ S	12 15	CQQA DSFPP TF	13 12
014S - D01	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYYGS GSYPDW	880	RASQGIS SHZN	10 96	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
014S - E01	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYYGS GSYPDW	880	RASQSIZ YZZN	11 05	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
014S - G01	Fzd 4	GTFSS YAIS	29 5	GWM NPNN GNTT YA	58 1	CARHYYGS GNYRDW	879	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPF TF	13 68
014S - A02	Fzd 4	FTFSS NAM H	22 3	SGISG SGGS TYA	60 8	CAKPGIAA AGTNNWF DPW	725	RASQGIS SALA	10 76	GAS TVE S	12 18	CQQS YSTPR TF	13 73
014S - B02	Fzd 4	FTFSS YAM H	22 7	SGISG SGSST YYA	61 1	CARPSTTSF GMDVW	902	RASQSVS SNLA	11 16	GAS TRA T	12 17	CQQY DTPLR TF	14 03
014S - C02	Fzd 5	YTFTS YYMH	39 2	GRIN PNSG GTNY A	53 7	CARVPDF WSGYLDY W	943	RASQGIS SALA	10 76	AAS SLQ S	11 75	CQQT YSMPI TF	13 92
014S - D02	Fzd 5	GTFST YAIS	29 9	GIINP SGGS TSYA	51 3	CARAKGSG WYVGSFA DIW	744	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
014S - E02	Fzd 5	FTFSD SYMS	20 6	GFIRS KAYG GTTE YA	49 0	CARATQEL LLPYGMDV W	758	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
014S - F02	Fzd 5	YTFTS YYMH	39 2	GRIN PNSG GTNY A	53 7	CARVPDF WSGYLDY W	943	RASQGV STZLS	10 79	AAS SLQ S	11 75	CQQT YSMPI TF	13 92
014S -	Fzd 6	YTFTS YYMN	39 2	GIISP SGGS TSYA	51 6	CARWGDY GDLYYFDY W	951	RASQGIS SALA	10 76	ATS TLQ S	11 83	CQQV NSYPP TF	13 99

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
G 02													
01 4S - H0 2	Fzd 6	YIFTD YMH	36 8	GRIN PNSG GTNY A	53 7	CARARSSG WTDADFIDW	751	RASQSVS SWLA	11 20	AAS TLQ T	11 80	CQQS YSTPT F	13 76
01 4S - A0 3	Fzd 6	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYGSG SYPDW	880	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - B0 3	Fzd 6	FTFSS YNM N	23 2	GRIKS KANG GTDT YA	53 5	CARAGDSP DYW	739	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - E0 3	Fzd 8	GTFSS YAIS	29 5	GWIS PYNG YTKY A	57 4	CARAMWS YGQQNAFDIW	745	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - G 03	Fzd 8	FTFTS SAVQ	25 1	GWM NPNS GNTG YA	58 3	CARRTAVA GTIDYW	914	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - H0 3	Fzd 8	YTFTS SAIH	38 7	GRIN PNSG GTNY A	53 7	CARVKWEL AIDYW	940	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - B0 4	Fzd 8	YIFTD YMH	36 8	GWM NPNS GNTG YA	58 3	CARGGSRY DFWSGHW YFDLW	837	RASQGIS NYLA	10 74	AAS SLQ S	11 75	CQQS YSTPF TF	13 68
01 4S - E0 4	Fzd 8	YTFTG YMH	37 9	GRIN PNSG GTNY A	53 7	CARDVPLK VTRGVAYG MDVW	804	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - F0 4	Fzd 8	YSFTT YGM N	37 1	GWIN AGNG NTTY A	55 8	CARAAAGS YGGGYW	736	RASQGIS NNLN	10 72	EAS SVA S	11 97	CQQS YTSTP LNSF	13 81
01 4S - G 04	Fzd 8	FTFSS YGMS	23 1	SAISG SGGS TYA	60 0	CARDLTPF TQQQLVLG LL	780	RASQSVS GYLA	11 12	GAS TRA A	12 16	CQQY NYWP PAF	14 23
01 4S -	Fzd 8	FTFTS SAVQ	25 1	GRIVP AIGFT QYA	54 0	CARSGYNR RGYFDYW	919	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
H04													
014S-A05	Fzd8	GTFSSY AIS	295	GGIPIFGTANYA	499	CARVTLGASVDAFDIW	949	RASQGISNNLN	1072	DASLES	1189	CLQHNSLPFTF	1278
014S-B05	Fzd8	GTFSSY AIS	295	GWVSPNTGNTVYA	587	CTTDRRYS TYFDLW	1021	RASQSVSNLA	1116	GVSNRAT	1223	CQQYNIWPRTF	1418
014S-C05	Fzd8	YTFAS YGMH	373	GWINAGNGNTTYA	558	CARLSVWKWEQVTN WFDPW	890	RASQSSISYLN	1098	AASSLQS	1175	CQQSYSTPLTF	1372
014S-D05	Fzd8	GTFTSY AIS	305	GWINAGNGNTKYS	557	CTTGLFPYRYNWNND AFDIW	1022	RASQSSISYLN	1098	AASSLQS	1175	CQQSYSTPLTF	1372
014S-F05	Fzd9	FTFTG SAVQ	247	GGILPIYGTTKYA	509	CARGARLYGCDYW	821	RASQZVSRZZA	1127	GAS TRAT	1217	CQQR SNWPITF	1335
014S-G05	Fzd9	FTFSS SWMH	226	SAIGTGGGTYYA	595	CARKVKGYCSGGSCYGYW	884	RVSQGIS SALA	1151	AASSLQS	1175	CQQTF SVPWTF	1384
014S-H05	Fzd9	FTFSN YAMT	216	STISGSGVSTFYA	648	CARHGRIADIW	876	RASQSSISYLN	1098	AASSLQS	1175	CQQSYSTPLTF	1372
014S-A06	Fzd9	FTFZZ SZVQ	254	GGILPIYGTTKYA	509	CARGARLYGFDYW	822	RASQSVSRNLA	1114	GAS TRAT	1217	CQQR SNWPITF	1335
014S-B06	Fzd9	FTFSS YSMN	233	SYIENDGSITTYA	654	CARAPYYY GSGSLFRLDYW	748	RASQSSISYLN	1098	AASSLQS	1175	CQQSYSTPLTF	1372
014S-C06	Fzd10	FTFTG SAVQ	247	GGILPIYGTTKYA	509	CARGARLYGFDYW	822	RASQSVSRNLA	1114	GAS TRAT	1217	CQQR SNWPITF	1335
014S-	Fzd10	FTFSR YAMH	219	SGIGVGGGTYYA	605	CARDAYN WFDPR	763	RASQSSISRYLN	1095	AASSLQS	1175	CQQR YSTPLTF	1340

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
D06													
014S-F06	Fzd10	YIFTDYMH	368	GVIFPVYPTPDYA	551	CARGGSTGYGMDVW	839	RASQSVGRWMA	1107	AASLQS	1175	CQQA NTFPFTF	1321
014S-G06	Fzd10	FTFSSYAMH	227	SAIGAGGGTYA	593	CARDAYNWFDPW	764	RASQSYSLN	1098	AASLQS	1175	CQQSYSTPLTF	1372
014S-H06	Fzd10	FTFSSYDMN	229	SAIGTGGTYA	595	CARDAYNWFDPW	764	RASQSYSLN	1098	AASLQS	1175	CQQSYSTPLTF	1372
014S-A07	Fzd10	FTFSNAQMS	210	SAIGTGGTYA	595	CAREGSYDWFYDLW	809	RASQNIGSRLA	1080	GASNRAS	1208	CQQYNHWPPLFTF	1417
017S-E08	Fzd8	IIFSPNDMG	313	ALISSGGSTSYA	450	CHFGVASVGLNYW	980						
017S-H08	Fzd8	RTFSSFVMG	346	AAVSASGGYTWAYA	432	CNLAQRGETYW	998						
017S-A09	Fzd8	LAFNGYTMG	317	AAISWSDNTYYA	414	CAAGFPTVFVVDGEYDYW	680						
017S-B09	Fzd8	FTLDY Y AIS	255	ADITSGGSTNYA	437	CNAVTYNGYTIW	994						
017S-C09	Fzd8	LTFSDYTVG	319	ASSTGGGVFENYA	464	CNAVTYNGYTIW	994						
018S-D06	Fzd4	RIFSSYAQA	330	PRIPSDSTFYA	590	CEVHNFGATYW	979						
018S-	Fzd4	RTFSNYVMG	344	AVISRSSGN TYYT	472	CNAVSTDWTTDYW	992						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
E06													
018S-F06	Fzd4	RTFSTYGMG	349	AAISWSDNTYYA	414	CNSFPLRLHDW	1002						
018S-G06	Fzd5	LAIDDYVMV	318	SYISTSDGSTYYA	673	CNAVTYNGYSIW	993						
018S-H06	Fzd5	LAFNGYTMG	317	AQISWTG GSTDYA	460	CNADYGTWYGIGW	985						
018S-A07	Fzd5	LAFNGYTMG	317	AAISWMSNTYYA	412	CNMGLGYSEYRPLGYW	999						
018S-B07	Fzd5	SAFSNYAMG	355	AAITWSGARTYYA	426	CNAVWKF GTTHW	995						
018S-C07	Fzd7	LTIDDDYVV	323	SYISAGDGF TYA	656	CNAVTYNGYTIW	994						
017S-F09	Fzd4	GSFSGYYWS	277	GEINHSGSTNYN	489	CARDLRFYSSSWRRVGM DVW	778	RSSRSLHTSGYNYLD	1147	LGSNRAS	1237	CMQGTRWPTF	1290
017S-G09	Fzd4	YTITTYAIIH	396	GWINADTGDTAYS	555	CARGWTTISSLGVW	872	RSSRSLHTNGYNYLD	1146	LGSNRAS	1237	CMQALQTPLTF	1281
017S-H09	Fzd5	NIFRIYAIA	326	AALTQQRTTNYA	427	CNTVTYNA GCYKKYW	1004						
017S-A10	Fzd5	LAFNGYTMG	317	ASITWNGRYTYA	462	CNARLDAVYGH SRYDSW	988						
017S-	Fzd5	NFFS NYPLG	325	GAISR TGSGTFYA	484	CAAGVTGS WRYW	684						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
B1 0													
01 7S - C1 0	Fzd 8	RSFSN YRVA	33 5	AVSW SVGM TYA	47 9	CNAVTYN GYTIW	994						
01 7S - D1 0	Fzd 8	GTFG SYAV G	28 8	GLISR NAGN TLA	51 8	CNAVNGRL NYW	991						
01 7S - E1 0	Fzd 8	RTFSS YSLA	34 8	AAVS ASGA NTYY A	43 1	CAAPQSPN MYIRTDQL WWYKYW	687						
01 8S - D0 7	Fzd 1	RSFST YPMG	33 6	TVISG SGGS TYA	67 5	CAAGPTLP FRYW	683						
01 8S - E0 7	Fzd 1	RAFS NYA MG	32 8	AAIN WSG DSAY YA	40 6	CNARLSFA GGMGYW	989						
01 8S - F0 7	Fzd 1	IKSMF DMNF MG	31 4	AFITR GGTT RYG	43 8	CNAVSTD WTRDYW	992						
01 8S - G 07	Fzd 1	LTIDD YYMV	32 2	SYIGT SDGT TYA	65 5	CNAVTYN GYTIW	994						
01 8S - H0 7	Fzd 4	RVFSS YAQA	35 4	AGIAS DSTTF YA	43 9	CKVHNFGA TYW	983						
01 8S - A0 8	Fzd 4	RIFSS YAQA	33 0	ASIPS DGTTFYA	46 1	CKVHNFEA TYW	982						
01 8S - B0 8	Fzd 4	LTFST YGM G	32 1	AAIN WSGR STVY A	40 7	CNSFPLRL HDW	100 2						
01 8S -	Fzd 4	RTLSS YVVG	35 1	ALISL SGAS TYA	44 9	CNAVSTD WTTDYW	992						

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
C08													
018S-DO8	Fzd5	IKSMFDMNFMG	314	AFITRGGTRYG	438	CNAVSTDWTRDYW	992						
018S-E08	Fzd5	RTDGMQAMG	338	GAITWSLGSIFYA	486	CNVLAQNDGDYRTYG	1007						
018S-F08	Fzd5	RTFSSFVMG	346	AAVSASGGYTWAYA	432	CNAVWKFGTTHW	995						
018S-G08	Fzd5	RTFSSFVMG	346	AAVSASGGYTWAYA	432	CNAVCKFGTTHW	990						
018S-H08	Fzd5	RTFSSFVMG	346	AAVTASGGYAWYA	434	CNAVWKFGTTHW	995						
018S-A09	Fzd8	ITFSFNSVG	316	AVFIAGYGAYYA	470	CNGVTYNGYTIW	997						
018S-B09	Fzd8	HDFSSTYGVG	310	ATISWGGTNIA	468	CAAQKPYYNGHFIYADDKHYDHW	688						
018S-C09	Fzd8	ITFGFDSVG	315	AVFNAGYRAYYA	471	CNAVTYNGYTIW	994						
018S-DO9	Fzd8	RTFSWYSMG	350	AAVSWSGVSTYYP	433	CNAVTYNGYTIW	994						
018S-E09	Fzd8	ITFSFNSVG	316	AVFIAGYGAYYA	470	CIGVTYNGYTIG	981						
018S-	Fzd8	RTDGMQAMG	338	GAITWSLGSIFYA	485	CNVLAQNDGDYRTYW	1008						

Cl on e ID	Init ial Bin ding	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
F09													
018S - G09	Fzd8	HDFS STYG VG	311	AAIS WRGT NIA	413	CAAQKPYY NGHFYAD DKHYDHW	688						
021S - A01	Fzd8	DSVS SNSA AWN	160	GRAY YKSR WYYD YA	524	CVRDLRPS GDLNFDY W	1029	RASQSIG SSLH	1087	YAS QSV S	1260	CHQS GRVP VTF	1268
021S - C01	Fzd1	GSISS GGYS WS	283	GSIYH SGSTY YN	547	CARFYYDIL NGYSYFDY W	817	RSSRLL DTDDGN TYLD	1142	TLS HRA S	1259	CMQSI QLPW TF	1295
021S - D01	Fzd1	FTFSS YGM H	230	AVISY DGSN KYA	475	CAKGSVFG LKAGGYAD YW	721	RSSQSLV HSDGNT YLS	1140	KISN RFS	1230	CMQA TQFP TF	1283
021S - E02	Fzd8	YTFTS YGIS	391	GWIS AYNG NTNY A	570	CARDGTPF YSGSYG W	772	QGDSLRT YYAS	1052	GKN NRP S	1219	CNSRD NSGK HKVF	1300
021S - G02	Fzd8	DSVS SNSG AWN	162	GRTY YRSKY YNGY A	544	PRLDYW	1034	RSSQSLL DSDDGN TYLD	1133	MLS SRA P	1240	CMQR LEFP TF	1294
021S - A03	Fzd8	DSVS SNSA AWN	160	GRTY YRSK WYN DYA	542	CARSQATG ERFDYW	921	RSSQNIF QSLN	1131	SAS SLQ S	1254	CQQS YNSPI TF	1349
022S - H06	Fzd4	FTFSS YAMS	228	SVIST SGGT VLYT	652	CADGSGTS HR	690	RASQSIS SYLN	1098	AAS SLQ S	1175	CQQS YSTPL TF	1372
022S - A11	Fzd10	YIFTD YYMH	368	GGIFP IFGTA NYA	493	CAKGSYYY DNSGYW DAFDIW	722	RASQGIS NNIN	1071	AAS NLE T	1166	CQQT YSIPFT F	1391
OMP-18R5		GFTFS HYTLS	270	VISGD GSYT YYAD SVKG	677	NFIKYVFA N	1033	SGDKLGK KYAS or SGDNIGS FYVH	1152 or 1153	EKD NRP SG or DKS NRP SG	1200 or 1201	SSFAG NSLE or QSYA NTLSL	1435 or 1436

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
02 7S - HO 2	Fzd 5	FTFSS YAMS	22 8	SAISG SGGS TYA	60 0	CAKGLWG PLLNW	718	RASQSVS SNYLS	11 18	GAS SRA P	12 12	CQQR TNWP PRVTF	13 37
02 7S - BO 3	Fzd 8	DSVS SNSA TWN	16 1	GRTY YRSK WYSD YA	54 3	CTRGNWN VGLANW	101 4	SGTSSNI GAGYDV H	11 57	GNN NRP S	12 19	CSAW DDNL NGVV F	14 32
02 7S - EO 1	Fzd 5	RSFSI YNTA	33 4	AAIS WSG GSTY YA	41 8	CNVITIVRG MGPRAYW	100 6						
00 4S - DO 5	Fzd 5	LTFSI YAM H	32 0	SAISG DGAL TYA	59 7	CARGVYPY SSKHKPSY YYYGMDV W	870	QASQDIS NYLN	10 46	AAS SLQ S	11 75	CQQS YSTPL FTF	13 71
00 4S - DO 4	Fzd 5	YDFTT YGIH	36 7	GGVI PAFG ATDY S	51 1	CARGYYYG MDVW	874	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - BO 5	Fzd 5	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CASGLGYF DYW	957	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - G 03	Fzd 5	YTFTN NFMH	38 3	GGIPI FGTP HYA	50 2	CARTLTTPP YYYGMDV W	929	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - FO 3	Fzd 5	FTFSN SDM N	21 4	SAIGT GGDT YYA	59 4	CTRDLYGG YRDYW	101 3	KSSQSLL HSDGYTY LY	10 36	LGS NRA S	12 37	CMQG LQTP WTF	12 86
00 4S - CO 4	Fzd 5	YIFTG YYMH	36 9	GRIN PNSG GTNY A	53 7	CARGGEYS SGWTYYYY YGMDVW	827	RATQTIS TYLN	11 29	AAS RLQ S	11 71	CQQY YSYP WTS	14 27
00 4S - BO 6	Fzd 5	YTFTY RYLH	39 4	GMIN PIGGS INYA	52 2	CARDVMD VW	803	RASQGIS NNLN	10 72	AAS ALQ S	11 65	CQHL NNFPL TF	13 03
00 4S - FO 6	Fzd 5	FSVG SNYM T	18 6	SSISS GNSYI YYA	63 4	CARGPKT MWEDRPD YW	851	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 4S - A0 4	Fzd 5	FTFST YSMI	24 5	GFIRS KDYG GTTE YA	49 1	CARLTGGA VAGTHR DYW	892	RASQGIS NNLN	10 72	GAS SLQ S	12 11	CQQS HSSPR TF	13 46
00 4S - A0 5	Fzd 5	FTFSS YVMS	23 7	SAIGT GGGT YYA	59 5	CARGSSGY YVAW	862	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - F0 5	Fzd 5	FTFSN HYMS	21 2	AGVSI DANK KYA	44 7	CARDQND SWYRSD YW	785	RSSQSLL HSDGYT LY	11 35	LGS HRA S	12 35	CMQG LQTPH TF	12 85
00 3S - C0 1	Fzd 1	GTFSS YAIS	29 5	GRIN PNSG GTNY A	53 7	CARGSGYD FFDYGMD VW	861	RASQSIS NNLN	10 92	AAS SLQ S	11 75	CQQS YNTPF TF	13 50
00 3S - H0 1	Fzd 1	DTFS NYVL S	16 4	GLVD PEDG ETIYA	52 0	CAKASTPM VQGAPD YW	697	RASQSIG SNLD	10 85	AAS TLQ S	11 79	CQQN YATPR TF	13 33
00 3S - H0 2	Fzd 1	GTFN RYAIT	28 9	GGIPI FGTA NYA	49 9	CATTQGVY SSSWYGG GRAFDIW	976	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - H0 4	Fzd 1	YTFTY RYLH	39 4	GRIN PNSG GTNY A	53 7	CWGGSY GDYW	103 0	RASQGIS NNLN	10 72	AAS SLQ S	11 75	CQQA NSFPI TF	13 16
00 3S - A0 5	Fzd 2	FTFSS YAMH	22 7	SSISW NSGR VDYA	63 8	CARGSGIA ASGSYW	860	TSSQSLL HSDGKY LY	11 62	LGS NRA S	12 37	CMQG THWP YTF	12 89
00 3S - B0 5	Fzd 2	FTFSN AWMS	21 1	STIAG SGGR TYYS	64 3	CAKDSIGR RGRGAPQ PYYYYGM DVW	709	KSSQSLL HSDGKY LY	10 36	LGS NRA S	12 37	CMQS LQSPL TF	12 96
00 3S - F0 5	Fzd 2	FSFST YTMS	18 4	SRING DGSS TRYA	62 4	CARAIVGA TGLNRFKA FDIW	743	KSSQSLL HSDGKY LY	10 36	LGS NRA S	12 37	CMQN THWP LTR	12 93
00 3S - G 05	Fzd 2	STFTN AWMS	36 3	SAIGT GGGT YYA	59 5	CARDRVTL RGGYSYGT DAFDIW	796	RSSRSLL HSNGNT YLR	11 45	LAS RRA S	12 31	CIQNT HWPL TR	12 70

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 3S - H0 5	Fzd 2	FTLST YNM N	25 7	SRINY DGSAT TYA	62 6	CARDRDIV VVPAQRG EGGFDPW	786	KSSQSLL HSDGKTY LY	10 36	MG SYR AS	12 39	CMQG THWP LTF	12 87
00 3S - A0 7	Fzd 2	FTFSS YAMS	22 8	SAISG SGGS TYA	60 0	CAKGGRD GYKGYFDY W	714	KSSQSLL HSDGKTY LY	10 36	LGS NRA S	12 37	CMQN THWP LTL	12 92
00 3S - C0 7	Fzd 2	FSFRS YSMS	17 8	SAIGT GGGT YYA	59 5	CTTTVTTS W	102 6	RTSQSVS SNLA	11 50	DAS NRA S	11 87	CQQY GSSPY NF	14 12
00 3S - F0 7	Fzd 2	FSFSS YGMS	18 3	SHISS GGAT IDYA	61 9	CARDGGY W	768	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - G 07	Fzd 2	FTFSS YWM H	23 9	SYISG DSGY TNYA	65 8	CARDNGYC SGGSCYAT YYGMDVR	783	RASQAIS SYLA	10 60	KAS TLD T	12 28	CQQA DTFPF TF	13 13
00 3S - B0 8	Fzd 2	FTFSS ZZMH	24 0	AVISY DGSN RZYA	47 6	CARSYYDS SGYPRKDA FDIW	927	KSSQSLL HSDGKTY LY	10 36	LGS NRA S	12 37	CMQT LKAPL TF	12 99
00 3S - F0 8	Fzd 2	ZSVSS NYMS	40 1	SRINS DGSTI SYA	62 5	CARARLLG GYTTPDR MDVW	750	RSSQYLS SAYLA	11 41	GAS SRA T	12 13	CQQY GSSPT F	14 11
00 3S - H0 8	Fzd 2	FTFN RHALL S	19 7	ALISS NGDH KYYT	45 1	CARDLMV GRNKLDY W	777	QASQGIS NNLN	10 49	AAS SLQ S	11 75	CQQS YSTPA FTF	13 67
00 3S - A0 9	Fzd 2	FTFSS SNM N	22 5	SGISG SGSST YYA	61 1	CARGRVW SSRDYW	859	RSSQSLL HSDGYTY LY	11 35	LGS NRA S	12 37	CMQG THWP LTF	12 87
00 3S - B0 9	Fzd 2	FNIRR ZNMZ	17 4	SAIGT GGGT YYA	59 5	CARGDSGS YRDYW	823	RSSESLL HSDGKTY LY	11 30	LGS NRA S	12 37	CTQTV QFPIT F	14 33
00 3S - C0 9	Fzd 2	FTFSS SAMH	22 4	SGISG SGTTT YYR	61 2	CARRLIAV AGAEFDP W	912	RASQGIS NNLN	10 72	SAS NLQ S	12 52	CQQS YSTP WTF	13 78

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 3S - F0 9	Fzd 4	FTFSN SDM N	21 4	GRIKS KAYG GTTE YA	53 6	CARQYYFD YW	909	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - H0 9	Fzd 4	FTFSS FGMH	22 1	SVISS GGSP YYA	65 1	CATASGDF DYW	968	RASQSIG SNLN	10 86	RAS TLES	12 48	CQQT YTTPR F	13 98
00 3S - A1 0	Fzd 4	FTFD DYA MH	19 1	AIVSY DGTY KYYS	44 8	CARQTRG GTDDGW	907	RASQSIG NNLN	10 72	YAS SLQ S	12 62	CQQS HSPPG TF	13 45
00 3S - B1 0	Fzd 4	FTFSS HSTH	22 2	SAISA SGDS TFYA	59 6	CARPVGA TAFDIW	900	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - G 10	Fzd 4	FTZSS YSMN	26 4	SYSSG NSGY TNYA	67 4	CARGVVGS GAFDIW	868	RASQSIV SYLN	11 04	DAS NLQ S	11 86	CQQG YSAP WTF	13 29
00 3S - B1 1	Fzd 4	FTFSD YYMS	20 8	SAIDG AGRT YYT	59 1	CARAIPGD YDYW	742	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - C1 1	Fzd 4	FTFTS YAM H	25 2	GGIPI FGIAN YA	49 6	CARTGRGY YGMDDVW	928	RASQSIG SNLD	10 85	AAS TLQ S	11 79	CQQS YSTPR TF	13 73
00 3S - D1 1	Fzd 4	FTFSS YSMS	23 4	SYISG DSGY TNYA	65 8	CARAGVAT IAFDYW	741	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - F1 1	Fzd 4	FTFD DYG MH	19 2	SAISG SGGS TYA	60 0	CTTPNYD SR	102 3	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 3S - E1 2	Fzd 4	GTFSS YAIS	29 5	GWIN AGNG NTTY A	55 8	CARHYGGS GSPDW	880	ZPZQTZZ SHLN	11 64	PAS SLQ S	12 42	CQQS YSTPL TF	13 72
00 4S - A0 1	Fzd 4	FTFST YGM H	24 4	SYISS SSSAI YYA	67 1	CARGGLDG PIDYR	830	RASQSIG NNLN	10 72	AAS TLQ S	11 79	CQQG NNFPF TF	13 26

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 4S - G 01	Fzd 4	FTVSS HSMG	26 0	SLVSF DGSK EHYA	62 1	CARLGSTP DYW	887	RASQGIS NNLN	10 72	AAS SLQ S	11 75	CQQY YTPY TF	14 28
00 4S - C0 2	Fzd 4	FTFSS YGM H	23 0	AVISY DGSN KYA	47 5	CASDPVTA ATR	956	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - D0 2	Fzd 4	FSFSS YGMS	18 3	SGISG SGRS TYA	61 0	CAKDGyw	699	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - A0 3	Fzd 4	FTFSS YAM H	22 7	SGIN WNG GSTG YA	60 6	CARPAGSA QNWFDP W	899	RASQGIS NNLN	10 72	DAS NLE T	11 85	CHQSY SIPRTF	12 69
00 4S - B0 3	Fzd 4	FSFSR YGMS	18 0	SGVG SGSG STZYA	61 7	CARDGSW	771	RASQDV DTWLA	10 66	DAS TLET	11 91	CQQG YNIP WTF	13 28
00 4S - C0 3	Fzd 4	YTFTS YAIS	38 8	GIINP SGGS TSYA	51 3	CARQIGWE LMPDIW	906	QASQDIS SYLN	10 47	AAS TLQ S	11 79	CQQA SFPLTF	13 15
00 4S - C0 5	Fzd 5	ZZZTD YYZQ	40 3	GGM NZNR GNTG YA	51 0	CANGSYA QHLW	732	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - G 05	Fzd 5	FTFSS YWM H	23 9	STISP SGLYI YQA	64 9	CAKDKVPY SYGPNFDY W	703	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - E0 6	Fzd 5	FFFSG YWM S	16 9	ANIK QDGS EKYY V	45 9	CARVFPLH DYW	934	QASQDIS NYLN	10 46	KAS SLES	12 26	CQQA NSFPY TF	13 19
00 4S - C0 6	Fzd 5	FPFST FSMN	17 6	AGIS WNS GTIDY A	44 6	CARSGPAA MVYYYYG MDVW	918	RSSQNV SYLA	11 32	GAS TRA T	12 17	CQHR ANWP QTF	13 05
00 4S - E0 7	Fzd 6	FTLSS HHM N	25 6	SAIGT GGGT YYA	59 5	CAAPDYW	686	RASQGIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 4S - F0 7	Fzd 6	FSFSK KYMT	17 9	SSIDG NGDH VFYA	62 9	CARPYYYD SSGYDPM GDYW	904	QASQDIT NYLN	10 48	KAS TLES	12 29	CQQS YSAPY TF	13 56
00 4S - C0 8	Fzd 6	FTVSS NYM N	26 1	SAIGT GGGT YYA	59 5	CAQGTYW	735	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - F0 8	Fzd 6	FTFD DYMM N	19 3	SAVS GNGG GTFY A	60 4	CARGGNY GSGDYW	833	RASQSIG ZWLA	11 02	EAS TLQ S	11 98	CQQT YTPPF TF	13 97
00 4S - G 09	Fzd 6	GTLN NHTL S	30 8	GRIPI FGTA NYA	52 6	CARDRRGY GMDVW	795	RASQAIS NSLA	10 58	DAS NLE T	11 85	CQQA YSFP WTF	13 24
00 4S - B1 0	Fzd 6	FTFSD YYMS	20 8	SGIN WNS AKIGY V	60 7	CARIGAGG AFDIW	881	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - H1 0	Fzd 6	FIFSD YYMS	17 0	AVITS GGTF KYA	47 7	CARNGIAA AEDYW	896	RASQSIG TYLS	11 01	GAS SLES	12 10	CQQS YSPPF TF	13 62
00 4S - B1 1	Fzd 6	FTFSS SWM H	22 6	SGIS WNS GSIGY A	61 5	CARYSSGG SLDYW	955	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - D1 1	Fzd 6	YZFZZ ZYM H	40 0	GRIN PNSG GTNY A	53 7	CARARSSG WTDAFDI W	751	RASQSVS SWLA	11 20	AAS TLQ T	11 80	CQQS YSTPT F	13 76
00 4S - F1 1	Fzd 6	FTFSS YAMS	22 8	SSISG GGRH TYA	63 2	CARPYSSS RQGDYW	903	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 4S - G 11	Fzd 6	YIFTD YYMH	36 8	GWIN PNSG GTNY A	56 4	CARDRPGF DPW	790	RASQSVS SYLA	11 21	GAS SRA T	12 13	CQQY AISYTF	14 00
00 4S - B1 2	Fzd 6	FTFSS YWIH	23 8	SYISG DSGY TNYA	65 8	CAKGIRWF DPW	716	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 4S - C1 2	Fzd 6	YIFTD YYMH	36 8	GWM NPNS GNTG YA	58 3	CASSHYAP GMDVW	962	RASQGIS SYLA	10 76	RTS TLES	12 50	CQQS YSTP WTF	13 78
00 4S - F1 2	Fzd 7	FTVG NNY MS	25 8	SSITT TSTLY A	64 0	CARGKEGR YSNYEAA W	844	RASQSIS SYLN	10 98	AAS TLQ T	11 80	CQQS YSIPFT F	13 58
00 5S - B0 1	Fzd 7	FTFRS YGM H	20 2	SLISG SGDN TNYA	62 0	CARREPLY SSRRGAFDI W	910	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - C0 1	Fzd 7	FTFSS YSMS	23 4	SAISG SGGS TYA	60 0	CTRTIVGAT PHYW	101 7	RASQGIS NNLN	10 72	KAS SLQ S	12 27	CQQS YSLPY TF	13 60
00 5S - F0 1	Fzd 7	FTVSS NYMS	26 2	SAISG SGAT TYA	59 8	CAKGAGY GSGSWQA AW	711	RASQSVS SSYLS	11 19	GAS SRA T	12 13	CQQR YKSYT F	13 38
00 5S - B0 2	Fzd 8	YSFTN YAM H	37 0	GRIIPI FGTA ZYA	52 7	CARGTFLE WLLTNYG MDVW	866	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - D0 2	Fzd 8	GTFSS YVIS	29 7	GWIG PHNG NTNY A	55 4	CATGWPR YYYGMDV W	971	RASQSVS SNLA	11 16	NTS NRA T	12 41	CQHY NNWP FTF	13 08
00 5S - G 02	Fzd 8	YTFTS YYMH	39 2	GIIPI FGTA ZYA	50 0	CARLPYYD FWSGYG GRTGFDY W	889	RASQSVS TNLA	11 22	DAS NRA T	11 88	CQQR SNWP PQITF	13 36
00 5S - H0 2	Fzd 8	YTFTY RYLH	39 4	GWIN AGNG NTTY A	55 8	CARASLYY DYVWGSY RHYFDY W	753	QASQDIS HYLN	10 44	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - B0 3	Fzd 8	GTFSS YAIS	29 5	GIINP SGGR TTYA	51 2	CATSFGGG WIVVDTSL WYW	975	RASQSIN SNLA	10 91	GAS SRA T	12 13	CQQY GSSPY TF	14 13
00 5S - C0 3	Fzd 8	GSFS GYAIS	27 5	GIIPI FGTA NYA	49 9	CRVDAFDI W	100 9	RASQSVS SSYLS	11 19	DTS NRA T	11 94	CQQY GSSPI TF	14 08

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 5S - E0 3	Fzd 8	FTFTS SAVQ	25 1	GGIPI FGTA NYA	49 9	CARSSGW QNRFAFDI W	923	RTSQSISS YLN	11 49	AAS TSQ S	11 81	CQQSF SSWTF	13 43
00 5S - F0 3	Fzd 8	YTFTY RYLH	39 4	GWIN AGNG NTKY S	55 7	CATDLPVR KGFTYYDIL TGSYGMD VW	970	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - B0 4	Fzd 8	YTFTN NFMH	38 3	GGIPI FGTA NHA	49 8	CARGLRYF DWPQGIY YYYGMDV W	848	QASHDI NIALN	10 39	AAS SLQ S	11 75	CQQS YSSPL TF	13 65
00 5S - C0 4	Fzd 8	YTFTS YMH	39 2	GRIN PNSG GTNY A	53 7	CARGGLLF DYW	831	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - D0 4	Fzd 8	FTFST YSMS	24 6	STIGT GGGT YYA	64 5	CARVGWL RFLDYW	938	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - G 04	Fzd 8	GTFSS YAIS	29 5	GWM SPSSG NAGY A	58 5	CARNNFLR AFDIW	897	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - A0 5	Fzd 8	FAFSS YAMS	16 7	SRIDT DGST TVYA	62 2	CARAPSYS SGWYVRW	747	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - C0 5	Fzd 8	YTFTY YAM H	39 5	GIINP SGGS TSYA	51 3	CARELLPM TTVTSPFI W	812	RASQGIS NNLN	10 72	RAS SLQ S	12 47	CQQA NSYPL TF	13 20
00 5S - E0 5	Fzd 8	GTFSS YAIS	29 5	GGIPI FGTA NYA	49 9	CAIRAFDI W	694	RASQSISS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - C0 6	Fzd 8	ZTFSZ YDM H	40 2	SSISS SSHY KYA	63 5	CARVRSKA VAGTLPKR LFDIW	947	RASQSVS SSYLS	11 19	AAS RRA T	11 72	CQQY SNWP FTF	14 24
00 5S - E0 6	Fzd 8	YTFTS YMH	39 2	GWM NPNS GNTG YA	58 3	CARGNPTS GHIVVPA ATFSDYW	850	QASQDIS NRLN	10 45	SAS RLQI	12 53	CQQS YRTPR TF	13 54

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 5S - G 06	Fzd 8	GTFSZ ZTIS	30 2	GWM NPDS GKTG YA	57 9	CARWAFPI PNAFDIW	950	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - H0 6	Fzd 8	YTFTN NFMH	38 3	GGIFP IYGIS TYA	49 4	CARDRPSS SWYAFDY W	791	RASQSIG NNLN	10 72	DAS TLQ T	11 93	CQQSF SAPITF	13 42
00 5S - A0 8	Fzd 9	GTFSZ YAIS	30 1	GGIPI FGTA NYA	49 9	CARGGLLR FGDGWG MGMDVW	832	RASQSIG SKSLA	10 97	GAS TRA T	12 17	CQQY GIAPT F	14 07
00 5S - C0 8	Fzd 9	YTFTD YHMH	37 5	GWIN AGNG NTTY A	55 8	CARASSWY LHYYYGM DVW	755	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - E0 8	Fzd 9	FIFSZ YAMS	17 1	SSISA AGAY KYA	63 1	CARRGYSS GWRDAFD IW	911	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - F0 8	Fzd 9	YTFTS YYMH	39 2	GWIN AGNG NTTY A	55 8	CAKDVNY W	710	QASQSIG NYLN	10 50	AAS SLQ S	11 75	CQQT YSTPT TF	13 95
00 5S - H0 8	Fzd 9	GTFSS YAIS	29 5	GRIPI LGTP NYA	53 1	CARDRLAF DYW	789	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - A0 9	Fzd 9	FAFSS HWMH	16 6	SAISV SGGT TFYA	60 2	CARWKGK LRGSPYYF DYW	952	RASQSIG SNLD	10 85	RAS TLQ S	12 49	CQQS YSTPS F	13 75
00 5S - F0 9	Fzd 9	FTFSI YGMH	20 9	SGIS WNS GNIG YA	61 4	CARGPLPT KIGGHY DVW	852	RASQSIG SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - B1 0	Fzd 9	FTFST XWMS	24 1	AVMY SGGT TYA	47 8	CARLSYYY DSSGPKGD AFDIW	891	RASQSIG NNLN	10 72	AAS SLQ S	11 75	CQQG NNFPL TF	13 27
00 5S - C1 0	Fzd 9	FSLSS YGMH	18 5	SSISS SSSYI YYA	63 6	CARSGMV KWLRSE FDYW	917	RASQDIG SFLA	10 61	AAS SLQ S	11 75	CQKY NRAPF TF	13 10

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 5S - E1 0	Fzd 9	FTFTS SAM Q	24 9	GVIN PGSG GTSY N	55 2	CARGYGDY VWGENYF DYW	873	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - F1 0	Fzd 9	YTLN YGIS	39 7	GWIS AYNG DTKY A	56 8	CARFDYFG GMDVW	816	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - G 10	Fzd 9	YTFTR YAVH	38 5	GGIIP FFNT VNYA	49 5	CAADRSPY YYDSSGY PDAFDIW	679	RASQGIS NNLN	10 72	QAS SLD S	12 44	CQQS YNVPY TF	13 52
00 5S - A1 1	Fzd 9	FTFSS YDM N	22 9	SGIS WNS GYIGY A	61 5	CAKGSLLL GYYGMDV W	720	RASQSIS NNLN	10 92	DAS TLK R	11 92	CQQS YNTPR TF	13 50
00 5S - B1 2	Fzd 10	FTZSS YDM H	26 3	SSISG LGGS TYZA	63 3	CAREAGTT GGWFDP W	805	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 5S - D1 2	Fzd 10	FTFSD HYM D	20 4	STIGP AGDT YYP	64 4	CARASTSG DYSLW	756	RASQSVS TSYLA	11 23	GAS TRA T	12 17	CQQY GASP WTF	14 06
00 6S - B0 1	Fzd 10	YTFTN YCTR	38 4	GLVC PSDG STSYA	51 9	CARRTSAS DIW	915	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
00 6S - C0 1	Fzd 10	FTFTZ SAVQ	25 3	GGFD PEDG ETIYA	49 2	CTTDPLELP WYW	102 0	RASQGIS SALA	10 76	SAS NLQ S	12 52	CQQA SFPLTF	13 15
00 6S - E0 1	Fzd 10	YTFTG YYMH	37 9	GIINP SSGR TDYA	51 4	CARDLTY YDSSGHSP LGAFDIW	781	RASQSVT SSLA	11 24	GAS TRA T	12 17	CQQY NDWP PTF	14 16
00 6S - G 01	Fzd 10	FTFSD FGM N	20 3	AGISG GGGS TDYA	44 3	CARDSDF WYYYGMD VW	797	KSSQSVL YSSNNK NYLA	10 37	STN TRS S	12 57	CQHR NFF	13 06
00 6S - B0 2	Fzd 10	VSFS GYA MH	36 6	AYINS GSSE MNY A	48 2	CAREEWEL FGMDVW	807	RASQSIS SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
00 6S - G 02	Fzd 10	YTVTS YAM H	39 9	GGIPI FGTA KYA	49 7	CAKGGQW LYGMDVW	713	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - A0 1	Fzd 1	YTFTS YMH	39 2	GWVS PSSG NTAY A	58 8	CARDEGA GYYYM DVW	766	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - C0 1	Fzd 2	FTFSN YAMT	21 6	SAIGT GGGT YYA	59 5	CATAYRRP GGLDVW	969	RSSQSLL HSDGKTY LY	11 34	LGS NRA S	12 37	CMQN THWP LTR	12 93
01 4S - F0 1	Fzd 4	FTFSS YAM H	22 7	SVIST SGDT VLYT	65 2	CARGGSSD VR	838	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - H0 1	Fzd 4	FTFSN YGM H	21 7	SYISS SSSTI YYA	67 2	CARAALGY CTGGVCP VDYW	737	RASQGIS NNLN	10 72	AAS RLQ S	11 71	CQQS YSPPL TF	13 63
01 4S - C0 3	Fzd 7	YTFTN NFMH	38 3	GIIZP GGGR TIYA	51 7	CAKGDYG ALDYW	712	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - D0 3	Fzd 7	FNFS YTMR	17 3	SVIYG GGNT NYA	65 3	CARGGSG GNLSYW	836	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - F0 3	Fzd 8	YTFTN NFMH	38 3	GGIIP LFGTA NYA	50 6	CARLVVRG GYGMDV W	893	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - A0 4	Fzd 8	GTFSS YAIS	29 5	GWIS SFNG NTKY A	57 5	CARADDYY DSSGY FDYW	738	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - C0 4	Fzd 8	FTFSS YTMN	23 5	SRING DGSN TNYA	62 3	CARGWAG FDYW	871	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - D0 4	Fzd 8	HTFS GYHI H	31 2	GWIN AGNG NTTY A	55 8	CARDLSPM VRGVISGM DVW	779	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
01 4S - E0 5	Fzd 8	YTFTN NFMH	38 3	GIISP GGGR TIYA	51 5	CAKGDYD ALDYW	712	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPL TF	13 72
01 4S - E0 6	Fzd 10	FTFG NYD MN	19 5	SSLS WNS GTIVY A	64 1	CARDSSSG WYASYG MDVW	798	RASQSI RYLN	10 95	AAS SLQ S	11 75	CLQH HSYPF TF	12 75
02 7S - C0 2	Fzd 5	YTLT WYM X	39 8	GWM NPNS GNTA YA	58 2	CARGALG MDVW	819	QASQDI NYLN	10 46	AAS SLH T	11 73	CQESY SSPYT F	13 02
02 7S - E0 3	Fzd 8	YTFTG HYM H	37 8	GWM NPNS GNTG YA	58 3	CARGTG DYW	867	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YSTPY TF	13 79
02 7S - F0 3	Fzd 8	YTFTG HYIH	37 7	GWM NPISG NTGY A	58 0	CARSTPD PW	925	RASHDIG TFLA	10 57	AAS TLQ S	11 79	CQQS YRTPY TF	13 55
02 7S - G 03	Fzd 8	YTFTH SYIH	38 0	GWIN AKSG GTFY A	55 9	CARGDYDF WSGYHEY YYYGMDV W	824	QATQNI KKYLN	10 51	KAS TLES	12 29	CQQS YSTPL TF	13 72
02 7S - H0 3	Fzd 8	YTFTS YMH	39 2	GWIN PNSG GTNY A	56 4	CARAPLDG SGSYVD W	746	RSSQSLL HSNGYN YLD	11 38	LGS NRA S	12 37	CMQA LQTPQ TF	12 82
02 7S - A0 4	Fzd 8	YTFTN HFMH	38 2	GWIS PNRG GTNY A	57 1	CARDSSSG SCYSHFDY W	765	RASQSI RSLA	10 93	AAS NLQ S	11 69	CQQA YSFPQ TF	13 23
02 7S - B0 4	Fzd 8	FTVG SWY MS	25 9	SAIGT GGGT YYA	59 5	CAKDITPY GDYSILSH W	702	RASQAIS NYLN	10 59	AAS SLQ S	11 75	CQQT SPPLT F	13 83
02 7S - C0 4	Fzd 8	YTFTS HWM H	38 6	GGIPI FGTT NYA	50 3	CARDSSSW YSYYYYYM DVW	799	RASQGIN NYLA	10 67	QAS NLE S	12 43	CQQT YSSPL TF	13 93
02 7S - D0 4	Fzd 8	YTFTT YFMH	39 3	GWII PNSG GTKY A	57 8	CTDRLRYD SSGPAAFDI W	101 9	QASQDI DNYLN	10 40	AAS SLQ S	11 75	CQQS YSTPV TF	13 77

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
02 7S - E0 4	Fzd 8	FTFSD HYMS	20 5	SGISG SGGT TYA	60 9	CATYGDFG YFDLW	978	RASQGIR NDLG	10 69	AAS TLQ S	11 79	CQQA YSFP WTF	13 24
02 7S - C0 5	Fzd 8	GSFST SVFG	27 9	GRIIP LFGTT NYA	53 2	CVKDRAW GFDYW	102 7	RASQGIR NDLA	10 68	AAS SLQ R	11 74	CQQS YSKPT F	13 59
02 7S - D0 5	Fzd 8	YTFTS YYMH	39 2	GWIN PKSG GTNY A	56 0	CARGGFVF DYW	828	QASQDIS NYLN	10 46	ASS TLQ T	11 82	CQQS YSAPY TF	13 56
02 7S - E0 5	Fzd 8	GTFSS YAIS	29 5	GMIN PSGG STTYA	52 3	CARQAGLH CSSTSCYL G NWFDPW	905	RASQGIT KSLA	10 77	AAS NLQ L	11 68	CQQY NTFPI TF	14 22
02 7S - F0 5	Fzd 8	GTFN RYGIS	29 0	GGIIP RLGA TDYA	50 8	CAKGNWA FDIW	719	RASQSI TYLA	11 00	GAS TRA T	12 17	CQQY GSSPT F	14 11
02 7S - G 05	Fzd 8	GTFSS YAIS	29 5	GWIS PYNG NTKY A	57 2	CARGVWT TPMGGGG NWFDPW	869	RASQSI SYLN	10 98	YAS SLQ N	12 61	CQQS YSTPF TF	13 68
02 7S - H0 5	Fzd 8	GTFG NYGI N	28 6	GWIN PNSG GTNY A	56 4	CARETTDY YGMVDVW	814	RASQSI TYLN	10 88	DAS NLE T	11 85	CQQA NSFPL TF	13 17
02 7S - A0 6	Fzd 8	GTFSS YAIN	29 4	GVID PSTG GTNY A	55 0	CARVLPGD SSGWYRG YYYYYGM DVW	941	RASQGI NNLN	10 72	KAS SLES	12 26	CQQA NSFPI TF	13 16
02 7S - C0 6	Fzd 8	GTFTS YPIS	30 6	GWIN TYNG NTIYA	56 6	CARDLDSG FDLW	776	RASQGV GDYLA	10 78	DAS NLQ S	11 86	CQQH NAYPL TF	13 30
02 7S - D0 6	Fzd 8	GTFSS YAIS	29 5	GWIS AYNG HTNY A	56 9	CARGGYSY GTVFDYW	842	RASQDI SWLA	10 64	KAS TLES	12 29	CQQS YGAPL TF	13 48
02 7S - E0 6	Fzd 8	YTFTK DYM H	38 1	GGIPI FGTA NYA	49 9	CARGLPPA AGGGGYF QHW	847	RASQNV NDWLA	10 82	SAS NLQ S	12 52	CQQS YSTPF TF	13 68

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
02 7S - F0 6	Fzd 8	FTFSS YAM H	22 7	AVTW YDGS NKYY A	48 0	CAKDLVPY CSGGSCPP SGW	705	RASQSI SYLN	10 98	GAS NLQ S	12 07	CQQS YSTPL TF	13 72
02 7S - G 06	Fzd 5	YTFTD YYMH	37 6	GWM SPNS GNAG FA	58 4	CARGKSGS FDYW	846	RASQSV NNTYVA	11 11	GTS TRA T	12 22	CQQY DTSP TF	14 04
02 7S - H0 6	Fzd 5	YTFTG HYIH	37 7	GIINP SGGS TSYA	51 3	CARGFCSG GSCLWYG MDVW	825	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS YTTP TF	13 82
02 7S - A0 7	Fzd 5	GTFG SYAIT	28 7	GGIPI FGTA NYA	49 9	CAKDNW YFDLW	706	RASQSI TNVN	10 99	AAS SLQ S	11 75	CQQS YSTPY TF	13 79
02 9S - B0 1	Fzd 1	GTFSS YAIS	29 5	GRIN PHNG NTNY A	14 61	CARATRV S AAGTVHF QHW	147 2	KSSQSV L HSSNNK NYLA	14 98	STN TRS S	12 57	CQQY YSTPF TF	15 44
02 9S - D0 1	Fzd 2	YTFTR YYIH	14 52	GWM NPNS GNTG YA	58 3	CARVRFLE EMDVW	149 4	RASQSLS SWLA	15 12	DAS TLQ S	15 20	CQQA I SFPLTF	13 15
02 9S - C0 2	Fzd 2	GTFSS YGIS	14 57	GIINP SGGS TSYA	51 3	CARGDIVA TMGMKKV DYYYMD VW	147 8	RASQDIS NNLN	15 00	GAS HLQ T	15 22	CQQA NSFPV TF	13 18
02 9S - F0 2	Fzd 2	YTFTR YYLH	14 53	GWM NPNS GNTG YA	58 3	CARGIGYW	148 1	RASQGIS NYLA	10 74	AAS RLQ T	15 15	CLQYN TYPW TF	15 28
02 9S - H0 2	Fzd 2	GTFST YAIS	29 8	GDIPI FGSA NYA	14 58	CARELGLG WFDPW	147 6	RSSQSLL HSNGYN YLD	11 38	LGS SRA S	15 25	CMQA LQTPL TF	12 81
03 0S - A0 2	Fzd 7	YTFTD YYMH	14 49	GWM NPNS GSTG YA	14 67	CARGDINY GNFDYW	147 7	RASQSI SYLN	10 98	KAS TLH N	15 23	CQQA I SFPLTF	13 15
03 0S - B0 2	Fzd 3	YTFTD YYMH	14 49	GWM NPNS GNTG YA	58 3	CARQGGSY SMGLDPW	148 8	RASQSIT TYLN	15 11	KTS SLQ S	15 24	CQQG DSFPY TF	15 31

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
02 9S - E0 3	Fzd 3	YTFTG YYMH	37 9	GWIN PNSG NTGY A	14 63	CARSYYGV IDAFDIW	149 2	RASQSI SYLN	10 98	AAS SLQ T	15 16	CQQSF RLPLT F	15 32
02 9S - G 03	Fzd 3	YTFTN YYMH	14 51	GWM NPNS GNTG YA	58 3	CAREDDF WSGGGM DVW	147 4	RASQSI SYLN	15 09	AAS SLQ S	11 75	CQQS WRFP YTF	15 35
03 0S - E0 3	Fzd 3	FTFSD YYMS	14 38	SAISG SGHS TYA	14 68	CAREGLRG WSIFDIW	147 5	KSSQSVL YSSNNK NYLA	10 37	WA STR ES	15 26	CQQY YSTPP TF	15 45
02 9S - D0 5	Fzd 3	YTFTD HYFH	14 47	GWA NPSS GNTG TA	14 62	CARSRLRW DWYFDLW	149 1	RASQTIS SYLN	15 13	DAS NLE T	11 85	CQQS YSIPLT F	15 36
03 0S - H0 3	Fzd 3	FSFSS HAMS	14 37	SAIGT GGGT YYA	59 5	CANPKHY W	147 0	RASQGV STYLA	15 05	AAS SLQ S	11 75	CQQY YSSPQ TF	15 43
02 9S - B0 6	Fzd 3	YTFSR HYIH	14 46	GWM NPNS GNTG YA	58 3	CARGGHT GYSSGWY NHW	147 9	RASQSVS SWLA	11 20	AAS SLQ S	11 75	CQQA FRFP TF	15 29
02 9S - E0 6	Fzd 3	YWFT ASYM H	14 55	GWM KPDS GNTG YA	14 65	CARRSSSW GWYFDLW	148 9	RASQNIN SWLA	15 06	AAS SLQ S	11 75	CQQY YSFPL TF	15 42
02 9S - H0 6	Fzd 3	YTFAK YYIH	14 44	GWM NPNS GNTG YA	58 3	CARHKRHT PYAFDIW	148 7	RASQSI SYLN	10 98	AAS SLQ S	11 75	CQQS HSTPL TF	15 33
02 9S - G 07	Fzd 3	YTFTD SYIH	14 48	GWIS AYNG NTNY A	57 0	CARGSGYF DLW	148 6	RASQSI KWLA	15 10	GAS TLQ S	12 15	CQQA YSFP WTF	13 24
02 9S - H0 8	Fzd 3	YTFTG HYM H	37 8	GWM NPNS GNTG YA	58 3	CARVGDY DRFNWYF DLW	149 3	RASRTVY NFLA	15 14	DAS NLR T	15 19	CQQS YSTPP TF	15 37
02 9S -	Fzd 3	GTFSS YAIT	14 56	GWIS AYNG NTNY A	57 0	CARANRGL RKNYYYG MDVW	147 1	RASQSIA RYLN	15 07	GAS SLQ S	12 11	CQQS YNTF WTF	13 51

Cl on e ID	Init ial Bin din g	CDRH 1	CD RH 1 SE Q ID	CDRH 2	CD RH 2 SE Q ID	CDRH3	CDR H3 SEQ ID	CDRL1	CD RL 1 SE Q ID	CDR L2	CD RL 2 SE Q ID	CDRL3	CD RL 3 SE Q ID
F09													
03 OS - F04	Fzd 3	YTFTS SYIH	14 54	GIINP SGGG AVYA	14 59	CARWTTV VTGAAFDI W	149 5	RASQGIR NDLN	15 02	DAS NLG T	15 18	CQQSS RIPPTF	15 34
02 9S - A10	Fzd 3	YSFTG YYLH	14 42	GWIN PNSG GTNY A	56 4	CARDHGT MIAVAGTF DYYYMD VW	147 3	RASQGIS KYLA	15 03	AAS SLQ S	11 75	CQQS YSTP WTF	15 38
02 9S - B11	Fzd 3	YTFN GYMH	14 45	GIVN PSGG GTNY A	14 60	CARGGNY GRWLQPW YFDLW	148 0	QASQDIS NYLN	10 46	GAS ALR S	15 21	CQQT KSFPL TF	15 40
02 9S - D11	Fzd 3	HTFTS HYMH	14 40	GWM NPNS ANAG YA	14 66	CARGLGIF DLW	148 3	RASQDIS RGLG	15 01	AAS TLY R	15 17	CQQA YSFP WTF	13 24
03 OS - H05	Fzd 7	YSFTN YYMH	14 43	GWM NPNS GNTG YA	58 3	CARSPDF WSGEGYF DLW	149 0	RASQSIG NYLN	15 08	AAS SLQ S	11 75	CQQA NSFPL TF	15 30
03 OS - A06	Fzd 7	YMFT GHD MH	14 41	GRIPI LGIAN YA	52 9	CARGIHGD YGLDYYM DVW	148 2	RASQAIG RRLA	14 99	AAS SLQ S	11 75	CQQY DTYW TF	15 41
02 9S - C12	Fzd 7	YTFTG YYMH	37 9	GWM NPNS GNTG YA	58 3	CARGMEY W	148 4	RASQGIS SYLA	10 76	AAS TLQ S	11 79	CLQYN TYPW TF	15 28
03 OS - C06	Fzd 7	YTFTG YYIH	14 50	GWM DPNS GYTG YA	14 64	CARGPADF WSGYKND YDFW	148 5	RASQGIS SWLA	15 04	DAS SLQ S	11 90	CQQS YSTPY SF	15 39
4A 12	Fzd 5	<u>GYTFT</u> <u>NYDI</u> <u>N</u>	14 39	<u>WIYP</u> <u>RDGS</u> <u>TKYN</u> <u>EKFK</u> <u>G</u>	14 69	<u>CVRSAWG</u> <u>FAY</u>	149 6	<u>KASQDV</u> <u>GTAVA</u>	14 97	<u>WA</u> <u>STR</u> <u>HT</u>	15 27	<u>QQYS</u> <u>TYPLT</u>	15 46

Table 1B: Anti-Fzd Antibody Clone IDs, Heavy Chain (HC) and Light Chain (LC) Seq ID Nos, and Binding Characteristics

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
001S-B01	1	38	Fzd1,2,7,9
001S-E02	2	39	Fzd1,2,7
001S-G02	3	40	Fzd1,2,7
001S-H02	4	41	Fzd1,2,7
001S-A03	5	42	Fzd1,2,7,9
001S-B03	6	43	Fzd1,2,7
004S-G06	7	44	Fzd5,8
002S-B01	8		Fzd1
002S-C02	9		Fzd1
002S-E02	10		Fzd1
002S-G02	11		Fzd1
002S-F03	12		Fzd1
002S-A04	13		Fzd1
002S-B04	14		Fzd1
002S-D04	15		Fzd1
004S-H04	16	45	Fzd5
001S-A04	17	46	Fzd1,2,5,7,8
003S-E07	18	47	Fzd2
003S-D10	19	48	Fzd4
004S-B08	20	49	Fzd6
004S-D08	21	50	Fzd6
004S-C09	22	51	Fzd6
004S-F10	23	52	Fzd6
004S-A11	24	53	Fzd6
004S-A12	25	54	Fzd6
005S-B07	26	55	Fzd9

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
005S-D08	27	56	Fzd9
005S-E09	28	57	Fzd9
005S-H10	29	58	Fzd9
005S-B11	30	59	Fzd9
005S-D11	31	60	Fzd9
014S-G02	32	61	Fzd6
014S-B04	33	62	Fzd8
014S-B06	34	63	Fzd9
014S-G06	35	64	Fzd10
014S-A07	36	65	Fzd10
017S-B09	37		Fzd8
004S-D01	129	130	Fzd4
004S-E09	131	132	Fzd6
004S-F09			Fzd6

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
004S-H09			Fzd6
004S-B10			Fzd6
004S-C10			Fzd6
004S-F10			Fzd6
004S-G10			Fzd6
004S-A11			Fzd6
004S-B11			n.b.
004S-D11			Fzd6
004S-E11			n.b.
004S-F11			Fzd6
004S-G11			Fzd6
004S-A12			Fzd6
004S-B12			Fzd6

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
004S-C12			n.b.
004S-D12			n.b.
004S-F12			n.b.
004S-F12			n.b.
004S-G12			n.b.
005S-B02			n.b.
005S-C02			n.b.
005S-D02			Fzd5,8
005S-E02			Fzd5,8
005S-H02			Fzd5,8
005S-A03			Fzd5,8
005S-C03			n.s.
005S-E03			n.s.

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
005S-F03			Fzd8
005S-B04			Fzd5,8
005S-F04			n.b.
005S-G04			Fzd5,8
005S-H04			n.b.
005S-E05			n.b.
005S-G05			Fzd5,8
005S-H05			Fzd5,8
005S-D06			Fzd8
005S-F06			n.b.
005S-G06			n.b.
005S-A07			Fzd9,10
005S-B07			Fzd9

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
005S-A08			Fzd9
005S-B08			Fzd9
005S-D08			Fzd9
005S-E08			Fzd9
005S-F08			n.b.
005S-C09			Fzd9
005S-D09			Fzd9
005S-E09			Fzd9
005S-F09			Fzd9
005S-A10			Fzd9
005S-B10			Fzd9
005S-E10			Fzd9
005S-H10			Fzd9

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
005S-B11			Fzd9
005S-D11			Fzd9
005S-G11			n.b.
005S-H11			n.b.
005S-E12			Fzd10
006S-A01			Fzd10
006S-H01			n.b.
006S-A02			Fzd10
006S-D02			n.b.
006S-H02			Fzd10
006S-A03			n.b.
006S-B03			n.b.
006S-C03			n.b.

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
014S-A01			Fzd1,2,7
014S-B02			n.b.
014S-G02			Fzd6
014S-B03			n.b.
014S-C03			Fzd1,2,7
014S-A04			n.b.
014S-B04			Fzd8
014S-B05			Fzd5,8
014S-B06			Fzd9
014S-F06			n.s.
014S-G06			Fzd10
014S-A07			Fzd10
017S-E08			Fzd8

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
017S-H08			n.b.
017S-A09			n.b.
017S-B09			Fzd8
018S-F06			Fzd4
018S-H06			n.b.
018S-B07			n.b.
017S-A10			n.b.
017S-B10			n.b.
017S-D10			n.b.
018S-H08			n.b.
018S-B09			Fzd5,8
021S-A01			n.b.
021S-E02			Fzd5,8

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
021S-G02			n.s.
021S-A03			n.b.
029S-B01			n.b.
029S-D01			Fzd1,2,7
029S-C02			Fzd1,2,7
029S-H02			Fzd1
030S-A02			Fzd7
029S-E06			Fzd2, 6, 3
030S-F04			Fzd3
030S-H05			Fzd7
030S-A06			Fzd1,2,7,5
029S-C12			Fzd7
030S-C06			Fzd1

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
001S-A01			Fzd1,2,7
001S-H01			Fzd1,2,7

In certain embodiment, the Fzd binding domain may be selected from any binding domain that binds a Fzd with an affinity of, e.g., a K_D of at least about 1×10^{-4} M, at least about 1×10^{-5} M, at least about 1×10^{-6} M, 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. In certain embodiment, the Fzd binding domain may be selected from any binding domain that binds one or more Fzd receptor at high affinity, e.g., a K_D of less than about 1×10^{-7} M, less than about 1×10^{-8} M, less than about 1×10^{-9} M, or less than about 1×10^{-10} M. In certain embodiment, the Fzd binding domain may be selected from any binding domain that binds Fzd at high affinity, e.g. a K_D of less than or equal to about 1×10^{-4} M, less than or equal to about 1×10^{-5} M, less than or equal to about 1×10^{-6} M, less than or equal to about 1×10^{-7} M, less than or equal to about 1×10^{-8} M, less than or equal to about 1×10^{-9} M, or at least about 1×10^{-10} M in the context of a Wnt surrogate molecule.

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; VHH or single domain antibody derived binding domains; knottin-based engineered scaffolds; norrin and engineered binding fragments derived therefrom, naturally occurring Fzd binding domains, and the like. A Fzd binding domain may be affinity selected to enhance binding to a desired Fzd protein or plurality of Fzd proteins, e.g. to provide tissue selectivity.

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 Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, Fzd10. In

some embodiments, the Fzd binding domain binds to Fzd1, Fzd2, and Fzd 7. In some embodiments, the Fzd binding domain binds to Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8. In other embodiments the Fzd binding domain is selective for one or more frizzled protein of interest, e.g. having a specificity for the one or more desired
5 frizzled protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other frizzled proteins.

In certain embodiments, the Fzd binding domain comprises the six CDR regions of the pan specific frizzled antibody OMP-18R5 (vantictumab). In certain embodiments, the Fzd binding domain is an scFv comprising the six CDR
10 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:270), a heavy chain CDR2 comprising VISGDGSYTTYADSVKG (SEQ ID NO:677), and a heavy chain CDR3 comprising
15 NFIKYVFAN (SEQ ID NO:1033), and (ii) a light chain CDR1 comprising SGKLGKKYAS (SEQ ID NO:1152) or SGDNIGSFYVH (SEQ ID NO:1153), a light chain CDR2 comprising EKDNRPSG (SEQ ID NO:1200) or DKSNRPSG (SEQ ID NO:1201), and a light chain CDR3 comprising SSFAGNSLE (SEQ ID NO:1435) or QSYANTLSL (SEQ ID NO:1436). In particular embodiments, the Fzd binding
20 domain is an antibody or derivative thereof, including without limitation scFv, minibodies, VHH or single domain antibodies (sdAb) and various antibody mimetics comprising any of these CDR sequences. In certain embodiments, these CDR sequences comprise one or more amino acid modifications.

In other embodiments, the Fzd binding domain comprises a variable
25 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. 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 Fzd9 (CD349); antibodies available from Abcam, e.g. ab64636 specific for Fzd7; ab83042 specific for human Fzd4; ab77379 specific for human Fzd7; ab75235 specific for human Fzd8; ab102956 specific for human Fzd9; and the like.

- 5 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; etc., each herein specifically incorporated by reference.

The Fzd binding region of a Wnt surrogate molecule may be an
10 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
15 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.

In particular embodiments, a Wnt surrogate molecule comprises an LRP5/6 binding domain, e.g., an anti-LRP5/6 antibody, or antigen-binding fragment
20 thereof, fused to a polypeptide that specifically binds to one or more Fzd receptors. In particular embodiments, the polypeptide that specifically binds to LRP5/6 is an antibody or antigen-binding fragment thereof. In certain embodiments, it is an antibody or antigen-binding fragment thereof disclosed in the U.S. provisional patent application no. 62/607,879, titled, "Anti-LR5/6 Antibodies and Methods of
25 Use," Attorney docket number SRZN-005/00US, filed on December 19, 2017, which is incorporated herein by reference in its entirety. In particular embodiments, the LRP5/6 binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to LRP5 and/or LRP6 provided in Table 2A. In particular

embodiments, the LRP5/6 binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 2A, wherein the CDRs collectively comprise one, two, three, four, five, six, seven, or
5 eight amino acid modifications, e.g., substitutions, deletions, or additions. In certain embodiments, the LRP5/6 binding domain is a VHH or sdAb or was derived from a VHH or sdAb, so Table 2A only includes the three heavy chain CDRs. In certain embodiments, the LRP5/6 binding domain comprises the three heavy chain CDRs shown in Table 2A or variants wherein the CDRs collectively comprise one, two,
10 three, four, five, six, seven or eight amino acid modifications. In particular embodiments, the LRP5/6 binding domain comprises the heavy chain fragment and/or light chain fragment of any of the illustrative antibodies or fragments thereof that bind to LRP5 and/or LRP6 provided in Table 2B or SEQ ID NOs:66-88 or 133 (or an antigen-binding fragment or variant of either). In certain embodiments, the
15 LRP5/6 binding domain is an Fab or was derived from an Fab, so Table 2B includes VH and CH1 sequence, but not CH2 or CH3 sequences. In certain embodiments, the LRP5/6 binding domain is a VHH or sdAb or was derived from a VHH or sdAb, so Table 2B includes the VHH domain. In certain embodiments, the LRP5/6 binding region is a polypeptide, e.g., an antibody or antigen-binding
20 fragment thereof, that competes with one of these antibodies for binding to LRP5 and/or LRP6.

Table 2A: Anti-LRP5/6 Antibody Clone IDs and CDR sequences.

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
001S-C08	LRP6e1e2	YTIISYYIH	1682	GMINPSGGST TYA	1762	CAIVRGKKWYFDLW	1842	RASQYISNYL N	2098	AASSLQS	2110	COQSYITPLTF	2160
001S-C10	LRP6e1e2	RTFGTYPNG	1632	AAISWGGRTA YA	1700	CYARTVIGGFGAFRA HW	2061						
001S-D10	LRP6e1e2	RTFSRYAMA	1642	AAIRWSGGGT YYA	1689	CAASMEAMNSLRVN KERYQSW	1836						
001S-E10	LRP6e1e2	LTFSSNAAM A	1614	AAISRSAGANTA YS	1696	CTLVNEIKTWW	2039						
001S-F10	LRP6e1e2	RTFSSYAMA	1645	AAIKWSGTNT YYA	1684	CAASMEAMNSLRVN KERYQSW	1834						
001S-G10	LRP6e1e2	RTFSRYVM G	1644	AAITWRGGST YYA	1706	CATGPNISY	1987						
001S-A11	LRP6e1e2	RTFGNYDM G	1630	AGIRWSGSTL YA	1709	CYARTVIGGFGAFRA HW	2062						
001S-B11	LRP6e1e2	RRFTTYGM G	1623	AAVTWRSGST YYA	1708	CAAGSTVVAEFNYW	1828						
001S-C11	LRP6e1e2	SISSFNTMG	1659	AVITTTGGDTSY S	1741	CNKVNATKL	2025						
001S-E11	LRP6e1e2	RTLSRYSMG	1651	AAISRSGDRIY YS	1697	CTLVNEIKTWW	2040						
001S-F11	LRP6e1e2	RTFSSYAMS	1646	AVIGRSGGIKY YA	1736	CATRRPFNSYNTEQS YDSW	1989						
001S-G11	LRP6e1e2	SIFRLGTMY	1655	ASIGKSGSTNY A	1719	CKQHPNGYR	2005						
001S-H11	LRP6e1e2	RTLSSFAMG	1652	ATISRSGGNTY YA	1732	CNLREWNNSGAGY W	2026						
001S-A12	LRP6e1e2	IAFRYVDMG	1608	AAITWNGRSS DYA	1704	CAAVFTGRFYGRPPR EKDYW	1838						
001S-B12	LRP6e1e2	RLLSYALA	1622	AAISRNGDKS HYS	1694	CTLVNEIKTWW	2038						
001S-C12	LRP6e1e2	RTFSNVAVG	1641	AAISRFGGSTY YV	1693	CAADRIENYLGRYYD PSEYEW	1824						

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
001S-D12	LRP6e1e2	RTFSRYAM G	1643	GAISRSNNNT YYA	1744	CTLVNEIKTWW	2041						
001S-F12	LRP6e1e2	RTFSRYTMG	1637	AAISGSGGTT YA	1690	CNADIKTTTYSPLRNY W	2009						
008S-B01	LRP5	TIFSINTMG	1664	ATMTSGGNT NYA	1734	CYRRQWASSWGARGAR NYEYW	2064						
008S-C01	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CHGRDYGSNAPQY W	2001						
008S-D01	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CVVKLRDDDDYYVR	2065						
008S-E01	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CNAVTYNGYTIR	2023						
008S-G01	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CVARTQRMGVVNSY W	2060						
008S-A02	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CNAVTEGGNTIR	2021						
008S-C02	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CNAVTYDGY	2022						
008S-D02	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CAAQFRNDYGLRYQ STNNYW	1832						
008S-E02	LRP5	NINSIETLG	1617	ANMRGGGY MKYA	1716	CNANYRGNRYW	2019						
009S-C01	LRP6e3e4	GSFSGYYWT	1595	GEINHSYGATN YN	1745	CVRYAWPEFDHW	2053	RASQSVSNY LN	2089	AASSLQ	2110	CQQSYSVPYTF	2178
009S-B02	LRP6e3e4	GSLSGYYWS	1596	GEINHSYGSTNY N	1746	CVRYAWPEFDHW	2055	RASQSVSNY N	2090	AASSLQ	2110	CQQSYSPLTF	2170
009S-C02	LRP6e3e4	GSFSDYYWS	1594	GEINHSYGSTNY N	1746	CVRYAWPEFDHW	2054	RASQSVSNY N	2090	AASSLQ	2110	CQQSYSMPPLTF	2171
009S-D02	LRP6e3e4	GTFSYVMS	1603	GGIPIFGTAN YA	1749	CVYGRDFDYW	2056	SGSSSNVGN NVVS	2105	DNDKRPS	2122	CESWDSSLSSE VF	2139
010S-A02	LRP6e1e2	HTFSSYAM G	1607	AAISQSGYVRY YA	1691	CKIYGLNGQPLGWSW	2003						
010S-B02	LRP6e1e2	RTFNSGTM G	1634	AAITWRGGIT YYA	1705	CNADGYSWDGRSG RRLELW	2008						

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
010S-D02	LRP6e1e2	RTFSSYAVG	1647	AAISVGGSTK YA	1702	CAASVVISRRDSDYG YW	1837						
010S-E02	LRP6e1e2	LSSGRPFSSY VMG	1612	AAISWGGST KYA	1701	CKLQVRPIGYSSAYS R NYW	2004						
010S-F02	LRP6e1e2	RSFNSYVIG	1625	AAIRWSGDNT YYA	1688	CAASMEAMNSLRVN KERYQSW	1835						
009S-E02	LRP6e1e2	RRFTTYGM G	1623	AAVTWRSST YYA	1708	CAAGSTVVAEFNYW	1829						
009S-F02	LRP6e1e2	RTFSYAMG	1649	AAISRSGGIY A	1698	CNTVRPLWAW	2029						
009S-G02	LRP6e1e2	SIFSIVAMG	1658	AVITSGGKTVY A	1740	CYADSRSSWYDEYLE HW	2058						
009S-H02	LRP6e1e2	SIVRSLPMA	1660	ATINDAQRY A	1727	CNTSPYMHVDVW	2027						
009S-A03	LRP6e1e2	RTFSYVGVG	1648	AAVASGGYT WYA	1707	CKAAPRWGGATAY W	2002						
010S-G02	LRP6e1e2	SIVRSLPMA	1660	ATINDAQRY A	1727	CNTSPYMHVDVW	2028						
010S-A03	LRP6e1e2	RTFRRYAM G	1636	ATISASGGNTA YA	1731	CNAPAWLYDDDDYW	2020						
009S-B03	LRP6e1e2	RTFSNYAVG	1641	AAISRFGGSTY YV	1693	CAADRIENYLGRYYD PSEYEW	1825						
010S-B03	LRP6e1e2	RTFSNYAVG	1641	AAISRFGGSTY YA	1692	CHAKQLRNGQMITY W	1999						
010S-D03	LRP6e1e2	ISSVYGMG	1609	AAIQWSADNT FYA	1686	CAARTSGGLFHYYRS DHWDTW	1833						
009S-C03	LRP6e1e2	LPFSRYAMA	1610	AGMSGEGRN TKYR	1713	CSSRGYW	2034						
009S-D03	LRP6e1e2	SIFSDDGAMG	1656	AVISGGRTGY A	1737	CNTYFPPIYKKGYPF W	2030						
009S-E03	LRP6e1e2	RRFTTYGM G	1623	AAVTWRSST YYA	1708	CAAGSTVVAEFNYW	1830						
009S-F03	LRP6e1e2	RTFSSYAMS	1646	AVIGRSGGIKY YA	1736	CATRRPFNSYNTEQS YDSW	1990						

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
010S-E03	LRP6e1e2	RSVSIYPMG	1628	AANWSGDST KYA	1685	CNAVVGSLRRIDNI W	2024						
010S-F03	LRP6e1e2	RTFSRYVM G	1644	AAITWRGGST YYA	1706	CATGPNISY	1988						
009S-G03	LRP6e1e2	RSVSSVNM G	1629	AAISRRGGIIEY G	1695	CHAVENILGRFVDY W	2000						
009S-H03	LRP6e1e2	SIFSINTMG	1657	AVITSGGKTVY A	1740	CYADSRSSWYDEYLE HW	2057						
009S-A04	LRP6e1e2	RTLSAYDM G	1650	GGIRWSGGTT LYP	1753	CYARTVIGGFGAFRA HW	2063						
009S-B04	LRP6e3e4	SIFMINTMA	1654	ATIRPVSETT YA	1728	CNAKRPWGTREY W	2018						
010S-G03	LRP6e3e4	RSFNSYTTT	1624	AAIRGSSGSTF YA	1687	CNAASTVTAWPYVG PDYW	2006						
009S-C04	LRP6e3e4	FRFSISTMG	1553	AVITGGGRTM DG	1743	CNAFVRSDFDRYDY W	2011						
009S-D04	LRP6e3e4	TIVSIYRIN	1665	AGITSSGRTTY A	1712	CNAASTVTAWPYVG PDYW	2007						
010S-H03	LRP6e3e4	RIFSIDMG	1621	SGIRWSGGTS YA	1789	CSSRGYW	2035						
009S-E04	LRP6e3e4	RIFAIYDIA	1618	AMIRPVVTEID YA	1715	CNAKRPWGSREY W	2012						
010S-A04	LRP6e3e4	SLFSFNAV	1662	ASISSGGRTNY A	1722	CSKGGVYGGTYVPD SW	2032						
009S-F04	LRP6e3e4	RSLSSFAMG	1627	ARISRGDGYT DEA	1718	CAAVQAVIGGTLTTA YDYW	1839						
010S-B04	LRP6e3e4	RVLSYVAMIA	1653	AGITRGGATTY YS	1711	CAAGPNWSTNRREY DYW	1827						
009S-G04	LRP6e3e4	GTFSRYHM G	1601	SAITWSGGRT YYA	1788	CALTWAPTPTNRRS DYAYW	1872						
009S-H04	LRP6e3e4	RIFAIYDMA	1619	ATIRPVSETT YA	1728	CNAKRPWGTREY W	2017						
010S-C04	LRP6e3e4	SLFSFNAMG	1661	ASISSGRTNY A	1723	CSKGGVYGGTYVPD SW	2033						

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
010S-D04	LRP6e3e4	RIFAIDIA	1618	ATIRPVVTQID YA	1730	CNAKRPWGSRDEY W	2015						
010S-E04	LRP6e3e4	RTFGSDVM G	1631	ALTGWGDGS TTYVE	1714	CAAAARRSGTYDIGQY LRESAVFW	1820						
010S-F04	LRP6e3e4	RTFSRYAM G	1643	AAITRSGSNTY YA	1703	CAADPRGVTLPRATA YEYW	1823						
009S-A05	LRP6e3e4	RTFSDYSMG	1639	AGISWIADNR YYA	1710	CTAGRSRYLYGSSIN GPVDYW	2036						
010S-G04	LRP6e3e4	VIFALYDIA	1666	ATIRPVVTETD YA	1729	CNAKRPWGSRDEY W	2014						
010S-H04	LRP6e3e4	RSFSDFFMG	1626	ATISWGSSEA NYE	1733	CAAAYSYSQYGSSYS YW	1821						
010S-A05	LRP6e3e4	LSFSSYAMG	1611	AAISRSRGVSTY YA	1699	CAAKFGVLATTESRH DYW	1831						
010S-C05	LRP6e3e4	RTFNIDDM G	1633	ASIRWSGQSP YYA	1720	CNAETYSGNTIW	2010						
010S-D05	LRP6e3e4	RTFSDYSMA	1638	AGISWIADNR YYA	1710	CAGDRSRYLYGDSL RPVGYW	1841						
010S-E05	LRP6e3e4	SVFTTFAKG	1663	ASITASSDRTF YA	1725	CAAYSTFNTDVSAM KPDYW	1840						
010S-F05	LRP6e3e4	RIFSVIDIA	1620	ATIRPVVTETD YA	1729	CNAKRPWGSRDEY W	2013						
013S-G04	LRP6e3e4	RIFAIDIA	1618	ATIRPVSETT YA	1728	CNAKRPWGTREY W	2016						
013S-H04	LRP6e3e4	RTFSMYDM G	1640	ASIRWSGNT WYA	1721	CYANIYTRRAPEEY W	2059						
013S-A05	LRP6e3e4	RTFNTYAM G	1635	ASVSWRYDRT YTT	1726	CAADTNWRAGPRV GIDEYAYW	1826						
013S-B05	LRP6e3e4	FAFSTTAMS	1549	STINPGGLSKS YA	1806	CTKGGIQ	2037						
013S-C05	LRP6e3e4	NIFPIDMIS	1616	ATVTSGRINY A	1735	CNVDRTLGKYKEY W	2031						
013S-D05	LRP6e3e4	RIFSVIDMG	1621	SGIRWSGGTS YA	1789	CGSRGYW	1998						

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
013S-E05	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTADY A	1748	CARDWELYGMDVW	1907	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
013S-F05	LRP6e3e4	GTFSSYALS	1603	GINPSGGSTS YA	1761	CARAGYYDSSGYAF DIW	1882	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
013S-G05	LRP6e3e4	YFTYRYLH	1681	GGVPIFGTAD YA	1755	CASDIWDDAFDTW	1969	RASQDISNY LN	2079	AASTLQS	2113	CQQGNSFPYT F	2152
010S-G06	LRP6e3e4	FSFETYGMS	1555	SGISGGGRTH YA	1792	CARDLDYW	1897	QASQDISNY LN	2077	AASSLQS	2110	CQQSYRIHWT F	2163
009S-B05	LRP6e3e4	FTFDAYAM H	1560	STLSGDANNA YYA	1811	CARGSGWNSNYG MDVW	1931	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-C05	LRP6e3e4	YFTYRYLH	1681	GRIIPVLKITNY A	1768	CAVVDDAFDIW	1996						
009S-D05	LRP6e3e4	FTLRNHWLS	1591	SAISGGGSTY YA	1786	CATRTGVSYGFNF AFDIW	1991	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-E05	LRP6e3e4	YFTTNFM H	1676	GHVDPGDGET IYA	1756	CARDWGIAAAGDYY YGMVW	1908	RASQINSY LA	2081	DAKGHP	2114	CQQSYSAPLSF	2166
009S-F05	LRP6e3e4	FTFDDYGM S	1561	SAIGTGGGTY A	1781	CARLGSYGSPPYYG MDVW	1959	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-G05	LRP6e3e4	FTFSDYMS	1568	SGVSWNGSRT HYA	1799	CAKDSGLV	1852	QASQDISNY LN	2077	AASTLQR	2112	CQQSYSAPLTF	2167
009S-C06	LRP6e3e4	YTFASVDIH	1671	GWMNPNSG NTGYA	1776	CARATGSGWYTDLG YW	1883	RASRNINRY LN	2099	AASSLLS	2109	CQQSYNVFFT F	2162
009S-D06	LRP6e3e4	FTFSSHSTH	1573	STISDTNSGT YA	1807	CAKAQATGWSGYT FDYW	1843	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-E06	LRP6e3e4	FTFTDYGLH	1587	AVISYGGSNKY YA	1739	CASGYSGLYYGM DVW	1973	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-F06	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CATEAALDAFDIW	1985	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-G06	LRP6e3e4	YIFTDYMH	1669	GWINPNSGGT NYA	1774	CARDFLGSTGDYW	1892	RASQINIGLY LN	2088	DASSLQR	2121	CQQSYSTPYTF	2176
009S-H06	LRP6e3e4	FTFSSAMH	1574	SAIGTGGSTY A	1783	CAKGGDYFYYYGM DVW	1856	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A07	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CATAYGSSSLNIDYW	1980	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
009S-B07	LRP6e3e4	YTFTGYMH	1675	GWINPNSGGT NYA	1774	CVKDDGGFPLAYAFD IW	2049	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-D07	LRP6e3e4	FFFRYYGMS	1551	ARIGWNGGSI VYA	1717	CARDYSDRSGIDYW	1910	RSSQSLHLS NGYNYLD	2102	LGSNRAS	2131	CMQATQFPLT F	2146
009S-F07	LRP6e3e4	GTFSSYALS	1603	GINPSGGSTS YA	1761	CARAAGNFWSGYYT FDYW	1876	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-G07	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CARGSYGMDVW	1947	RASQGISNY LA	2083	DASNLET F	2115	CLQDFSPWTF F	2140
009S-H07	LRP6e3e4	YTFTGYMH	1675	GWMNPNSG NTGYA	1776	CASSVVPAGPAGVY AFDIW	1975	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A08	LRP6e3e4	GTFSSHAIN	1602	GWISANNNGN TDYA	1775	CARDQDYGIDYGYW YVGMDVW	1902	RASQGISNY LA	2083	GSSTLQS	2127	CQQTYSIPPTF	2181
011S-C01	LRP6e3e4	LTFTSHGMS	1615	SVSDSGSSVY YA	1818	CARHPGSGGGYSYA WYNYGMDVW	1956	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-C08	LRP6e3e4	FSFNTEGIH	1556	AVISYDGSNKY YA	1738	CAKSIAAAAGTGYG MDVW	1868	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-D08	LRP6e3e4	YTFTSYDIN	1679	GGIPIFGTAN YA	1749	CARGPYFYDYW	1939	RASQGISNN LN	2082	DASSLES	2120	CLQHNSYPPTF	2143
011S-F01	LRP6e3e4	FSFSDYYMS	1558	SGISESGRTY YA	1790	CASAADFIDW	1966	RASQDISNY LN	2079	AASSLQS	2110	CLQDYSYPRTF	2141
009S-E08	LRP6e3e4	YGFTGYIYH	1668	GWMNPNSG NTGYA	1776	CARGYGDYDLW	1951	QASQDISNY LN	2077	DASSLES	2120	CQQSYRYPTF	2165
009S-F08	LRP6e3e4	DTFANYGFS	1547	GXVNAAGN TTYA	1777	CAKGWLDIDYW	1866	QASQDISNY LN	2077	DASSLES	2120	CQQSYSTSITF	2177
009S-G08	LRP6e3e4	FTFSDFAMT	1566	SVISGDSGVTN YA	1813	CARLGSYPGPYYM DVW	1961	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-H08	LRP6e3e4	YTFTDYFMN	1673	GINPSGDSTR FA	1758	CARDGDLGMDVW	1888	QASQDISNY LA	2076	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A09	LRP6e3e4	YTFTYRYLH	1681	GRIPILGSTNY A	1767	CTTDLWDYW	2047	QASQGITNY LN	2078	AASSLQS	2110	CLQDYTDPTTF	2142
011S-F02	LRP6e3e4	FTFSTYGMH	1584	SSISVSSGTTTH YA	1804	CARGGSGYYAFDI W	1929	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-G02	LRP6e3e4	YTFTSYAMN	1678	GGIPIFGTAN YA	1749	CARDASGGSTGWY FDSW	1886	RASQGISSYL A	2087	AASSLQS	2110	CQQAYSFPWTF F	2150

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
011S-A03	LRP6e3e4	FTFSSYWM H	1580	STISGGGRTY YA	1808	CATSPYGVFTLDVW	1993	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-C03	LRP6e3e4	YTFSYRYLH	1672	GGIPIFGTAN YA	1749	CASTVTDDAFDIW	1977	QASQDISNY LN	2077	DASSLES	2120	CQQSYSFPPFT F	2168
011S-D03	LRP6e3e4	FSFDDYGM S	1554	SVISSGGTIYYA	1812	CARHLSSGYLSYGM DVW	1954	RASQSISSYL A	2093	AASTLQS	2113	CQQSYSTPLTF	2174
011S-F03	LRP6e3e4	FTFSSYAMS	1577	SAISGGGGSTY YA	1786	CAKGGRDGKGYGFD YW	1859	KSSQSVLYTT TNRNHIA	2073	WASSRKS	2135	CQQYVSTPYTF	2189
011S-C04	LRP6e1e2	GTFNSNAIS	1598	GWMPNPSG NTGYA	1776	CARDYYGSGSYNYG MDVW	1912	GASQSVPR NSLA	2066	GASQRAT	2124	COQYHNWPP EYTF	2184
011S-D04	LRP6e1e2	YTFTSYDIN	1679	GIINPSGGSTS YA	1761	CAREAYYYYGMDV W	1915	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-H04	LRP6e1e2	YIFTDYYMH	1669	GRIIPILGRANY A	1765	CARGGYSTLDVW	1932	QASQDISNY LN	2077	AASTLQS	2113	CQQSFSTPRTF	2156
008S-F02	LRP5	YTFINYCM H	1677	GIINPSDGSTS HA	1757	CAKDMVHLIVALAID YW	1851	RSSQSLHS DGYTYLY	2101	TLSYRAS	2134	CMQALEALT F	2144
010S-C06	LRP6e1e2	FTFNSYSMD	1563	SSISPRGGSTY YA	1802	CAPYYYDKSAKPLRSY FDHW	1875	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-E06	LRP6e3e4	LTVSSNYMS	1615	SGISWNSGSIG YA	1796	CARGSCSGGSCYYS FDYW	1944	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-F06	LRP6e3e4	FTFSSWWM H	1575	SAIGTGGGTYY A	1781	CAREVAVKDYYYYY MDVW	1921	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-H06	LRP6e3e4	YTFTSYDIN	1679	GRIIPILGRITNY A	1766	CAREERGATGRAFDI W	1918	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-A07	LRP6e3e4	FTFSSYAMH	1576	ASISSTSGSKYY A	1724	CAKTYDFWSGYTTF DYW	1870	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-B07	LRP6e3e4	FTFSDYMS	1568	SMISYNGGRA FYA	1800	CARGNPPYFDVW	1937	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-C07	LRP6e3e4	FTFSKTDMMH	1569	STITDSRGTY YA	1810	CAKGGDYYYYYYGM DVW	1858	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-D07	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CANGLEDAYAFDIW	1873	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-D05	LRP6e3e4	FTLRNHWLS	1591	SAISGGGGSTY YA	1786	CATRTGYSYGFNF AFDIW	1992	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
009S-E05	LRP6e3e4	YFTTNFMH	1676	GHVDPPGDGET IYA	1756	CARDWGIAAAGDYY YGMDVW	1909	RASQGINSYLA	2081	DAKGLHP	2114	CQQSYSAPLSF	2166
010S-E07	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CAKDDFSLYGMVDV W	1845	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-F05	LRP6e3e4	FTFDDYGM S	1561	SAITGGGGTYA	1781	CARLGSYGSPYYYG MDVW	1960	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-F07	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CARLDYGETEGNDW	1958	RASQVYSNLA	2097	DTSNRAT	2123	CQQYNNWPPITF	2185
010S-G07	LRP6e3e4	FTFSSYAMH	1576	STISGSGSTY YA	1809	CARAGYGRYYYGMD VW	1880	RVSQGISSYLN	2103	AASSLQS	2110	CQQTYTIPITF	2182
009S-G05	LRP6e3e4	FTFSDYMS	1568	SGVSWNGSRT HYA	1799	CAKDSGLV	1853	QASQDISYLN	2077	AASLQRLQ	2112	CQQSYSAPLTF	2167
010S-H07	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CARDDSMGAFDIW	1890	QASQDISYLN	2077	GTSNLQS	2128	CQQSYSTPYTF	2176
010S-A08	LRP6e3e4	HTFLTVDIN	1606	GRITPRLGIAN YA	1770	CASYFGVMDVW	1979	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A07	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CATAYGSSSLNIDYW	1981	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-B07	LRP6e3e4	YFTGYVMH	1675	GWINPNSSGT NYA	1774	CVKDDGGFPLAYAFD IW	2050	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-B06	LRP6e3e4	YFTYRYLH	1681	GGIPIFGTAN YA	1749	CAPALTDAGSFDYW	1874	RVSQISSYLN	2103	AASSLQS	2110	CQQSYSTPLTF	2174
010S-B08	LRP6e3e4	YFTYRYLH	1681	GGIPIVFGTAD YA	1751	CARDREQQILDYW	1904	RASQISNNLN	2082	DASNLET	2115	CQQSYTSRLTF	2179
010S-C08	LRP6e3e4	FTFSTFGMH	1582	STITSSGGSTY A	1809	CARAGIAAAPGSRNY YGMDVW	1878	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-C06	LRP6e3e4	YTFASVDIH	1671	GWMNPNNSG NTGYA	1776	CARATGSGWYTDLG YW	1884	RASRNINRYLN	2099	AASSILLS	2109	CQQSYNVPFTF	2162
009S-D06	LRP6e3e4	FTFSSHSTH	1573	STISDTNSGTY YA	1807	CAKAQATGW5GYYT FDYW	1844	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-D08	LRP6e3e4	FTFSSWMH	1575	SAITGGGGTYA	1781	CAKEDYDSSGYYFY FQHW	1855	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-E06	LRP6e3e4	FTFTDYLH	1587	AVISYGGSNKYA	1739	CASGYSYGLYYGMDVW	1974	RASQISSYLN	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
010S-E08	LRP6e3e4	YSFTRTDMH	1670	GVSAYTGHTS YA	1778	CARDLGGTADYW	1898	RASQSISSYL N	2094	ZASSLQS	2137	CQQSYSTPLTF	2174
010S-F08	LRP6e3e4	LTDDHAMH	1613	SYSSSGRTIFY A	1815	CVRGDSGWGILYYV MDVW	2052	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-F06	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CATEAALDAFDIW	1986	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-G08	LRP6e3e4	YIFTDYVMH	1669	GGFDPEDGET IYA	1747	CARGGGPNEHDYF DYW	1927	RASQSVRSS DLA	2096	GSSSRAT	2126	CQQYGRSPRY SF	2183
010S-H08	LRP6e3e4	FTFZNAWMS	1590	SGISGGGGSTY YA	1793	CARGGRKKNNYYGM DVW	1942	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-A09	LRP6e3e4	FTFSTYMS	1586	SGISWNGGKT HYV	1794	CARGGDFDYW	1925	QASQDIANY LN	2075	AASSLQS	2110	CQQSYSTPYTF	2176
010S-B09	LRP6e3e4	GTFSSYALS	1603	GWINPNSGDT NVA	1773	CARGEQWLWVGFD PW	1924	RASQSISSYL N	2092	KASSLES	2130	CQQSYSDSPWTF	2159
009S-G06	LRP6e3e4	YIFTDYVMH	1669	GWINPNSGGT NVA	1774	CARDFLGSTGDYW	1893	RASQNIPLY LN	2088	DASSLQR	2121	CQQSYSTPYTF	2176
010S-C09	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CARDEVEGGMDVW	1891	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-H06	LRP6e3e4	FTFSSAMH	1574	SAIGTGGSTY A	1783	CAKGGDYFYYYGM DVW	1857	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-D09	LRP6e3e4	GTFSSYTIS	1603	GGIVPAYRRA NVA	1754	CAKGGYELDYW	1865	QASQDISNY LN	2077	AASSLQS	2110	CQQIHSYPLTF	2155
010S-E09	LRP6e3e4	GDLSTYTIN	1593	GWINAGNGN TTYA	1772	CARGGDSGGYYYAF DIW	1926	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A07	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CATAYGSSSLNIDYW	1982	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-B07	LRP6e3e4	YTFTGYMH	1675	GWINPNSGGT NVA	1774	CVKDDGGSFPLAYAFD IW	2051	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-D08	LRP6e3e4	YTFTSYDIN	1679	GGIPIFGTAN YA	1749	CARGPYFDYW	1940	RASQGISNN LN	2082	DASSLES	2120	CLQHNSYPFTF	2143
010S-F09	LRP6e3e4	FTFDEVAMH	1562	STISGSGGSTY YA	1809	CASAKNDFWSGYFA FDYW	1968	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-G09	LRP6e3e4	GTFENTHTIT	1599	GWMPNPSNG NTGYA	1776	CARGNLDFDYW	1936	QASQDISNY LN	2077	DASNLET	2115	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
010S-H09	LRP6e3e4	FTFSDHYMS	1567	SAISSGSDRTY YA	1787	CARYSGYDFDVW	1965	RASQGISNY LN	2084	AASLTQS	2113	CQQGYGTPP MF	2153
010S-A10	LRP6e3e4	FSFSSYSIMIN	1559	SYISSSSSTIYYA	1816	CARGSGYGPYGYG MDVW	1946	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-D07	LRP6e3e4	PPFRYGMMS	1551	ARIGWNGGSI VYA	1717	CARDYSDRSGIDYW	1911	RSSQSLHS NGYNYLD	2102	LGSNRRAS	2131	CMQATQFPLT F	2146
010S-B10	LRP6e3e4	FAFKDYMIT	1548	SAIGAGGGTY YA	1779	CARESALYSSSWYYY YGMDDW	1920	RASQISSYL N	2094	GTSSLHT	2129	CQQANSFPPT F	2148
010S-C10	LRP6e3e4	FTFSSYAMS	1577	SAISGGGGTY YA	1786	CAKGGRDGYKGVFD YW	1860	KSSQSLSSS SNRDSLA	2072	WASSRKS	2135	CQQYNNIPYSF	2187
009S-E07	LRP6e3e4	YTFTGYIHH	1674	ZHVDPEDGETI YA	1819	CARGPAAIGILGWFD PW	1938	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-D10	LRP6e3e4	YIFTDYVMH	1669	GWMPNPSG NTGYA	1776	CARTLSGYSSSWYVF DYW	1964	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-E10	LRP6e3e4	FTFSSYSMIN	1579	SGISWNSGTT GYS	1797	CARDHSSGW/RHYFD YW	1895	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-F10	LRP6e3e4	FTFSNSDM N	1570	SYISGNSGTYN YA	1814	CASGSYYSDFDYW	1971	RASQISNYL N	2090	AASTLES	2111	CQQANSFPPT F	2148
010S-G10	LRP6e3e4	GTFSSYALS	1603	GRINPNNGGT IYA	1769	CAREGGYDFYW	1919	RASQGISNY LA	2083	AASSLQS	2110	CQQSYSTPWT F	2175
009S-F07	LRP6e3e4	GTFSSYALS	1603	GIINPSGGSTS YA	1761	CARAAGNFWSGYYT FDYW	1877	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-G07	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CARGSYGMDVW	1948	RASQGISNY LA	2083	DASNLET	2115	CLQDFSFPWT F	2140
010S-H10	LRP6e3e4	YTFTSYVMH	1680	GWINPNNGGT NYA	1774	CAREAAEIPVGAFDI W	1914	KSSHLLYSS DNKNYLA	2071	WSSTRES	2136	CQQYSTPQT F	2188
010S-A11	LRP6e3e4	FTFSNSDM N	1570	SYISGNSGTYN YA	1814	CASGSYYSDFDYW	1972	RASQISNYL N	2095	ZASTLES	2138	CQQANSFPPT F	2148
010S-B11	LRP6e3e4	FTFRNYAIH	1564	SAIGTGGDTTY A	1780	CARDGGIRDYDFYW	1894	QASQDISNY LN	2077	AASLTQS	2113	CQQSYSTPLTF	2174
010S-C11	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CAADDLGLIELHYW	1822	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-H07	LRP6e3e4	YTFTGYVMH	1675	GWMPNPSG NTGYA	1776	CASSVVPAGPAGVY AFDIW	1976	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
009S-A08	LRP6e3e4	GTFSHAIN	1602	GWISANNNGN TDYA	1775	CARDQDYGDYGWY YGMDVW	1903	RASQGISNY LA	2083	GSSTLQS	2127	CQQTYSIPPTF	2181
010S-D11	LRP6e3e4	YFTFYRYLH	1681	GGIIPVFGTAN YA	1752	CATDEYSSSYAFDIW	1983	RASQSVSSN LA	2097	GASTRAT	2125	CQQFDRSPLT F	2151
010S-E11	LRP6e3e4	FTFSAHGM H	1565	SGISEGGSTY YA	1791	CARGRGYSYGYAFD IW	1943	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-F11	LRP6e3e4	YFTFYRYLH	1681	GGIIPFGTAN YA	1749	CARDSDWGVVDPW	1905	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-G11	LRP6e3e4	YFTFYRYLH	1681	GRIIPVLKITNY A	1768	CAVVDDAFDIW	1997	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-H11	LRP6e3e4	YFTFYRYLH	1681	GGIIPFGTAN YA	1749	CAKDGTDGRFDPW	1846	RASQDISYL A	2080	SASTLQS	2133	CQQSNSFPYT F	2157
009S-B08	LRP6e3e4	FTFTSSAVQ	1589	GWINAGNGN TTYA	1772	CARRGGDVTVPAA YAMDVW	1963	RASQISSYL N	2094	ZASSLQS	2137	CQQSYSTPLTF	2174
010S-A12	LRP6e3e4	VTFSRYPIS	1667	GGIIPFGTAN YA	1749	CAKDSGNVGYGMD VW	1854	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-B12	LRP6e3e4	FTFSSYDMH	1578	SGITSNGGATY YA	1798	CARGTTGKGYYYG MDVW	1949	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-C12	LRP6e3e4	FTFSNVWIH	1571	SAIGTGGGTYY A	1781	CTTAGYKAARRSVYP RIFNFDYW	2044	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-D12	LRP6e3e4	YFTFYRYLH	1681	GRIIPFGTANY A	1763	CAREEGVGGMDVW	1917	RPSQSIGSW LA	2100	DASNLQS	2116	CQQSSSTPYTF	2158
010S-E12	LRP6e3e4	FTFSSYAMH	1576	SAIGAGGGTY YA	1779	CARGVSSGYYYYG MDVW	1950	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
010S-F12	LRP6e3e4	FTVSSNYMS	1592	SAIGTGGGTYY A	1781	CARAGTNWGGWYF DLW	1879	RASQISRD LA	2085	AASTLQS	2113	CQQSYSPPTF	2172
010S-G12	LRP6e3e4	FALSGYMS	1550	SSISSSTVIRY A	1803	CATVTGYSSAGAFDI W	1995	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-A01	LRP6e3e4	FTFSTHAFH	1583	SAIRGSGERTY YA	1784	CARDLRNWGSPYW YFDLW	1901	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-B01	LRP6e3e4	GTFSHYTIS	1600	GWINAGNGN TKYS	1771	CAKGGSLDMDVW	1864	RASQGISNY LA	2083	AASSLHS	2108	CQQSYRTPLTF	2164
011S-C01	LRP6e3e4	LTFTSHGMS	1615	SVSDSGSSVY YA	1818	CARHPGSGGYSYA WYYYGMDVW	1957	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
011S-D01	LRP6e3e4	GTISDYTVS	1605	GINPSGGSTS YA	1761	CARGYYDFDYW	1953	RASQGISNY LA	2083	AASSLQS	2110	CQQSYSTPLTF	2174
009S-C08	LRP6e3e4	FSFNFTGHIH	1556	AVISYDGSNKY YA	1738	CAKSIAAAAGTGYG MDVW	1869	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-E01	LRP6e3e4	PPFZYYSMIN	1552	SAISGRDGRTY YA	1785	CAKDLGILQLPDYYFD YW	1847	RASQGISSA LA	2086	AASTLQS	2113	CQQSYSPPTF	2173
009S-D08	LRP6e3e4	YTFTSYDIN	1679	GGIPIFGTAN YA	1749	CARGPYDFDYW	1941	RASQGISNN LN	2082	DASSLES	2120	CLQHNSYPPTF	2143
011S-F01	LRP6e3e4	FSFSDYYMS	1558	SGISESGGRTY YA	1790	CASAAADF DYW	1967	RASQDISNY LN	2079	AASSLQS	2110	CLQDYSYPRTF	2141
009S-E08	LRP6e3e4	YGFTGYIHH	1668	GWMNPNSSG NTGYA	1776	CARGYGDYDLW	1952	QASQDISNY LN	2077	DASSLES	2120	CQQSYRYPTF	2165
009S-F08	LRP6e3e4	DTFANYGFS	1547	GXVNAGNGN TTYA	1777	CAKGWLD FDYW	1867	QASQDISNY LN	2077	DASSLES	2120	CQQSYSTSITF	2177
011S-G01	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1750	CTDDYGDQYGM VW	2046	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-H01	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CTDDYGD LTHDY W	2045	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-A02	LRP6e3e4	GTFSYAIS	1603	GWMNPNSSG NTGYA	1776	CARDKGYAFDIW	1896	RSSQSLHS NGYNYLD	2102	AASSLQS	2110	CMQALQTPIT F	2145
011S-B02	LRP6e3e4	YSFTRTDMH	1670	GVISAYTGHTS YA	1778	CARDLGGTADYW	1899	RZSQSZSYL N	2104	AASSLQS	2110	CQQSYSTPLTF	2174
011S-C02	LRP6e3e4	FTFSTYSMIN	1585	SGISWNSGRI GYA	1795	CARDVGA FDIW	1906	QASQDISNY LN	2077	AASILQS	2107	CQQSYSPPTF	2169
009S-G08	LRP6e3e4	FTFSDFAMT	1566	SYISGDSGYTN YA	1813	CARLGSYPGPYYM DVW	1962	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-D02	LRP6e3e4	FTFSSYAMS	1577	SSISGSGGYTY YA	1801	CARGGNTY YYYGM DVW	1928	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-H08	LRP6e3e4	YTFTDYFMN	1673	GINPSGDSTR FA	1758	CARDDDLGGMDVW	1889	QASQDISNY LA	2076	AASSLQS	2110	CQQSYSTPLTF	2174
011S-E02	LRP6e3e4	YTFTYRYLH	1681	GGIPIFGTAN YA	1749	CATDYG DYYGMDV W	1984	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-A09	LRP6e3e4	YTFTYRYLH	1681	GRIPILGSTNY A	1767	CTTDLWDYW	2048	QASQGITNY LN	2078	AASSLQS	2110	CLQDYTD PPTF	2142

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
011S-F02	LRP6e3e4	FTFSTYGMH	1584	SSISVSSGTH YA	1805	CARGGSGYYAFDI W	1930	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-G02	LRP6e3e4	YFTTSYAMN	1678	GGIPIFGTAN YA	1749	CARDASGGSTGWY FDSW	1887	RASQGISSYL A	2087	AASSLQS	2110	CQQAYSFPWT F	2150
011S-H02	LRP6e3e4	YFTTNFM H	1676	GINPSGGSTS YA	1761	CARGLYKRYSGYG MDVW	1935	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
009S-B09	LRP6e3e4	FSFNTYAM N	1557	AVTSYDGGKK NVA	1742	CARDAGGDYDWW	1885	QASQDISNY LN	2077	AASSLQS	2110	CQQSYNTPT F	2161
009S-C09	LRP6e3e4	GTFHTYGLS	1597	GGIPIFGTAN YA	1749	CARGSGWSGLDWW	1945	QASQDISNY LN	2077	DASNLET	2115	CQQSYTTPFTF	2180
011S-A03	LRP6e3e4	FTFSSYWM H	1580	STISGGGRTY YA	1808	CATSPYGVFTLDWW	1994	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-B03	LRP6e3e4	GTFZYAIS	1604	GINPSGGSTN YA	1760	CARAGYWSGYGYG MDVW	1881	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-C03	LRP6e3e4	YTFSVRYLH	1672	GGIPIFGTAN YA	1749	CASTVTDDAFDIW	1978	QASQDISNY LN	2077	DASSLES	2120	CQQSYSEPPPT F	2168
011S-D03	LRP6e3e4	FSFDDYGM S	1554	SVISSGGTIYA YA	1812	CARHLSSGYLSYGM DWW	1955	RASQISSYL A	2093	AASTLQS	2113	CQQSYSTPLTF	2174
009S-F09	LRP6e3e4	YSFTRTDMH	1670	GYISAYTGHTS YA	1778	CARDLGGTADWW	1900	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-E03	LRP6e3e4	FTFSSYAMS	1577	SAISGGGSTY YA	1786	CAKGGRDGYKGYFD YW	1861	KSSHLLSTS TNRNQLA	2070	WASSRKS	2135	CQQYNNWPY TF	2186
009S-G09	LRP6e3e4	FTFSRHSMN	1572	SYSSGNSGYT NVA	1817	CARGDLEFDWW	1923	RASQGISNY LA	2083	SASSLOS	2132	CQQGYNTPT F	2154
011S-F03	LRP6e3e4	FTFSSYAMS	1577	SAISGGGSTY YA	1786	CAKGGRDGYKGYFD YW	1862	KSSQSVLYTT TNRNHIA	2074	WASSRKS	2135	CQQYSTPTTF	2189
009S-H09	LRP6e3e4	FTFSSYAMS	1577	SAISGGGSTY YA	1786	CAKGGRDGYKGYFD YW	1863	KSSHLLSTS TNRNHIA	2069	WASSRKS	2135	CQQYNNIPVSF	2187
011S-G03	LRP6e3e4	YFTYRYLH	1681	GRIPIHGIAN A	1764	CARESYGYFRYW	1922	RASQISSYL A	2087	DASNLET	2115	CQQANSLTF	2149
009S-A10	LRP6e3e4	FTFTSSAMQ	1588	GINPSGGSTY A	1759	CASGDTVDLYSLDV W	1970	RASQISRW LA	2091	AASSLQS	2110	CQQAYSFPWT F	2150
009S-B10	LRP6e3e4	YIFTDYVMH	1669	GWINAGNGN TTYA	1772	CAKVASGWSW/PFDI W	1871	RASQISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174

Clone ID	Confirmed Binding	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID
011S-B04	LRP6e1e2	YTFTSYDIN	1679	GIINPSGGSTS YA	1761	CTREHSYVYGGMDV W	2042	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-C04	LRP6e1e2	GTFNSNAIS	1598	GWMPNPSG NTGYA	1776	CARDYVGSYNYG MDVW	1913	GASQSVPR NSLA	2066	GASQRAT	2124	CQYHNWPP EYTF	2184
011S-D04	LRP6e1e2	YTFTSYDIN	1679	GIINPSGGSTS YA	1761	CAREAYVYGGMDV W	1916	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-E04	LRP6e1e2	FTFSSZIMH	1581	SAIGTGGGTZY A	1782	CAKDLGRAAAGSMD VW	1850	WASQSVRG NYVA	2106	DASNRAA	2117	CQHRSNWPLT F	2147
011S-F04	LRP6e1e2	YIFTDYYMH	1669	GRIIPILGRANY A	1765	CARGGYSTLDYW	1933	HGSQDISNY LN	2067	DASNROS	2119	CQQSFSTPRTF	2156
011S-H04	LRP6e1e2	YIFTDYYMH	1669	GRIIPILGRANY A	1765	CARGGYSTLDYW	1934	QASQDISNY LN	2077	AASLTQS	2113	CQQSFSTPRTF	2156
011S-A05	LRP6e1e2	FTFSSYAMH	1576	SAIGTGGGTYY A	1781	CAKDLGRAAAGSMD VW	1848	WASQSVRG NYVA	2106	DASNRAA	2118	CQHRSNWPLT F	2147
011S-B05	LRP6e1e2	YZFTDYYMH	1683	GWMPNPSG NTGYA	1776	CTRVAVGLDYW	2043	RASQSISSYL N	2094	AASSLQS	2110	CQQSYSTPLTF	2174
011S-C05	LRP6e1e2	FTFSSYAMH	1576	SAIGTGGGTYY A	1781	CAKDLGRAAAGSMD VW	1849	WASQSVRG NYVA	2106	DASNRAA	2117	CQHRSNWPLT F	2147
111S.3	LRP6e1e2	GFSTST		NLNGGS		ELAGYTPFAY		KASQSISSYL H		YTSQIS		QQNSNWPLT	
421.1	LRP6e1e2	GYTFTTY		FPGNVNT		EELQYVFDY		SANSSVRFEM F		RTSNLAS		QQYHSYPWT	
YW211.31 .57	LRP6e3e4	GFTFTSY		SPYSGS		RARPPILHPRGSVM DY		RASQDVSTA VA		SASFLYS		QQSYTTPPT	

Table 2B. Anti-LRP5/6 Antibody Clone IDs, Heavy Chain (HC) Seq ID Nos, and Binding Characteristics.

Clone ID	HC Seq ID NO	Confirmed Binding
001S-F11	66	LRP6e1e2
009S-G02	67	LRP6e1e2
009S-A03	68	LRP6e1e2
009S-D03	69	LRP6e1e2
009S-F03	70	LRP6e1e2
009S-H03	71	LRP6e1e2
009S-A04	72	LRP6e1e2
009S-B04	73	LRP6e3e4
009S-D04	74	LRP6e3e4
009S-E04	75	LRP6e3e4
009S-F04	76	LRP6e3e4
009S-G04	77	LRP6e3e4
009S-H04	78	LRP6e3e4
009S-A05	79	LRP6e3e4
013S-G04	80	LRP6e3e4
013S-H04	81	LRP6e3e4
013S-C05	82	LRP6e3e4
013S-D05	83	LRP6e3e4
013S-G04	84	LRP6e3e4
013S-H04	85	LRP6e3e4
013S-A05	86	LRP6e3e4
013S-C05	87	LRP6e3e4
013S-D05	88	LRP6e3e4
008S-D01	133	LRP5

In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 with a K_D of less than or equal to about 1×10^{-4} M, less than or equal to about 1×10^{-5} M, less than or equal to about 1×10^{-6} M, less than or equal to about 1×10^{-7} M, less than or equal to about 1×10^{-8} M, less than or equal to about 1×10^{-9} M, or less than or equal to about 1×10^{-10} M in the context of a Wnt surrogate molecule. In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 with a K_D of greater than or equal to about 1×10^{-4} M, greater than or equal to about 1×10^{-5} M, greater than or equal to about 1×10^{-6} M, greater than or equal to about 1×10^{-7} M, greater than or equal to about 1×10^{-8} M, greater than or equal to about 1×10^{-9} M, or greater than about 1×10^{-10} M in the context of a Wnt surrogate molecule. In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 at high affinity, e.g. a K_D of less than about 1×10^{-7} M, less than about 1×10^{-8} M, less than about 1×10^{-9} M, or less than about 1×10^{-10} M.

Other 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; VHH or sdAb derived binding domains; knottin-based engineered scaffolds; naturally occurring LRP5/6, including without limitation, DKK1, DKK2, DKK3, DKK4, sclerostin; Wise; 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.

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. The C-terminal domain may comprise

5 the sequence:

KMYHTKGQEGSVCLRSSDCASGLCCARHFWKICKPVLKEGQVCTKHRRKGS
HGLEIFQRCYCGEGLSCRIQKDHQASNSSRLHTCQRH (SEQ ID NO:2190)
(see Genbank accession number NP_036374) or a biologically active fragment thereof.

10 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:

15 KMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSH
GLEIFQRCDCAKGLSCKVWKDATYSSKARLHVCQK (SEQ ID NO:2191) or a biologically active fragment thereof.

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
20 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,
25 which was raised against synthetic LRP5/6 of human origin and binds to both the full length and proteolytic fragment of LRP6 and LRP5 of mouse and human origin; the monoclonal antibody 2B11; Cell Signaling Technology antibody specific for LRP5 (D80F2), catalog number 5731; etc.

In certain embodiments, Wnt surrogate molecules disclosed herein
30 comprise one or more polypeptides comprising two or more binding regions. For example, the two or more binding regions may be two or more Fzd binding

regions or two or more LRP5/6 binding regions, or they may comprise one or more Fzd binding region and one or more LRP5/6 binding region. The binding regions may be directly joined or contiguous, or may be separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, etc. 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 surrogate molecule. 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. In some embodiments the linker is a rigid linker, in other embodiments the linker is a flexible linker. In certain embodiments where the linker is a peptide linker, 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.

In particular embodiments, a Wnt surrogate molecule comprises a polypeptide sequence having at least 90%, at least 95%, at least 98% or at least 99% identity to a polypeptide sequence disclosed in any of SEQ ID NOs:89-128 or 134-157, or having at least 90%, at least 95%, at least 98% or at least 99% identity to an antigen-binding fragment of a polypeptide sequence disclosed in any of SEQ ID NOs:89-128 or 134-157. In certain embodiments, the Wnt surrogate molecules comprises or consists of a polypeptide sequence set forth in any of SEQ ID NOs:89-128 or 134-157, or an antigen-binding fragment thereof. In particular embodiments, the antigen-binding fragment binds one or more Fzd receptors and also binds LRP5 and/or LRP6.

Wnt surrogate molecule can be multimerized, e.g. through an Fc domain, by concatenation, coiled coils, polypeptide zippers, biotin/avidin or streptavidin multimerization, and the like. The Wnt surrogate molecules can also

be joined to a moiety such as PEG, Fc, etc., as known in the art to enhance stability in vivo.

In certain embodiments, a Wnt surrogate molecule directly activates canonical Wnt signaling through binding to one or more Fzd proteins and to LRP5/6, particularly by binding to these proteins on a cell surface, e.g.,
5 the surface of a human cell. The direct activation of Wnt signaling by a Wnt surrogate molecule is in contrast to potentiation of Wnt signaling, which enhances activity only when native Wnt proteins are present.

Wnt surrogate molecules may activate Wnt signaling, e.g., by
10 mimicking the effect or activity of a Wnt protein binding to a frizzled protein. The ability of the Wnt surrogate molecules of the invention to mimic the activity of Wnt can be confirmed by a number of assays. The Wnt surrogate molecules typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the Wnt surrogate molecules of the
15 invention enhance the canonical Wnt/ β -catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/ β -catenin signaling compared with the level in the absence of a Wnt surrogate molecule of the invention.

Various methods are known in the art for measuring the level of
20 canonical Wnt/ β -catenin signaling. These include, but are not limited to assays that measure: Wnt/ β -catenin target gene expression; TCF reporter gene expression; β -catenin stabilization; LRP phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP. The canonical Wnt/ β -catenin signaling pathway ultimately leads to changes in gene expression through the
25 transcription factors TCF7, TCF7L1, TCF7L2 (a.k.a. TCF4), and LEF. The transcriptional response to Wnt activation has been characterized in a number of cells and tissues. As such, global transcriptional profiling by methods well known in the art can be used to assess Wnt/ β -catenin signaling activation or inhibition.

Changes in Wnt-responsive gene expression are generally
30 mediated by TCF and LEF transcription factors. A TCF reporter assay assesses changes in the transcription of TCF/LEF controlled genes to determine the level

of Wnt/ β -catenin signaling. A TCF reporter assay was first described by Korinek, V. et al., 1997. Also known as TOP/FOP this method involves the use of three copies of the optimal TCF motif CCTTTGATC, or three copies of the mutant motif CCTTTGGCC, upstream of a minimal c-Fos promoter driving luciferase

5 expression (pTOPFL_ASH and pFOPFL_ASH, respectively) to determine the transactivational activity of endogenous β -catenin/TCF4. A higher ratio of these two reporter activities (TOP/FOP) indicates higher β -catenin/TCF4 activity, whereas a lower ratio of these two reporter activities indicates lower β -catenin/TCF4 activity.

10 Various other reporter transgenes that respond to Wnt signals exist intact in animals and therefore, effectively reflect endogenous Wnt signaling. These reporters are based on a multimerized TCF binding site, which drives expression of LacZ or GFP, which are readily detectable by methods known in the art. These reporter genes include: TOP-GAL, BAT-GAL, ins-TOPEGFP, ins-
15 TOPGAL, LEF-EGFP, Axin2-LacZ, Axin2-d2EGFP, Lgr5tm1 (cre/ERT2), TOPdGFP.

The recruitment of dephosphorylated β -catenin to the membrane, stabilization and phosphorylation status of β -catenin, and translocation of β -catenin to the nucleus (Klapholz- Brown Z et al., PLoS One. 2(9) e945, 2007), in
20 some cases mediated by complex formation with TCF transcription factors and TNIK are key steps in the Wnt signaling pathway. Stabilization is mediated by Disheveled family proteins that inhibit the "destruction" complex so that degradation of intracellular β -catenin is reduced, and translocation of β -catenin to the nucleus follows thereafter. Therefore, measuring the level and location of β -
25 catenin in a cell is a good reflection of the level of Wnt/ β -catenin signaling. A non-limiting example of such an assay is the "BioImage β -Catenin Redistribution Assay" (Thermo Scientific) which provides recombinant U20S cells that stably express human β -catenin fused to the C-terminus of enhanced green fluorescent protein (EGFP). Imaging and analysis is performed with a fluorescence
30 microscope or HCS platform allowing the levels and distribution of EGFP- β -catenin to be visualized.

Another way, in which the destruction complex is inhibited, is by removal of Axin by recruitment of Axin to the cytoplasmic tail of the Wnt co-receptor LRP. Axin has been shown to bind preferentially to a phosphorylated form of the LRP tail. Visualization of Axin translocation, for example with a GFP-Axin fusion protein, is therefore another method for assessing levels of Wnt/ β -catenin signaling.

In certain embodiments, a Wnt surrogate molecule enhances or increases canonical Wnt pathway signaling, e.g., β -catenin signaling, by at least 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 150%, 200%, 250%, 300%, 400% or 500%, as compared to the β -catenin signaling induced by a neutral substance or negative control as measured in an assay described above, for example as measured in the TOPFlash assay. A negative control may be included in these assays. In particular embodiments, Wnt surrogate molecules may enhance β -catenin signaling by a factor of 2x, 5x, 10x, 100x, 1000x, 10000x or more as compared to the activity in the absence of the Wnt surrogate molecule when measured in an assay described above, for example when measured in the TOPFlash assay, or any of the other assays mentioned herein.

"Wnt gene product" or "Wnt polypeptide" when used herein encompass native sequence 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.

For example, human native sequence Wnt proteins of interest in the present application include the following: Wnt-1 (GenBank Accession No. NM_005430); Wnt-2 (GenBank Accession No. NM_003391); Wnt-2B (Wnt-13) (GenBank Accession No. NM_004185 (isoform 1), NM_024494.2 (isoform 2)), Wnt-3 (RefSeq.: NM_030753), Wnt3a (GenBank Accession No. NM_033131), Wnt-4 (GenBank Accession No. NM_030761), Wnt-5A (GenBank Accession No. NM_003392), Wnt-5B (GenBank Accession No. NM_032642), Wnt-6 (GenBank Accession No. NM_006522), Wnt-7A (GenBank Accession No. NM_004625),

Wnt- 7B (GenBank Accession No. NM_058238), Wnt-8A (GenBank Accession No. NM_058244), Wnt-8B (GenBank Accession No. NM_003393), Wnt-9A (Wnt-14) (GenBank Accession No. NM_003395), Wnt-9B (Wnt-15) (GenBank Accession No. NM_003396), Wnt-1 OA (GenBank Accession No. NM_025216),
 5 Wnt-10B (GenBank Accession No. NM_003394), Wnt-11 (GenBank Accession No. NM_004626), Wnt- 16 (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
 10 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
 15 fish, fruit fly, worm, etc.

"Wnt pathway signaling" or "Wnt signaling" is used herein to refer to the mechanism by which a biologically active Wnt exerts its effects upon a cell to modulate a cell's activity. Wnt proteins modulate cell activity by binding to Wnt receptors, including proteins from the Frizzled (Fzd) family of proteins, proteins
 20 from the ROR family of proteins, the proteins LRP5, LRP6 from the LRP family of proteins, the protein FRL1/crypto, and the protein Derailed/Ryk. Once activated by Wnt binding, the Wnt receptor(s) will activate one or more intracellular signaling cascades. These include the canonical Wnt signaling pathway; the Wnt/planar cell polarity (Wnt/PCP) pathway; the Wnt-calcium (Wnt/Ca²⁺) pathway
 25 (Giles, RH et al. (2003) Biochim Biophys Acta 1653, 1-24; Peifer, M. et al. (1994) Development 120: 369-380; Papkoff, J. et al (1996) Mol. Cell Biol. 16: 2128-2134; Veeman, M. T. et al. (2003) Dev. Cell 5: 367-377); and other Wnt signaling pathways as is well known in the art.

For example, activation of the canonical Wnt signaling pathway
 30 results in the inhibition of phosphorylation of the intracellular protein β -catenin, leading to an accumulation of β -catenin in the cytosol and its subsequent

translocation to the nucleus where it interacts with transcription factors, e.g. TCF/LEF, to activate target genes. Activation of the Wnt/PCP pathway activates RhoA, c-Jun N-terminal kinase (JNK), and nemo-like kinase (NLK) signaling cascades to control such biological processes as tissue polarity and cell
5 movement. Activation of the Wnt/Ca²⁺ by, for example, binding of Wnt-4, Wnt-5A or Wnt-11, elicits an intracellular release of calcium ions, which activates calcium sensitive enzymes like protein kinase C (PKC), calcium-calmodulin dependent kinase II (CamKII) or calcineurin (CaCN). By assaying for activity of the above
10 signaling pathways, the biological activity of an antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate molecule, can be readily determined.

In certain embodiments, functional properties of Wnt surrogate molecules may be assessed using a variety of methods known to the skilled person, including e.g., affinity/binding assays (for example, surface plasmon resonance, competitive inhibition assays), cytotoxicity assays, cell viability
15 assays, cell proliferation or differentiation assays in response to a Wnt, cancer cell and/or tumor growth inhibition using *in vitro* or *in vivo* models, including but not limited to any described herein. The Wnt surrogate molecules described herein may also be tested for effects on Fzd receptor internalization, *in vitro* and *in vivo* efficacy, etc. Such assays may be performed using well-established
20 protocols known to the skilled person (see e.g., Current Protocols in Molecular Biology (Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., NY, NY); Current Protocols in Immunology (Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober 2001 John Wiley & Sons, NY, NY); or commercially available kits.

25 In certain embodiments, a Fzd-binding region of a Wnt surrogate molecule (e.g., an antigen-binding fragment of an anti-Fzd antibody) comprises one or more of the CDRs of the anti-Fzd antibodies described herein. In certain embodiments, a LRP5/6-binding region of a Wnt surrogate molecule (e.g., an antigen-binding fragment of an anti-LRP5/6 antibody) comprises one or more of
30 the CDRs of the anti-LRP5/6 antibodies described herein. In this regard, it has been shown in some cases that the transfer of only the VHCDR3 of an antibody

can be performed while still retaining desired specific binding (Barbas *et al.*, *PNAS* (1995) 92: 2529-2533). See also, McLane *et al.*, *PNAS* (1995) 92:5214-5218, Barbas *et al.*, *J. Am. Chem. Soc.* (1994) 116:2161-2162.

Also disclosed herein is a method for obtaining an antibody or
5 antigen binding domain specific for a Fzd receptor, the method comprising
providing by way of addition, deletion, substitution or insertion of one or more
amino acids in the amino acid sequence of a VH domain set out herein or a VH
domain which is an amino acid sequence variant of the VH domain, optionally
combining the VH domain thus provided with one or more VL domains, and
10 testing the VH domain or VH/VL combination or combinations to identify a
specific binding member or an antibody antigen binding domain specific for one
or more Fzd receptor and optionally with one or more desired properties. The VL
domains may have an amino acid sequence which is substantially as set out
herein. An analogous method may be employed in which one or more sequence
15 variants of a VL domain disclosed herein are combined with one or more VH
domains.

In particular embodiments, Wnt surrogate molecules are water
soluble. By "water soluble" it is meant a composition that is soluble in aqueous
buffers in the absence of detergent, usually soluble at a concentration that
20 provides a biologically effective dose of the polypeptide. Compositions that are
water soluble form a substantially homogenous composition that has a specific
activity that is at least about 5% that of the starting material from which it was
purified, usually at least about 10%, 20%, or 30% that of the starting material,
more usually about 40%, 50%, or 60% that of the starting material, and may be
25 about 50%, about 90% or greater. Wnt surrogate molecules disclosed herein
typically form a substantially homogeneous aqueous solution at concentrations of
at least 25 μ M and higher, e.g. at least 25 μ M, 40 μ M, or 50 μ M, usually at least
60 μ M, 70 μ M, 80 μ M, or 90 μ M, sometimes as much as 100 μ M, 120 μ M, or 150
 μ M. In other words, Wnt surrogate molecules disclosed herein typically form a
30 substantially homogeneous aqueous solution at concentrations of about 0.1
mg/ml, about 0.5 mg/ml, of about 1 mg/ml or more.

An antigen or epitope that "specifically binds" or "preferentially binds" (used interchangeably herein) to an antibody or antigen-binding fragment thereof is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule, e.g., a Wnt surrogate molecule, is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. A molecule or binding region thereof, e.g., a Wnt surrogate molecule or binding region thereof, "specifically binds" or "preferentially binds" to a target antigen, e.g., a Fzd receptor, if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, a Wnt surrogate molecule or binding region thereof that specifically or preferentially binds to the Fzd1 receptor is an antibody that binds to the Fzd1 receptor with greater affinity, avidity, more readily, and/or with greater duration than it binds to other Fzd receptors or non-Fzd proteins. It is also understood by reading this definition that, for example, a Wnt surrogate molecule or binding region thereof that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

In some embodiments, any of the one or more Fzd binding region of a Wnt surrogate molecule binds to one, two, three, four, five or more different frizzled proteins, e.g., one or more of human frizzled proteins Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, Fzd10. In some embodiments, any of the Fzd binding regions binds to Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8. In various embodiments, any of the Fzd binding regions binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii) Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8. In some embodiments, the Fzd binding

region is selective for one or more Fzd protein of interest, e.g. having a specificity for the one or more desired Fzd protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other Fzd proteins. In some embodiments, any of the one or more Fzd binding region of a Wnt surrogate molecule is

- 5 monospecific and binds or specifically binds to only one of Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, or Fzd10.

In some embodiments, any of the one or more LRP5/6 binding region of a Wnt surrogate molecule binds to one or both of LRP5/6. For convenience, the term "LRP5/6" is used to refer collectively to either or both of

10 LRP5 and/or LRP6.

Immunological binding generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific, for example by way of illustration and not limitation, as a result of electrostatic, ionic, hydrophilic and/or

15 hydrophobic attractions or repulsion, steric forces, hydrogen bonding, van der Waals forces, and other interactions. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity.

Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the

20 rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate

25 constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d . See, generally, Davies *et al.* (1990) *Annual Rev. Biochem.* 59:439-473.

30 In certain embodiments, the Wnt surrogate molecules or binding regions thereof described herein have an affinity of less than about 10,000, less

than about 1000, less than about 100, less than about 10, less than about 1 or less than about 0.1 nM, and in some embodiments, the antibodies may have even higher affinity for one or more Fzd receptor or LRP5 or LRP6 receptor.

The constant regions of immunoglobulins show less sequence
5 diversity than the variable regions, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans, there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing features between these antibody classes are their
10 constant regions, although subtler differences may exist in the V region.

The Fc region of an antibody interacts with a number of Fc receptors and ligands, imparting an array of important functional capabilities referred to as effector functions. For IgG, the Fc region comprises Ig domains CH2 and CH3 and the N-terminal hinge leading into CH2. An important family of
15 Fc receptors for the IgG class are the Fc gamma receptors (Fc γ Rs). These receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). In humans this protein family includes Fc γ RI (CD64), including isoforms Fc γ RIa, Fc γ RIb, and Fc γ RIc;
20 Fc γ RII (CD32), including isoforms Fc γ RIIa (including allotypes H131 and R131), Fc γ RIIb (including Fc γ RIIb-1 and Fc γ RIIb-2), and Fc γ RIIc; and Fc γ RIII (CD16), including isoforms Fc γ RIIIa (including allotypes V158 and F158) and Fc γ RIIIb (including allotypes Fc γ RIIIb-NA1 and Fc γ RIIIb-NA2) (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). These receptors typically have an extracellular domain
25 that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells.
30 Formation of the Fc/Fc γ R complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important

subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack.

The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic cells that express Fc γ Rs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ghetie *et al.*, 2000, Annu Rev Immunol 18:739-766; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express Fc γ Rs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). All Fc γ Rs bind the same region on Fc, at the N-terminal end of the C γ 2 (CH2) domain and the preceding hinge. This interaction is well characterized structurally (Sondermann *et al.*, 2001, J Mol Biol 309:737-749), and several structures of the human Fc bound to the extracellular domain of human Fc γ RIIIb have been solved (pdb accession code 1E4K) (Sondermann *et al.*, 2000, Nature 406:267-273.) (pdb accession codes 1IIS and 1IIX) (Radaev *et al.*, 2001, J Biol Chem 276:16469-16477.)

The different IgG subclasses have different affinities for the Fc γ Rs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4 (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). All Fc γ Rs bind the same region on IgG Fc, yet with different affinities: the high affinity binder Fc γ RI has a K_d for IgG1 of 10^{-8} M $^{-1}$, whereas the low affinity receptors Fc γ RII and Fc γ RIII generally bind at 10^{-6} and 10^{-5} respectively. The extracellular domains of Fc γ RIIIa and Fc γ RIIIb are 96% identical; however, Fc γ RIIIb does not have an intracellular signaling domain. Furthermore, whereas Fc γ RI, Fc γ RIIa/c, and Fc γ RIIIa are positive regulators of immune complex-triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM), Fc γ RIIIb has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Thus the former are

referred to as activation receptors, and Fc γ RIIb is referred to as an inhibitory receptor. The receptors also differ in expression pattern and levels on different immune cells. Yet another level of complexity is the existence of a number of Fc γ R polymorphisms in the human proteome. A particularly relevant

5 polymorphism with clinical significance is V158/F158 Fc γ RIIIa. Human IgG1 binds with greater affinity to the V158 allotype than to the F158 allotype. This difference in affinity, and presumably its effect on ADCC and/or ADCP, has been shown to be a significant determinant of the efficacy of the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals

10 Corporation). Subjects with the V158 allotype respond favorably to rituximab treatment; however, subjects with the lower affinity F158 allotype respond poorly (Cartron *et al.*, 2002, Blood 99:754-758). Approximately 10-20% of humans are V158/V158 homozygous, 45% are V158/F158 heterozygous, and 35-45% of humans are F158/F158 homozygous (Lehrnbecher *et al.*, 1999, Blood 94:4220-

15 4232; Cartron *et al.*, 2002, Blood 99:754-758). Thus 80-90% of humans are poor responders, that is, they have at least one allele of the F158 Fc γ RIIIa.

The Fc region is also involved in activation of the complement cascade. In the classical complement pathway, C1 binds with its C1q subunits to Fc fragments of IgG or IgM, which has formed a complex with antigen(s). In

20 certain embodiments of the invention, modifications to the Fc region comprise modifications that alter (either enhance or decrease) the ability of a Fzd-specific antibody as described herein to activate the complement system (see *e.g.*, U.S. Patent 7,740,847). To assess complement activation, a complement-dependent cytotoxicity (CDC) assay may be performed (See, *e.g.*, Gazzano-Santoro *et al.*,

25 J. Immunol. Methods, 202:163 (1996)).

Thus in certain embodiments, the present invention provides anti-Fzd antibodies having a modified Fc region with altered functional properties, such as reduced or enhanced CDC, ADCC, or ADCP activity, or enhanced binding affinity for a specific Fc γ R or increased serum half-life. Other modified Fc

30 regions contemplated herein are described, for example, in issued U.S. Patents 7,317,091; 7,657,380; 7,662,925; 6,538,124; 6,528,624; 7,297,775; 7,364,731;

Published U.S. Applications US2009092599; US20080131435; US20080138344; and published International Applications WO2006/105338; WO2004/063351; WO2006/088494; WO2007/024249.

In certain embodiments, Wnt surrogate molecules comprise
5 antibody variable domains with the desired binding specificities fused to immunoglobulin constant domain sequences. In certain embodiments, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. In particular embodiments, the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at
10 least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three
15 polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant effect on the yield of the desired
20 chain combination.

Wnt surrogate molecules disclosed herein may also be modified to include an epitope tag or label, *e.g.*, for use in purification or diagnostic applications. There are many linking groups known in the art for making antibody conjugates, including, for example, those disclosed in U.S. Pat. No. 5,208,020 or
25 EP Patent 0 425 235 B1, and Chari *et al.*, Cancer Research 52: 127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

30 In certain embodiments, anti-LRP5/6 antibodies and antigen-binding fragments thereof and/or anti-Fzd antibodies and antigen-binding

fragments thereof present within a Wnt surrogate molecule are monoclonal. In certain embodiments, they are humanized.

The present invention further provides in certain embodiments an isolated nucleic acid encoding a polypeptide present in a Wnt surrogate molecule disclosed herein. Nucleic acids include DNA and RNA. These and related 5 embodiments may include polynucleotides encoding antibody fragments that bind one or more Fzd receptors and/or LRP5 or LRP6 as described herein. The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin, or some combination thereof, which by virtue 10 of its origin, the isolated polynucleotide: (1) is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature; (2) is linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence. An isolated polynucleotide may include naturally occurring and/or artificial sequences.

15 The term "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a transcription control sequence "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions 20 compatible with the transcriptional activity of the control sequences.

The term "control sequence" as used herein refers to polynucleotide sequences that can affect expression, processing or intracellular localization of coding sequences to which they are ligated or operably linked. The nature of such control sequences may depend upon the host organism. In 25 particular embodiments, transcription control sequences for prokaryotes may include a promoter, ribosomal binding site, and transcription termination sequence. In other particular embodiments, transcription control sequences for eukaryotes may include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, transcription 30 termination sequences and polyadenylation sequences. In certain embodiments,

"control sequences" can include leader sequences and/or fusion partner sequences.

The term "polynucleotide" as referred to herein means single-stranded or double-stranded nucleic acid polymers. In certain embodiments, the nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine, ribose modifications such as arabinoside and 2',3'-dideoxyribose and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate and phosphoroamidate. The term "polynucleotide" specifically includes single and double stranded forms of DNA.

The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" includes oligonucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. See, e.g., LaPlanche *et al.*, 1986, Nucl. Acids Res., 14:9081; Stec *et al.*, 1984, J. Am. Chem. Soc., 106:6077; Stein *et al.*, 1988, Nucl. Acids Res., 16:3209; Zon *et al.*, 1991, Anti-Cancer Drug Design, 6:539; Zon *et al.*, 1991, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, pp. 87-108 (F. Eckstein, Ed.), Oxford University Press, Oxford England; Stec *et al.*, U.S. Pat. No. 5,151,510; Uhlmann and Peyman, 1990, Chemical Reviews, 90:543, the disclosures of which are hereby incorporated by reference for any purpose. An oligonucleotide can include a detectable label to enable detection of the oligonucleotide or hybridization thereof.

The term "vector" is used to refer to any molecule (e.g., nucleic acid, plasmid, or virus) used to transfer coding information to a host cell. The term "expression vector" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control

expression of inserted heterologous nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and RNA splicing, if introns are present.

As will be understood by those skilled in the art, polynucleotides may include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the skilled person.

As will be also recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide according to the present disclosure, and a polynucleotide may, but need not, be linked to other molecules and/or support materials. Polynucleotides may comprise a native sequence or may comprise a sequence that encodes a variant or derivative of such a sequence.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encodes an antibody as described herein. Some of these polynucleotides bear minimal sequence identity to the nucleotide sequence of the native or original polynucleotide sequence encoding a polypeptide within a Wnt surrogate molecule. Nonetheless, polynucleotides that vary due to differences in codon usage are expressly contemplated by the present disclosure. In certain embodiments, sequences that have been codon-optimized for mammalian expression are specifically contemplated.

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, may be employed for the preparation of variants and/or derivatives of the polypeptides described herein.

By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provide a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments, the inventors contemplate the mutagenesis of the polynucleotide sequences that encode a polypeptide present in a Wnt surrogate molecule, to alter one or more properties of the encoded polypeptide, such as the binding affinity, or the function of a particular Fc region, or the affinity of the Fc region for a particular Fc γ R. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phages are readily commercially available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site

directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

In many embodiments, one or more nucleic acids encoding a polypeptide of a Wnt surrogate molecule are introduced directly into a host cell, and the cell incubated under conditions sufficient to induce expression of the encoded polypeptides. The Wnt surrogate polypeptides of this disclosure may be prepared using standard techniques well known to those of skill in the art in combination with the polypeptide and nucleic acid sequences provided herein. The polypeptide sequences may be used to determine appropriate nucleic acid sequences encoding the particular polypeptide disclosed thereby. The nucleic acid sequence may be optimized to reflect particular codon "preferences" for various expression systems according to standard methods well known to those of skill in the art.

According to certain related embodiments there is provided a recombinant host cell which comprises one or more constructs as described herein, e.g., a vector comprising a nucleic acid encoding a Wnt surrogate molecule or polypeptide thereof; and a method of production of the encoded product, which method comprises expression from encoding nucleic acid therefor. Expression may conveniently be achieved by culturing under appropriate conditions recombinant host cells containing the nucleic acid. Following production by expression, an antibody or antigen-binding fragment

thereof, may be isolated and/or purified using any suitable technique, and then used as desired.

Polypeptides, and encoding nucleic acid molecules and vectors, may be isolated and/or purified, e.g. from their natural environment, in substantially pure or homogeneous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes of origin other than the sequence encoding a polypeptide with the desired function. Nucleic acid may comprise DNA or RNA and may be wholly or partially synthetic. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable host cells include bacteria, mammalian cells, yeast and baculovirus systems. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary cells, HeLa cells, baby hamster kidney cells, NSO mouse melanoma cells and many others. A common, preferred bacterial host is *E. coli*.

The expression of polypeptides, e.g., antibodies and antigen-binding fragments thereof, in prokaryotic cells such as *E. coli* is well established in the art. For a review, see for example Pluckthun, A. Bio/Technology 9: 545-551 (1991). Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production of antibodies or antigen-binding fragments thereof, see recent reviews, for example Ref, M. E. (1993) Curr. Opinion Biotech. 4: 573-576; Trill J. J. et al. (1995) Curr. Opinion Biotech 6: 553-560.

Suitable vectors can be chosen or constructed, containing appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Vectors may be plasmids, viral e.g. phage, or phagemid, as appropriate. For further details see, for example, Molecular Cloning: a Laboratory Manual: 2nd edition, Sambrook et al., 1989, Cold Spring

Harbor Laboratory Press. Many known techniques and protocols for manipulation of nucleic acid, for example in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into cells and gene expression, and analysis of proteins, are described in detail in Current Protocols
5 in Molecular Biology, Second Edition, Ausubel *et al.* eds., John Wiley & Sons, 1992, or subsequent updates thereto.

The term "host cell" is used to refer to a cell into which has been introduced, or which is capable of having introduced into it, a nucleic acid sequence encoding one or more of the herein described polypeptides, and which
10 further expresses or is capable of expressing a selected gene of interest, such as a gene encoding any herein described polypeptide. The term includes the progeny of the parent cell, whether or not the progeny are identical in morphology or in genetic make-up to the original parent, so long as the selected gene is present. Accordingly there is also contemplated a method comprising
15 introducing such nucleic acid into a host cell. The introduction may employ any available technique. For eukaryotic cells, suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, *e.g.* vaccinia or, for insect cells, baculovirus. For bacterial cells, suitable techniques
20 may include calcium chloride transformation, electroporation and transfection using bacteriophage. The introduction may be followed by causing or allowing expression from the nucleic acid, *e.g.* by culturing host cells under conditions for expression of the gene. In one embodiment, the nucleic acid is integrated into the genome (*e.g.* chromosome) of the host cell. Integration may be promoted by
25 inclusion of sequences which promote recombination with the genome, in accordance-with standard techniques.

The present invention also provides, in certain embodiments, a method which comprises using a construct as stated above in an expression system in order to express a particular polypeptide such as a Whyt mimetic
30 molecule as described herein. The term "transduction" is used to refer to the transfer of genes from one bacterium to another, usually by a phage.

"Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by retroviruses. The term "transfection" is used to refer to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of
5 transfection techniques are well known in the art and are disclosed herein. See, e.g., Graham *et al.*, 1973, *Virology* 52:456; Sambrook *et al.*, 2001, *MOLECULAR CLONING, A LABORATORY MANUAL*, Cold Spring Harbor Laboratories; Davis *et al.*, 1986, *BASIC METHODS IN MOLECULAR BIOLOGY*, Elsevier; and Chu *et al.*, 1981, *Gene* 13:197. Such techniques can be used to introduce one or more
10 exogenous DNA moieties into suitable host cells.

The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transfection or transduction,
15 the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, or may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is considered to have been stably transformed when the DNA is replicated with the division of the cell. The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid
20 molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by a human. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by a human.

25 The terms "polypeptide" "protein" and "peptide" and "glycoprotein" are used interchangeably and mean a polymer of amino acids not limited to any particular length. The term does not exclude modifications such as myristylation, sulfation, glycosylation, phosphorylation and addition or deletion of signal sequences. The terms "polypeptide" or "protein" means one or more chains of
30 amino acids, wherein each chain comprises amino acids covalently linked by peptide bonds, and wherein said polypeptide or protein can comprise a plurality

of chains non-covalently and/or covalently linked together by peptide bonds, having the sequence of native proteins, that is, proteins produced by naturally-occurring and specifically non-recombinant cells, or genetically-engineered or recombinant cells, and comprise molecules having the amino acid sequence of
5 the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms "polypeptide" and "protein" specifically encompass Wnt surrogate molecules, Fzd binding regions thereof, LRP5/6 binding regions thereof, antibodies and antigen-binding fragments thereof that bind to a Fzd receptor or a LRP5 or LRP6 receptor
10 disclosed herein, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of any of these polypeptides. Thus, a "polypeptide" or a "protein" can comprise one (termed "a monomer") or a plurality (termed "a multimer") of amino acid chains.

The term "isolated protein," "isolated Wnt surrogate molecule
15 or "isolated antibody" referred to herein means that a subject protein, Wnt surrogate molecule, or antibody: (1) is free of at least some other proteins with which it would typically be found in nature; (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species; (4) has been separated from at least about 50 percent of
20 polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature; (5) is not associated (by covalent or noncovalent interaction) with portions of a protein with which the "isolated protein" is associated in nature; (6) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature; or (7)
25 does not occur in nature. Such an isolated protein can be encoded by genomic DNA, cDNA, mRNA or other RNA, or may be of synthetic origin, or any combination thereof. In certain embodiments, an isolated protein may comprise naturally-occurring and/or artificial polypeptide sequences. In certain embodiments, the isolated protein is substantially free from proteins or
30 polypeptides or other contaminants that are found in its natural environment that

would interfere with its use (therapeutic, diagnostic, prophylactic, research or otherwise).

Amino acid sequence modification(s) of any of the polypeptides (e.g., Wnt surrogate molecules or Fzd binding regions or LRP5/6 binding regions thereof) described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the Wnt surrogate molecule. For example, amino acid sequence variants of a Wnt surrogate molecule may be prepared by introducing appropriate nucleotide changes into a polynucleotide that encodes the antibody, or a chain thereof, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution may be made to arrive at the final Wnt surrogate molecule, provided that the final construct possesses the desired characteristics (e.g., high affinity binding to one or more Fzd and/or LRP5/6 receptor). The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites. Any of the variations and modifications described above for polypeptides of the present invention may be included in antibodies of the present invention.

The present disclosure provides variants of any of the polypeptides (e.g., Wnt surrogate molecules or Fzd binding regions or LRP5/6 binding regions thereof, or antibodies or antigen-binding fragments thereof) disclosed herein. In certain embodiments, a variant has at least 90%, at least 95%, at least 98%, or at least 99% identity to a polypeptide disclosed herein. In certain embodiments, such variant polypeptides bind to one or more Fzd receptor, and/or to one or more LRP5/6 receptor, at least about 50%, at least about 70%, and in certain embodiments, at least about 90% as well as a Wnt surrogate molecule specifically set forth herein. In further embodiments, such variant Wnt surrogate molecules bind to one or more Fzd receptor, and/or to one or more LRP5/6 receptor, with greater affinity than the Wnt surrogate molecules set forth herein,

for example, that bind quantitatively at least about 105%, 106%, 107%, 108%, 109%, or 110% as well as an antibody sequence specifically set forth herein.

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or VHH or sdAb may comprise: a) a heavy chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and/or b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., one or more Fzd receptors or LRP5 or LRP6 receptors). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody or antigen-binding fragment thereof wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10, 11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See e.g., Muller, 1998, Structure 6:1153-1167).

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or VHH or sdAb may have: a) a heavy chain variable region having an amino acid sequence that is at least 80% identical, at least 95% identical, at least 90%, at least 95% or at least 98% or 99% identical, to the heavy chain variable region of an antibody or antigen-binding fragments thereof described herein; and/or b) a light chain variable region having an amino acid sequence that is at least 80% identical, at least 85%, at least 90%, at least

95% or at least 98% or 99% identical, to the light chain variable region of an antibody or antigen-binding fragments thereof described herein. The amino acid sequence of illustrative antigen-binding fragments thereof are set forth in SEQ ID NOs:1-128.

5 A polypeptide has a certain percent "sequence identity" to another polypeptide, meaning that, when aligned, that percentage of 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
10 BLAST, available over the world wide 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
15 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
20 be utilized to align sequences. See J. Mol. Biol. 48: 443-453 (1970)

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
25 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
30 Madison, Wis., USA.

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

5 FastDB based upon the following parameters:
Mismatch Penalty: 1.00; Gap Penalty: 1.00; Gap Size Penalty: 0.33; and Joining Penalty: 30.0.

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or VHH or sdAb may comprise: a) a heavy

10 chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is

15 identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region that is

20 identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., a Fzd receptor, such as Fzd1). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10, 11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH

25 and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See e.g., Muller, 1998, Structure 6:1153-1167).

Determination of the three-dimensional structures of representative

30 polypeptides (e.g., variant Fzd binding regions or LRP5/6 binding regions of Wnt surrogate molecules as provided herein) may be made through routine

methodologies such that substitution, addition, deletion or insertion of one or more amino acids with selected natural or non-natural amino acids can be virtually modeled for purposes of determining whether a so derived structural variant retains the space-filling properties of presently disclosed species. See, for instance, Donate et al., 1994 *Prot. Sci.* 3:2378; Bradley et al., *Science* 309:1868-1871 (2005); Schueler-Furman et al., *Science* 310:638 (2005); Dietz et al., *Proc. Nat. Acad. Sci. USA* 103:1244 (2006); Dodson et al., *Nature* 450:176 (2007); Qian et al., *Nature* 450:259 (2007); Raman et al. *Science* 327:1014-1018 (2010). Some additional non-limiting examples of computer algorithms that may be used for these and related embodiments, such as for rational design of binding regions include VMD which is a molecular visualization program for displaying, animating, and analyzing large biomolecular systems using 3-D graphics and built-in scripting (see the website for the Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champaign, at ks.uiuc.edu/Research/vmd/). Many other computer programs are known in the art and available to the skilled person and which allow for determining atomic dimensions from space-filling models (van der Waals radii) of energy-minimized conformations; GRID, which seeks to determine regions of high affinity for different chemical groups, thereby enhancing binding, Monte Carlo searches, which calculate mathematical alignment, and CHARMM (Brooks et al. (1983) *J. Comput. Chem.* 4:187-217) and AMBER (Weiner et al (1981) *J. Comput. Chem.* 106: 765), which assess force field calculations, and analysis (see also, Eisenfield et al. (1991) *Am. J. Physiol.* 261:C376-386; Lybrand (1991) *J. Pharm. Belg.* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ. Health Perspect.* 61:185-190; and Kini et al. (1991) *J. Biomol. Struct. Dyn.* 9:475-488). A variety of appropriate computational computer programs are also commercially available, such as from Schrödinger (Munich, Germany).

Compositions

Pharmaceutical compositions comprising a Wnt surrogate molecule 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 or Norrin polypeptides.

In further embodiments, pharmaceutical compositions comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule 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 polypeptide or Norrin polypeptide. 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 Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In further embodiments, pharmaceutical compositions comprising an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule 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 polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide, e.g., expression cassette.

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 Wnt surrogate molecule 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 or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide 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.

The present disclosure contemplates pharmaceutical compositions comprising a first molecule for delivery of a Wnt surrogate molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide or Norrin polypeptide. 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).

The subject molecules, alone or in combination, can be combined with pharmaceutically-acceptable carriers, diluents, excipients 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, diluents and excipients 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
5 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
10 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.

Pharmaceutical compositions may further include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation
15 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 such that it can be drawn into a syringe or delivered to a subject from a syringe. In certain embodiments, it is stable under the conditions of manufacture
20 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
25 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
30 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.

Sterile solutions can be prepared by incorporating the anti-Fzd antibody or antigen-binding fragment thereof (or encoding polynucleotide or cell
5 comprising the same) 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
10 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.

In one embodiment, the pharmaceutical compositions are prepared
15 with carriers that will protect the antibody or antigen-binding fragment thereof 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.
20 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.

It may be advantageous to formulate the pharmaceutical
25 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 antibody or antigen-binding fragment thereof calculated to produce the desired therapeutic effect in association with the
30 required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on the unique characteristics of the antibody

or antigen-binding fragment thereof and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active antibody or antigen-binding fragment thereof for the treatment of individuals.

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

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
10 capable of providing (directly or indirectly) the biologically active antibody or antigen-binding fragment thereof.

The present invention includes pharmaceutically acceptable salts of a Wnt surrogate molecule described herein. The term "pharmaceutically acceptable salt" refers to physiologically and pharmaceutically acceptable salts of
15 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
20 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).

25 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-
30 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
5 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.

In some embodiments, the pharmaceutical composition provided herein comprise a therapeutically effective amount of a Wnt surrogate molecule
10 or pharmaceutically acceptable salt thereof 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
15 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
20 glycol. Preferably, this formulation is stable for at least six months at 4° C.

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
25 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 of Use

The present disclosure also provides methods for using the Wnt surrogate molecules disclosed herein, e.g., to modulate a Wnt signaling pathway,
30 e.g., to increase Wnt signaling, and the administration of a Wnt surrogate molecule disclosed herein in a variety of therapeutic settings. Provided herein

are methods of treatment using a Wnt surrogate molecule. In one embodiment, a Wnt surrogate molecule is provided to a subject having a disease involving inappropriate or deregulated Wnt signaling, e.g., reduced Wnt signaling.

Increasing Wnt Pathway Signaling and Related Therapeutic Methods

5 In certain embodiments, a Wnt surrogate molecule may be used to increase Wnt signaling in a tissue or cell. Thus, in some aspects, the present invention provides a method for increasing Wnt signaling or enhancing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a Wnt surrogate molecule or pharmaceutically acceptable
10 salt thereof disclosed herein, wherein the a Wnt surrogate molecule is a Wnt signaling pathway agonist. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro. In certain embodiments, the method comprises further contacting the tissue or cell with one or more Wnt polypeptides or Norrin
15 polypeptides.

 In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a polynucleotide comprising a Wnt surrogate molecule disclosed herein. In certain embodiments, the target tissue or cell
20 also contacted with a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. 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
25 embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

30 In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell

with an effective amount of a vector comprising a nucleic acid sequence encoding a Wnt surrogate molecule. In certain embodiments, the tissue or cell is also contacted with a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. 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 a Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same vector, e.g., in the same expression cassette.

10 In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue, comprising contacting the tissue with an effective amount of a cell comprising a nucleic acid sequence encoding a Wnt surrogate molecule of the present invention. In certain embodiments, the tissue is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide 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 Wnt surrogate molecule or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Wnt surrogate molecules disclosed herein 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 Wnt surrogate molecule; a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., a DNA or mRNA, optionally a modified mRNA; a vector comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., an expression vector or viral vector; or a cell comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., a cell transduced with an expression vector or viral vector encoding a Wnt surrogate 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.

15 In certain embodiments, the method comprises further contacting the subject with a pharmaceutical composition comprising one or more Wnt polypeptides or Norrin polypeptides. The present disclosure contemplates contacting a subject with a first molecule for delivery of a Wnt surrogate molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide or Norrin polypeptide. 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).

25 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 Wnt surrogate molecule disclosed herein. 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 or a Norrin polypeptide. 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 Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

15 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 Wnt surrogate molecule. 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 or a Norrin polypeptide. 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 Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same vector, e.g., in the same expression cassette.

30 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 Wnt surrogate molecule. In certain

5 embodiments, the subject is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same cell. In particular embodiments, the cell is a

10 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 Wnt surrogate molecule or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

15 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. Wnt surrogate molecule molecules are expected to provide benefit of healing and tissue repair in response to injuries and diseases. Causes of tissue damage and

20 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

25 damaged tissue, for use in tissue regeneration and for use in cell growth and proliferation, and/or for use in tissue engineering.

 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

30 evidence of involvement of Wnt signals in many disease conditions and further support utilization of a Wnt surrogate molecule 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, spinal cord injuries, including vertebral compression fractures, pre-operative spinal surgery optimization, 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 inner and outer auditory hair cells treatment of vestibular hypofunction, treatment of macular degeneration, treatment of retinopathies, including vitreoretinopathy, diabetic retinopathy, other diseases of retinal degeneration, Fuchs' dystrophy, other cornea disease, etc.; treatment of stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, multiple dystrophy, muscle atrophy as a result of sarcopenia or cachexia, and other conditions affecting the degeneration or integrity of the blood brain barrier; . The compositions of this invention may also be used in treatment of oral mucositis, treatment of short bowel syndrome, inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), in particular CD with fistula formation, other gastrointestinal disorders; treatment of metabolic syndrome, dyslipidemia, 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), pulmonary fibrosis, including idiopathic pulmonary fibrosis, enhanced

regeneration of lung tissues. 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 C or B 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.

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, vertebral compression fractures, pre-operative optimization for spinal surgeries, osteonecrosis of the jaw, dental implantation, periodontal diseases, maxillofacial reconstruction, and the like. Wnt surrogate molecules enhance and promotes 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.

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 Wnt surrogate molecule disclosed herein. Methods for regeneration of bone tissues benefit from administration of the Wnt surrogate molecule 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.

In particular embodiments, compositions comprising one or more

5 Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to treat or prevent a bone disease or disorder, including but not limited to any of the following, or to treat or prevent an injury associated with, but not limited to, any of the following: osteoporosis,

10 osteoporotic fractures, bone fractures including vertebral compression fractures, non-union fractures, delayed union fractures, spinal fusion, osteonecrosis, osteonecrosis of the jaw, hip, femoral head, etc., osseointegration of implants (e.g., to accelerate recovery following partial or total knee or hip replacement), osteogenesis imperfecta, bone grafts, tendon repair, maxillofacial surgery, dental

15 implant, all other bone disorders or defects resulting from genetic diseases, degeneration, aging, drugs, or injuries. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, and Fzd 7, and also LRP5 and/or LRP6, are used to treat or prevent any bone disease or disorder. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, Fzd 5, Fzd 7 and Fzd 8, and also

20 LRP5 and/or LRP6, are used to treat or prevent any bone disease or disorder. Other Fzd molecules that bind to additional Fzd receptors can also be used with LRP5 and/or LRP6 binders.

In particular embodiments, compositions and methods disclosed herein may be used to: increase bone mineral density, increase bone volume

25 (e.g., tibia and/or femur bone volume), increase cortical thickness (e.g., in trabecular region or in femur mid-diaphysis), increase mineral apposition rate, increase the number of osteoblasts and/or decrease the number of osteoclasts (e.g., in bone), increase bone stiffness, increase the ultimate load to fracture point, improve bone resistance to fracture, decrease bone resorption, decrease

30 bone loss associated with osteoporosis, or increase biochemical strength of bone, in a subject. In one embodiment, Wnt surrogate molecules that bind Fzd1,

Fzd 2, and Fzd 7 are used for any of these indicated uses. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, Fzd 5, Fzd 7 and Fzd 8 are used for any of these indicated uses.

Methods disclosed herein, including methods for treating or
5 preventing a bone disease or disorder include methods that comprise providing to a subject in need thereof both a Wnt surrogate molecule and an antiresorptive agent. In certain embodiments, the methods are used for the treatment of osteoporosis, optionally post-menopausal osteoporosis.

The disclosure also provides a method for inhibiting or reducing
10 bone resorption in a subject in need thereof, comprising providing to the subject an effective amount of a Wnt surrogate molecule, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway. In certain embodiments, the method further comprises providing to the subject an antiresorptive agent. In certain embodiments, the subject has been diagnosed with or is at risk for
15 osteoporosis, optionally postmenopausal osteoporosis. A variety of antiresorptive agents are known in the art and include, but are not limited to, those disclosed herein.

When a Wnt surrogate molecule is provide to the subject in combination with another therapeutic agent, such as an antiresorptive agent, the
20 two agent may be provided in the same or different pharmaceutical compositions. They may be provided to the subject at the same time, at different times, e.g., simultaneously, consecutively, or during overlapping or non-overlapping time periods. In certain embodiments, the two agents are therapeutically active in the subject during an overlapping time period.

25 Compositions comprising one or more Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) 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
30 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
5 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.

A Wnt surrogate molecule may also be used for treatment of periodontal diseases. Periodontal diseases are a leading cause of tooth loss and
10 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
15 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.

20 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
25 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
30 application to the ear for enhancement of auditory regeneration.

A Wnt surrogate molecule 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.

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, compositions comprising a Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to promote liver regeneration, reduce fibrosis,

and/or improve liver function. In certain embodiments, compositions and methods disclosed herein are used to: increase liver weight, increase the liver to body weight ratio, increase the number of PCNA and pH3 positive nuclei in liver, increase expression of Ki67 and/or Cyclin D1 in liver, increase liver cell proliferation and/or mitosis, decrease fibrosis following chronic liver injury, or increase hepatocyte function.

In particular embodiments, the compositions of this invention may be used in treatment of acute liver failure, acute alcoholic liver injuries, treatment of chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, chronic alcoholic liver diseases, alcoholic hepatitis, non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis (NASH), treatment of cirrhosis and severe chronic liver diseases of all causes, and enhanced regeneration of liver cells. 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.

In particular embodiments, compositions comprising a Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to treat or prevent a liver disease or disorder, including but not limited to, or to treat or prevent a liver injury or disorder resulting from any of the following: acute liver failure (all causes), chronic liver failure (all causes), cirrhosis, liver fibrosis (all causes), portal hypertension, alcoholic liver diseases including alcoholic hepatitis, 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.

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 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.

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. A Wnt surrogate molecule may benefit various disease conditions involving exocrine and endocrine pancreas, kidney, or lung. The Wnt surrogate molecules 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), pulmonary fibrosis, in particular idiopathic pulmonary fibrosis (IPF), and 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.

5 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
10 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.

 Stroke, traumatic brain injury, Alzheimer's disease, multiple
15 sclerosis and other conditions affecting the blood brain barrier (BBB) may be treated with a Wnt surrogate molecule. 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
20 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
25 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.

30 Wnt signals also play a role in angiogenesis. A Wnt surrogate molecule may benefit conditions where angiogenesis is beneficial, treatment of

myocardial infarction, coronary artery disease, heart failure, diabetic retinopathy, 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.

5 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
10 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.

 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
15 of a subject, or to a subject. Such administering or introducing may take place in vivo, in vitro or ex vivo.

 In particular embodiments, a pharmaceutical 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
20 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 Wnt surrogate molecule is performed ex vivo, with subsequent implantation of the cells or
25 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.

 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
30 disorder, the characteristics of the subject, and the subject's history. In particular embodiments, the amount of a Wnt surrogate molecule 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.

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 (e.g., a Wnt surrogate molecule) 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. 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.

Other embodiments relate, in part, to the use of the Wnt surrogate molecules disclosed herein to promote or enhance the growth or proliferation of cells, tissues and organoids, for example, by contacting cells or tissue with one

or more Wnt surrogate, optionally in combination with a Norrin or Rspodin polypeptide. In certain embodiments, the cells or tissue are contacted ex vivo, in vitro, or in vivo. Such methods may be used to generate cells, tissue or organoids for therapeutic use, e.g., to be transplanted or grafted into a subject.

- 5 They may also be used to generate cells, tissue or organoids for research use. The Wnt surrogate molecules have widespread applications in non-therapeutic methods, for example in vitro research methods.

The invention provides a method for tissue regeneration of damaged tissue, such as the tissues discussed above, comprising administering
10 a Wnt surrogate molecule to cells. The Wnt surrogate molecule may be administered directly to the cells in vivo, administered to a subject orally, intravenously, or by other methods known in the art, or administered to ex vivo cells. In some embodiments where the Wnt surrogate molecule is administered to ex vivo cells, these cells may be transplanted into a subject before, after or
15 during administration of the Wnt surrogate molecule.

Wnt signaling is a key component of stem cell culture. For example, the stem cell culture media as described in WO2010/090513, WO2012/014076, Sato et al., 2011 (GASTROENTEROLOGY 201 1; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5). The Wnt surrogate molecules
20 disclosed herein are suitable alternatives to Rspodin for use in these stem cell culture media, or may be combined with Rspodin.

Accordingly, in one embodiment, the disclosure provides a method for enhancing the proliferation of stem cells comprising contacting stem cells with one or more Wnt surrogate molecules disclosed herein. In one embodiment, the
25 disclosure provides a cell culture medium comprising one or more Wnt surrogate molecules disclosed herein. In some embodiments, the cell culture medium may be any cell culture medium already known in the art that normally comprises Wnt or Rspodin, but wherein the Wnt or Rspodin is replaced (wholly or partially) or supplemented by Wnt surrogate molecule(s) disclosed herein. For example, the
30 culture medium may be as described in as described in WO2010/090513, WO2012/014076, Sato et al., 2011 (GASTROENTEROLOGY 201 1; 141: 1762-

1772) and Sato et al., 2009 (Nature 459, 262-5), which are hereby incorporated by reference in their entirety.

Stem cell culture media often comprise additional growth factors. This method may thus additionally comprise supplying the stem cells with a growth factor. Growth factors commonly used in cell culture medium include epidermal growth factor (EGF, (Peprotech), Transforming Growth Factor-alpha (TGF-alpha, Peprotech), basic Fibroblast Growth Factor (bFGF, Peprotech), brain-derived neurotrophic factor (BDNF, R&D Systems), Hepatocyte Growth Factor (HGF) and Keratinocyte Growth Factor (KGF, Peprotech, also known as FGF7). EGF is a potent mitogenic factor for a variety of cultured ectodermal and mesodermal cells and has a profound effect on the differentiation of specific cells in vivo and in vitro and of some fibroblasts in cell culture. The EGF precursor exists as a membrane-bound molecule which is proteolytically cleaved to generate the 53-amino acid peptide hormone that stimulates cells. EGF or other mitogenic growth factors may thus be supplied to the stem cells. During culturing of stem cells, the mitogenic growth factor may be added to the culture medium every second day, while the culture medium is refreshed preferably every fourth day. In general, a mitogenic factor is selected from the groups consisting of: i) EGF, TGF-alpha, and KGF; ii) EGF, TGF-alpha, and FGF7; iii) EGF, TGF-alpha, and FGF; iv) EGF and KGF; v) EGF and FGF7; vi) EGF and a FGF; vii) TGF-alpha and KGF; viii) TGF-alpha, and FGF7; ix) or from TGF-alpha and a FGF. In certain embodiments, the disclosure includes a stem cell culture media comprising a Wnt surrogate molecule disclosed herein, e.g., optionally in combination with one or more of the growth factors or combinations thereof described herein.

These methods of enhancing proliferation of stem cells can be used to grow new organoids and tissues from stem cells, as for example described in WO2010/090513 WO2012/014076, Sato et al., 201 1 (GASTROENTEROLOGY 2011; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5).

In some embodiments, the Wnt surrogate molecules are used to enhance stem cell regeneration. Illustrative stem cells of interest include but are

not limited to: muscle satellite cells; hematopoietic stem cells and progenitor cells derived therefrom (U.S. Pat. No. 5,061,620); neural stem cells (see Morrison et al. (1999) Cell 96: 737-749); embryonic stem cells; mesenchymal stem cells; mesodermal stem cells; liver stem cells; adipose-tissue derived stem cells, etc.

5 Other embodiments of the present invention relate, in part, to diagnostic applications for detecting the presence of cells or tissues expressing one or more Fzd receptors or LRP5 or LRP6 receptors. Thus, the present disclosure provides methods of detecting one or more Fzd receptor or LRP5 or LRP6 receptor in a sample, such as detection of cells or tissues expressing
10 Fzd1. Such methods can be applied in a variety of known detection formats, including, but not limited to immunohistochemistry (IHC), immunocytochemistry (ICC), *in situ* hybridization (ISH), whole-mount *in situ* hybridization (WISH), fluorescent DNA *in situ* hybridization (FISH), flow cytometry, enzyme immuno-assay (EIA), and enzyme linked immuno-assay (ELISA), e.g., by detecting
15 binding of a Wnt surrogate molecule.

ISH is a type of hybridization that uses a labeled complementary DNA or RNA strand (*i.e.*, primary binding agent) to localize a specific DNA or RNA sequence in a portion or section of a cell or tissue (*in situ*), or if the tissue is small enough, the entire tissue (whole mount ISH). One having ordinary skill in
20 the art would appreciate that this is distinct from immunohistochemistry, which localizes proteins in tissue sections using an antibody as a primary binding agent. DNA ISH can be used on genomic DNA to determine the structure of chromosomes. Fluorescent DNA ISH (FISH) can, for example, be used in medical diagnostics to assess chromosomal integrity. RNA ISH (hybridization
25 histochemistry) is used to measure and localize mRNAs and other transcripts within tissue sections or whole mounts.

In various embodiments, the Wnt surrogate molecules described herein are conjugated to a detectable label that may be detected directly or indirectly. In this regard, an antibody "conjugate" refers to a Wnt surrogate
30 molecule that is covalently linked to a detectable label. In the present invention, DNA probes, RNA probes, monoclonal antibodies, antigen-binding fragments

thereof, and antibody derivatives thereof, such as a single-chain-variable-fragment antibody or an epitope tagged antibody, may all be covalently linked to a detectable label. In "direct detection", only one detectable antibody is used, *i.e.*, a primary detectable antibody. Thus, direct detection means that the
5 antibody that is conjugated to a detectable label may be detected, *per se*, without the need for the addition of a second antibody (secondary antibody).

A "detectable label" is a molecule or material that can produce a detectable (such as visually, electronically or otherwise) signal that indicates the presence and/or concentration of the label in a sample. When conjugated to an
10 antibody, the detectable label can be used to locate and/or quantify the target to which the specific antibody is directed. Thereby, the presence and/or concentration of the target in a sample can be detected by detecting the signal produced by the detectable label. A detectable label can be detected directly or indirectly, and several different detectable labels conjugated to different specific-
15 antibodies can be used in combination to detect one or more targets.

Examples of detectable labels, which may be detected directly, include fluorescent dyes and radioactive substances and metal particles. In contrast, indirect detection requires the application of one or more additional antibodies, *i.e.*, secondary antibodies, after application of the primary antibody.
20 Thus, the detection is performed by the detection of the binding of the secondary antibody or binding agent to the primary detectable antibody. Examples of primary detectable binding agents or antibodies requiring addition of a secondary binding agent or antibody include enzymatic detectable binding agents and haptens detectable binding agents or antibodies.

25 In some embodiments, the detectable label is conjugated to a nucleic acid polymer which comprises the first binding agent (*e.g.*, in an ISH, WISH, or FISH process). In other embodiments, the detectable label is conjugated to an antibody which comprises the first binding agent (*e.g.*, in an IHC process).

30 Examples of detectable labels which may be conjugated to Wnt surrogate molecules used in the methods of the present disclosure include

fluorescent labels, enzyme labels, radioisotopes, chemiluminescent labels, electrochemiluminescent labels, bioluminescent labels, polymers, polymer particles, metal particles, haptens, and dyes.

Examples of fluorescent labels include 5-(and 6)-

- 5 carboxyfluorescein, 5- or 6-carboxyfluorescein, 6-(fluorescein)-5-(and 6)-carboxamido hexanoic acid, fluorescein isothiocyanate, rhodamine, tetramethylrhodamine, and dyes such as Cy2, Cy3, and Cy5, optionally substituted coumarin including AMCA, PerCP, phycobiliproteins including R-phycoerythrin (RPE) and allophycoerythrin (APC), Texas Red, Princeton Red,
- 10 green fluorescent protein (GFP) and analogues thereof, and conjugates of R-phycoerythrin or allophycoerythrin, inorganic fluorescent labels such as particles based on semiconductor material like coated CdSe nanocrystallites.

Examples of polymer particle labels include micro particles or latex particles of polystyrene, PMMA or silica, which can be embedded with

- 15 fluorescent dyes, or polymer micelles or capsules which contain dyes, enzymes or substrates.

Examples of metal particle labels include gold particles and coated gold particles, which can be converted by silver stains. Examples of haptens include DNP, fluorescein isothiocyanate (FITC), biotin, and digoxigenin.

- 20 Examples of enzymatic labels include horseradish peroxidase (HRP), alkaline phosphatase (ALP or AP), β -galactosidase (GAL), glucose-6-phosphate dehydrogenase, β -N-acetylglucosaminidase, β -glucuronidase, invertase, Xanthine Oxidase, firefly luciferase and glucose oxidase (GO). Examples of commonly used substrates for horseradishperoxidase include 3,3'-
- 25 diaminobenzidine (DAB), diaminobenzidine with nickel enhancement, 3-amino-9-ethylcarbazole (AEC), Benzidine dihydrochloride (BDHC), Hanker-Yates reagent (HYR), Indophane blue (IB), tetramethylbenzidine (TMB), 4-chloro-1-naphtol (CN), .alpha.-naphtol pyronin (.alpha.-NP), o-dianisidine (OD), 5-bromo-4-chloro-3-indolylphosp- hate (BCIP), Nitro blue tetrazolium (NBT), 2-(p-iodophenyl)-3-p-
- 30 nitropheny- l-5-phenyl tetrazolium chloride (INT), tetranitro blue tetrazolium

(TNBT), 5-bromo-4-chloro-3-indoxyl-beta-D-galactoside/ferro-ferricyanide (BCIG/FF).

Examples of commonly used substrates for Alkaline Phosphatase include Naphthol-AS-B 1-phosphate/fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-phosphate/- fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-phosphate/new fuschin (NABP/NF), bromochloroindolyl phosphate/nitroblue tetrazolium (BCIP/NBT), 5-Bromo-4-chloro-3-indolyl-b-- d-galactopyranoside (BCIG).

Examples of luminescent labels include luminol, isoluminol, acridinium esters, 1,2-dioxetanes and pyridopyridazines. Examples of electrochemiluminescent labels include ruthenium derivatives. Examples of radioactive labels include radioactive isotopes of iodide, cobalt, selenium, tritium, carbon, sulfur and phosphorous.

Detectable labels may be linked to the antibodies described herein or to any other molecule that specifically binds to a biological marker of interest, e.g., an antibody, a nucleic acid probe, or a polymer. Furthermore, one of ordinary skill in the art would appreciate that detectable labels can also be conjugated to second, and/or third, and/or fourth, and/or fifth binding agents or antibodies, etc. Moreover, the skilled artisan would appreciate that each additional binding agent or antibody used to characterize a biological marker of interest may serve as a signal amplification step. The biological marker may be detected visually using, e.g., light microscopy, fluorescent microscopy, electron microscopy where the detectable substance is for example a dye, a colloidal gold particle, a luminescent reagent. Visually detectable substances bound to a biological marker may also be detected using a spectrophotometer. Where the detectable substance is a radioactive isotope detection can be visually by autoradiography, or non-visually using a scintillation counter. See, e.g., Larsson, 1988, Immunocytochemistry: Theory and Practice, (CRC Press, Boca Raton, Fla.); Methods in Molecular Biology, vol. 80 1998, John D. Pound (ed.) (Humana Press, Totowa, N.J.).

The invention further provides kits for detecting one or more Fzd or LRP5/6 receptor or cells or tissues expressing one or more Fzd or LRP5/6 receptors in a sample, wherein the kits contain at least one antibody, polypeptide, polynucleotide, vector or host cell as described herein. In certain
5 embodiments, a kit may comprise buffers, enzymes, labels, substrates, beads or other surfaces to which the antibodies of the invention are attached, and the like, and instructions for use.

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

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
15 and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

EXAMPLES

Example 1

20 Illustrative Wnt surrogate Molecule Formats

Wnt surrogates having a variety of different formats disclosed herein were made. These included the following illustrative formats, each comprising a binding domain ("binder") that binds to one or more Fzd receptor and a binding domain ("binder") that binds to an LRP5 and/or LRP6 receptor.

25 As shown in Fig. 1A, if a binder to one receptor is a Fab and to the other receptor is a Nab or scFv, they can be put together in several different configurations. In certain instances, the Fab binder first can be reformatted to a full IgG format, then the Nab binder can be fused to any of the 4 available termini of the IgG. For example, the Nab can be fused to the N-terminus of the IgG light
30 chain (LC, the fusion will be referred to as NL, shown in top left), N-terminus of the IgG heavy chain (HC, the fusion will be referred to as NH, shown in top right),

the C-terminus of LC (the fusion will be referred to as CL, shown in middle right), and the C-terminus of HC (the fusion will be referred to as CH, shown in middle left). The linkers and the length of the linkers between the IgG and the Nab can be varied. These four formats are bispecific and bivalent, they are bivalent
5 binders toward each of the receptors. An alternative way to put the two binders together is the Hetero-Ig format where the Fab binder is presented as a half antibody, and the Nab is fused to the N-terminus of an Fc (shown in lower middle). The two halves may be brought together by mutations in the CH3 domain (such as the knobs-into-holes) that favor the formation of the
10 heterodimer. The linker and its length between the Nab binder and the Fc can be varied. This format would be bispecific but monovalent toward each receptor. The Nab part of any of the formats described in this example can also be replaced by scFv fragments of binders as well.

As shown in Fig. 1B, if a binder to one receptor is a Fab and to the
15 other receptor is also a Fab, they can be put together in several different configurations. In one approach, one Fab binder is first reformatted to a full IgG format (shown in top). The second Fab binder can be fused to the N-terminus of the IgG. The two HC can be fused together with a linker in between. The LCs can be fused or unfused. The linker and its length can be varied. This format is a
20 bispecific and bivalent format. Alternatively, the second Fab binder LC can be fused to the HC of the IgG with a linker of various length in between. The second Fab binder HC can be fused or unfused to the LC of the IgG. A variation of this format has been called Fabs-in-tandem IgG (or FIT-Ig). In another approach, the
25 two binders can be brought together as a Hetero-Ig by mutations in the CH3 domain that favors the heterodimer assembly, the two arms will each bind to one receptor (shown in bottom). This format is a bispecific and monovalent binder.

As shown in Fig. 1C, if a binder to one receptor is a Nab and to the other receptor is also a Nab, they can be put together in several different configurations. In the bispecific bivalent formats, in certain instances, the two
30 Nab binders can be fused together in tandem (shown in top row) or fused to the two-different ends of the Fc (shown in middle row). The linker and its length

between Nab and Nab or Nab and Fc can be varied. Alternatively, the two Nabs can be assembled together as Hetero-Ig to generate a bispecific and monovalent format (shown in bottom row). Similar to Fig 1A, the Nab domains here can also be replaced by an scFv domain of a binder. In all the examples, the Nab and
5 scFv can be mixed in certain combinations as well.

As shown in Fig. 1D, the binders against Fzd and LRP can also be linked together in a diabody (or DART) configuration. The diabody can also be in a single chain configuration. If the diabody is fused to an Fc, this will create a bivalent bispecific format. Without fusion to Fc, this would be a monovalent
10 bispecific format.

A number of Wnt surrogates representing different configurations were produced. These included the Wnt surrogates described in Table 3. These illustrative Wnt surrogates include one, two or three polypeptides, the sequences of which are provided as Sequence 1, Sequence 2, and/or Sequence 3. The
15 sequence may include a leader peptide sequence, a Nab sequence, a linker, and/or a heavy or light chain sequence. Annotated sequences are provided in FIG. 19, in which the leader peptide sequence is italicized, the linker sequence is underlined, the Nab sequence is shown in bold, and the remaining sequence is the heavy chain or light chain sequence. The Fzd binder IDs and LRP binder IDs
20 correspond to the clone numbers provided in Tables 1A-B and 2A-B for various Fzd binding or LRP5/6 binding antibodies or antigen-binding fragments thereof.

The Wnt surrogates beginning with "R2M3" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 001S-A04. The first six Wnt
25 surrogates beginning with "18R5" in Table 3 include different LRP6 binding domains fused to the N-terminus of the anti-Fzd antibody or antigen-binding fragment thereof named 18R5. The Wnt surrogates beginning with "1R" include the anti-LRP6 antibody or antigen-binding fragment thereof named "009S-E04" fused to the N-terminus of different anti-Fzd antibodies or antigen-binding
30 fragment thereof. For "R2M3-26CH," the LRP6 binding region is fused to the C-terminus of the Fzd binding region. For "R2M3-26NH," the LRP6 binding region

is fused to the N-terminus of the Fzd binding region. For “R2M3-26CL,” the LRP6 binding region is fused to the C-terminus of the Fzd binding region. For “R2M3-26NL,” the LRP6 binding region is fused to the N-terminus of the Fzd binding region. For “R2M3-26Fab” and “R2M3-32Fab,” the LRP6 binding region is fused to the N-terminus of the Fzd binding region. For “Hetero-Ig,” the LRP6 binding region is fused to the N-terminus of human Fc_hole, and paired with Fzd binder light chain and heavy chain human IgG1_knob. The Wnt surrogates beginning with “17SB9” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 017S-B09. The Wnt surrogates beginning with “1R-C07” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 001S-B03. The Wnt surrogates beginning with “R2M13” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 004S-G06. The Wnt surrogates beginning with “3SD10” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 003S-D10. The Wnt surrogates beginning with “4SD1” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 004S-D01. The Wnt surrogates beginning with “14SB6” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 014S-B06.

Table 3. Wnt Surrogate Sequences

Name	Fzd binder ID	LRP binder ID	Sequence 1 SEQ ID NO	Sequence 2 SEQ ID NO	Sequence 3 SEQ ID NO
R2M3-23	001S-A04	009S-B04	89	95	N/A
R2M3-26	001S-A04	009S-E04	90	95	N/A

R2M3-28	001S-A04	009S-G04	91	95	N/A
R2M3-29	001S-A04	009S-H04	92	95	N/A
R2M3-31	001S-A04	013S-G04	93	95	N/A
R2M3-32	001S-A04	013S-H04	94	95	N/A
18R5-5	18R5	008S-G01	96	104	N/A
18R5-7	18R5	008S-C02	97	104	N/A
18R5-8	18R5	008S-D02	98	104	N/A
18R5-9	18R5	008S-E02	99	104	N/A
18R5-26	18R5	009S-E04	100	104	N/A
18R5-28	18R5	009S-G04	101	104	N/A
18R5-31	18R5	013S-G04	102	104	N/A
18R5-32	18R5	013S-H04	103	104	N/A
1R-B05-26	001S-E02	009S-E04	105	111	N/A
1R-C01-26	001S-B01	009S-E04	106	112	N/A
1R-C07-26	001S-B03	009S-E04	107	113	N/A

1R-E06-26	001S-H02	009S-E04	108	114	N/A
1R-G05-26	001S-G02	009S-E04	109	115	N/A
1R-G06-26	001S-A03	009S-E04	110	116	N/A
R2M3-26 CH	001S-A04	009S-E04	125	117	N/A
R2M3-26 NH	001S-A04	009S-E04	125	118	N/A
R2M3-26 CL	001S-A04	009S-E04	119	2254	N/A
R2M3-26 NL	001S-A04	009S-E04	120	2254	N/A
R2M3-26 Fab	001S-A04	009S-E04	120	122	N/A
R2M3-26F(ab') ₂	001S-A04	009S-E04	120	2252	
R2M3-32 Fab	001S-A04	013S-H04	123	122	N/A
R2M3-26 Hetero-Ig	001S-A04	009S-E04	125	126	127
26-17SB9	017S-B09	009S-E04	128	N/A	N/A
26:Fc:17SB9-criss-cross	017S-B09	009S-E04	2192	2193	N/A
26:5:17SB9:Fc	017S-B09	009S-E04	2194	N/A	N/A
26:10:17SB9:Fc	017S-B09	009S-E04	2195	N/A	N/A

26:15:17SB9:Fc	017S-B09	009S-E04	2196	N/A	N/A
17SB9:Fc:26	017S-B09	009S-E04	2197	N/A	N/A
26:Fc:26+17SB9:Fc:17SB9	017S-B09	009S-E04	2198	2199	N/A
1R-C07-3	001S-B03	008S-D01	134	113	N/A
1R-C07-36	001S-B03	013S-D05	135	113	N/A
R2M13-3	004S-G06	008S-D01	136	153	N/A
R2M13-26	004S-G06	009S-E04	137	153	N/A
R2M13-36	004S-G06	013S-D05	138	153	N/A
R2M3-3	001S-A04	008S-D01	139	2254	N/A
R2M3-36	001S-A04	013S-D05	140	2254	N/A
3SD10-3	003S-D10	008S-D01	141	154	N/A
3SD10-26	003S-D10	009S-E04	142	154	N/A
3SD10-36	003S-D10	013S-D05	143	154	N/A
4SD1-3	004S-D01	008S-D01	144	155	N/A
4SD1-26	004S-D01	009S-E04	145	155	N/A

4SD1-36	004S-D01	013S-D05	146	155	N/A
14SB6-3	014S-B06	008S-D01	147	156	N/A
14SB6-26	014S-B06	009S-E04	148	156	N/A
14SB6-36	014S-B06	013S-D05	149	156	N/A
R2M9-3	003S-E07	008S-D01	150	157	N/A
R2M9-26	003S-E07	009S-E04	151	157	N/A
R2M9-36	003S-E07	013S-D05	152	157	N/A
18R5:5:111 5.3:Fc	18R5	1115.3	2200	N/A	N/A
18R5:10:11 15.3:Fc	18R5	1115.3	2201	N/A	N/A
18R5:15:11 15.3:Fc	18R5	1115.3	2202	N/A	N/A
1115.3:5:18 R5:Fc	18R5	1115.3	2203	N/A	N/A
1115.3:10:1 8R5:Fc	18R5	1115.3	2204	N/A	N/A
1115.3:15:1 8R5:Fc	18R5	1115.3	2205	N/A	N/A
18R5:5: YW211.31. 57:Fc	18R5	YW211.3 1.57	2206	N/A	N/A

18R5:10: YW211.31. 57:Fc	18R5	YW211.3 1.57	2207	N/A	N/A
18R5:15: YW211.31. 57:Fc	18R5	YW211.3 1.57	2208	N/A	N/A
YW211.31. 57:5:18R5: Fc	18R5	YW211.3 1.57	2209	N/A	N/A
YW211.31. 57:10:18R5: Fc	18R5	YW211.3 1.57	2210	N/A	N/A
YW211.31. 57:15:18R5: Fc	18R5	YW211.3 1.57	2211	N/A	N/A
18R5:Fc:11 15.3	18R5	1115.3	2212	N/A	N/A
1115.3:Fc:1 8R5	18R5	1115.3	2213	N/A	N/A
18R5:Fc:Y W211.31.57	18R5	YW211.3 1.57	2250	N/A	N/A
YW211.31. 57:Fc:18R5	18R5	YW211.3 1.57	2267	N/A	N/A
421.1- R2M3 cp	001S- A04	421.1	2214	2215	2216
1RC07:5:10 SA7 cp	1RC07	10SA7	2217	2218	2219
1RC07:10:1 0SA7 cp	1RC07	10SA7	2217	2218	2222
1RC07:15:1 0SA7 cp	1RC07	10SA7	2217	2218	2225

1RC07:5:10 SG7 cp	1RC07	10SG7	2217	2227	2228
1RC07:10:1 0SG7 cp	1RC07	10SG7	2217	2227	2231
1RC07:15:1 0SG7 cp	1RC07	10SG7	2217	2227	2234
10SG7:5:1 RC07 cp	1RC07	10SG7	2227	2217	2237
10SG7:10:1 RC07 cp	1RC07	10SG7	2227	2217	2240
10SG7:15:1 RC07 cp	1RC07	10SG7	2227	2217	2243
1RC07:5:10 SA7 L->H	1RC07	10SA7	2244	2245	2246
1115.3:5:R2 M3 L->H	001S- A04	1115.3	2247	125	2248
1115.3:10:R 2M3 L->H	001S- A04	1115.3	2247	125	2249
10SG11- 1RC07	1RC07	10SG11	2252	2253	N/A
18R5:5:11 5.3:His	18R5	1115.3	2255	N/A	N/A
18R5:10:11 15.3:His	18R5	1115.3	2256	N/A	N/A
18R5:15:11 15.3:His	18R5	1115.3	2257	N/A	N/A
1115.3:5:18 R5:His	18R5	1115.3	2258	N/A	N/A
1115.3:10:1 8R5:His	18R5	1115.3	2259	N/A	N/A

1115.3:15:18R5:His	18R5	1115.3	2260	N/A	N/A
18R5:5:YW211.31.57:His	18R5	YW211.31.57	2261	N/A	N/A
18R5:10:YW211.31.57:His	18R5	YW211.31.57	2262	N/A	N/A
18R5:15:YW211.31.57:His	18R5	YW211.31.57	2263	N/A	N/A
YW211.31.57:5:18R5:His	18R5	YW211.31.57	2264	N/A	N/A
YW211.31.57:10:18R5:His	18R5	YW211.31.57	2265	N/A	N/A
YW211.31.57:15:18R5:His	18R5	YW211.31.57	2266	N/A	N/A

Example 2

Characterization of a Wnt Surrogate Molecule, R2M3-26

The R2M3-26 molecule consists of a Fzd binder (R2M3) and a LRP6 binder (26). The LRP6 binder 26 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 2A. R2M3 was in the form of an IgG. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 2B. The ability of R2M3-26 to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cell line (293STF). The 293STF reporter activity traces across the SEC

fractions were shown in Fig. 2B, the peak of the reporter activity correlated with the peak of the proteins. The peak fraction was further characterized by a dose response in 293STF cells in the absence and presence of R-spondin (Fig. 2D). R2M3-26 induced reporter activity in a dose dependent manner and was enhanced by the presence of R-spondin similar to a natural Wnt ligand, while R2M3 IgG alone without the attachment of the LRP binding arm did not induce reporter activity. The ability of R2M3-26 to interact with its target, a Fzd1 ECD, was performed in Octet interaction assay (Fig. 2C), and the results showed that the fusion of the LRP6 binding arm, 26, did not affect R2M3 interaction with its target, Fzd.

Example 3

Characterization of a Wnt Surrogate Molecule, R2M3-32

The R2M3-32 molecule consists of a Fzd binder (R2M3) and a LRP6 binder (32). The LRP6 binder 32 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 3A. R2M3 was in the form of an IgG. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 3B. The ability of R2M3-32 to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cell line (293STF). The 293STF reporter activity traces across the SEC fractions were shown in Fig. 3B, the peak of the reporter activity correlated with the peak of the proteins. The peak fraction was further characterized by a dose response in 293STF cells in the absence and presence of R-spondin (Fig. 3D). R2M3-32 induced reporter activity in a dose dependent manner and was enhanced by the presence of R-spondin, while R2M3 IgG alone without the attachment of the LRP binding arm did not induce reporter activity. The ability of R2M3-32 to interact with its target, a Fzd1 extracellular domain (ECD), was performed in Octet interaction assay (Fig. 3C). The results showed that the fusion of the LRP6 binding arm, 32, did not affect R2M3 interaction with its target, Fzd.

Example 4

R2M3-26 and R2M3-32 Activities Can Be Inhibited by Soluble Fzd ECD and by R2M3 IgG Alone without the LRP Binding Arm

5 The ability of soluble Fzd extracellular domain (ECD) or R2M3 IgG alone to inhibit Wnt surrogates was determined using the 293STF reporter assay. The Fzd1ECD-Fc or R2M3 IgG was titrated into the 293STF reporter assay, at a fixed concentration of R2M3-26 or R2M3-32. In a dose dependent manner, both Fzd1ECD-Fc and R2M3 IgG inhibited R2M3-26 (Fig. 4A) and R2M3-32 (Fig. 4B)
10 induced reporter signaling, while the negative control molecule, Fc alone had no impact.

Example 5

Characterization of R2M3-LRP6 Binder Fusions in 293, Huh7, A375, BNL.CL2 Wnt Dependent Reporter Assays

15 The Fzd binder, R2M3, was fused to additional LRP6 binders, 23, 25, 26, 27, 28, 29, 31, 32, 33, and 36. The LRP6 binders were Nab and were fused to the N-terminus of R2M3 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion
20 proteins were tested in Wnt dependent reporter assays in 293, Huh7, A375, and BNL.CL2 cell lines, and activated Wnt signaling to various levels. R2M3 was also fused to two non-LRP6 binder Nabs, 24 and 34, in the same format as the Lrp6 binders. These two non-binders displayed no activity in Wnt dependent 293 reporter assay (Fig. 5), suggesting that Wnt activities observed with R2M3
25 fusions to 23, 25, 26, 27, 28, 29, 31, 32, 33, and 36 are dependent on the presence of both Fzd and Lrp mimicking the nature ligand function.

Example 6

Characterization of 18R5-LRP6 Binder Fusions in 293, A375, and BNL.CL2 Wnt Dependent Reporter Assays

30

The Fzd binder, 18R5, was fused to LRP6 binders, 26, 28, 31, 32. The LRP6 binders were Nab and were fused to the N-terminus of 18R5 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion proteins were tested in Wnt dependent reporter assays in 293, A375, and BNL.CL2 cell lines and demonstrated ability to activate Wnt signaling (Fig. 6).

Example 7

Characterization of 18R5-LRP5 Binder Fusions in 293 Wnt Dependent Reporter Assays

The Fzd binder, 18R5, was fused to LRP5 binders, 5, 7, 8, 9. The LRP5 binders were Nab and were fused to the N-terminus of 18R5 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion proteins were tested in a Wnt dependent reporter assays in 293 cells and were able to activate Wnt signaling (Fig. 7).

Example 8

Characterization of Various Fzd binders-LRP6 Binder 26 Fusions in 293 Wnt Dependent Reporter Assays

The various Fzd binders, 1R-B05, 1R-C01, 1R-C07, 1R-E01, 1R-E06, 1R-G05, 1R-G06, 1R-H04, in IgG format were fused to LRP6 binders, 26. The LRP6 binder Nab was fused to the N-terminus of various Fzd binder LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The SDS-PAGE gel analysis of the SEC peak fractions were shown in Fig. 8A. The fusion proteins were tested in a Wnt dependent reporter assays in 293 cells in the presence of Rspo and were able to activate Wnt signaling (Fig. 8B).

Example 9

SAR Analysis of the IgG-Nab Fusion Format

SAR analysis of the IgG-Nab fusions was performed by rotating the attachment location of the Nab to the different termini of the IgG HC or LC as depicted in Fig. 1A. CH indicates attaching the Nab to the C-terminus of heavy chain; NH indicates attaching the Nab to the N-terminus of heavy chain; CL indicates attaching the Nab to the C-terminus of light chain; NL indicates attaching the Nab to the N-terminus of light chain. Three pairs of IgG-Nab fusions SARs were shown, the pairs were between R2M3 and 26, between R2M3 and 32, and between 18R5 and 26. The assays were performed on Wnt responsive 293 reporter cells in the presence of Rspo and activated Wnt signaling to various levels (Fig. 9). These results demonstrate that the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling.

Example 10

Characterization of R2M3-26 in the Fab Format

The molecule R2M3-26 Fab consists of a Fzd binder (R2M3) and a LRP6 binder (26). The LRP6 binder 26 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 10A. R2M3 was in the form of a Fab. The protein was purified by Ni-NTA affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions are shown in Fig. 10B. The ability of R2M3-26 as a Fab format to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cells (293STF). The 293STF reporter activity traces across the SEC fractions are shown in Fig. 10B. Unlike when R2M3 was in the IgG format shown in Fig. 2, the peak of the reporter activity from the R2M3 in the Fab format did not correlate with the peak of the proteins. These results suggest that R2M3-26 fusion in the Fab format is ineffective in inducing canonical Wnt signaling as detected by a reporter assay.

Example 11

Characterization of R2M3-32 in the Fab Format

The molecule R2M3-32 Fab consists of a Fzd binder (R2M3) and a LRP6 binder (32). The Lrp6 binder 32 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 11A. R2M3 was in the form of a Fab. The protein was purified by Ni-NTA affinity column followed by a size-
5 exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 11B. The ability of R2M3-32 as a Fab format to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cells (293STF). The 293STF reporter activity traces across the SEC fractions are shown in Fig. 11B. Unlike when R2M3 was in the
10 IgG format shown in Fig. 3, the peak of the reporter activity from the R2M3 in the Fab format did not correlate with the peak of the proteins. These results suggest that R2M3-32 fusion in the Fab format is ineffective in inducing canonical Wnt signaling as detected by a reporter assay.

15

Example 12

Characterization of R2M3-26 in the Heterolg Format

The molecule R2M3-26 Heterolg consists of a Fzd binder (R2M3) and a LRP6 binder (26) as depicted in Fig. 12A and described in Fig. 1A. The protein was purified by Protein A affinity column followed by a size-exclusion-
20 chromatography (SEC) step. The peak fraction from the SEC column was tested in a dose response in the Wnt responsive 293STF reporter cells in the absence or presence of R-spondin (Fig. 12B). Compared to R2M3-26 in the IgG format (as described in Fig. 2), R2M3-26 Heterolg was ineffective in inducing canonical Wnt signaling as detected in the 293 reporter assay.

25

Example 13

Characterization of 26-17SB9 in the Nab-Nab Format

The molecule 26-17SB9 Nab-Fc-Nab consists of a LRP6 binder (26) and a Fzd binder (17SB9) as depicted in Fig. 13A and described in Fig. 1C.
30 The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The peak fraction from the SEC column

was tested in a dose response in the Wnt responsive 293STF reporter cells in the absence or presence of R-spondin (Fig. 13B). 26-17SB9 in the Nab-Fc-Nab format induced canonical Wnt signaling as detected in the 293 reporter assay.

Additional combinations of 26 and 17SB9 were also constructed (Fig. 13C) and tested in 293 reporter assays. As shown in Fig. 13D and 13E, these various combinations where 26 and 17SB9 were arranged in different tandem formats or on different ends of the Fc fragment all activated Wnt signaling to various levels in the presence of 20nM R-spondin

10

Example 14

Characterization of 18R5-LRP6 Binder Fusions in Tandem scFv Formats

The Fzd binder 18R5, the LRP6E1E2 binder 1115.3 (as described in PCT Publication WO2009/064944), and the LRP6E3E4 binder YW211.31.57 (as described in PCT Publication WO2011/119661) were converted into scFv format. 1115.3_scFv or YW211.31.57_scFv is assembled to the N-terminus of 18R5_scFv with a 5, 10 or 15 - amino acid linker and 18R5_scFv C-terminus is fused to a human Fc domain. In another set of examples, 1115.3_scFv or YW211.31.57_scFv is assembled to the C-terminus of 18R5_scFv with a 5, 10 or 15 - amino acid linker and human Fc domain is fused to the C-terminus of LRP binders. These formats are depicted in Fig. 14G left panel. In another example, 18R5_scFv and LRP binder, 1115.3_scFv, or LRP binder, YW211.31.57_scFv were fused to the two ends of a human Fc domain (as depicted in Fig. 14G right panel). These proteins were purified by Protein A affinity column followed by a SEC step.

25

The fusion proteins were tested in a Wnt dependent reporter assays in 293 cells. 18R5_scFv-1115.3_scFv-Fc and 1115.3_scFv-18R5_scFv-Fc with 5, 10 or 15-mer linker were able to activate Wnt signaling (Fig. 14A and 14B). 18R5_scFv-YW211.31.57_scFv-Fc and YW211.31.57_scFv-18R5_scFv-Fc with different linkers activated Wnt signaling (Fig. 14C and 14D). In addition, 18R5_scFv and 1115.3_scFv or YW211.31.57 fused to the two ends of Fc also activated Wnt signaling (Fig. 14E and F). While all of these scFv formats

30

activated Wnt signaling, potency and overall maximal efficacy may differ depends on the binder combination, linker length, and relative orientation.

In another example, 1115.3_scFv or YW211.31.57_scFv is assembled to the N-terminus or C-terminus of 18R5_scFv with a 5, 10 or 15 - amino acid linker without the further fusion of Fc, to create a bispecific but monovalent binding to each of Fzd or LRP. As shown in Fig. 14H, the 1115.3_scFv and 18R5_scFv fusions were in effective in activating Wnt signaling in the presence of 20nM R-spondin in 293 reporter cells.

10

Example 15

Generation of Wnt Surrogate Molecules in the Fab-IgG Format

Wnt mimetic or surrogate molecules can be generated in various formats when both the FZD and LRP binders are Fabs. Various approaches, such as charge paring, “knobs-in-holes”, crossover of the heavy and light chains of Fabs, can be employed to ensure proper heavy and light chain pairing. Two examples are given below.

1. Charge-pairing (cp) approach for Fab-on-IgG format: The heavy chain (VH-CH1) domain of an anti-LRP6 Fab, through a linker of 5, 10, or 15-mer amino acids, was fused in tandem with the N-terminus of the heavy chain (VH-CH1-CH2-CH3) of an anti-FZD binder. Both VH-CH1 domains of anti-LRP6 and anti-FZD contain three amino acid mutations (Q39D, Q105D, S183K in the anti-LRP6 Fab; Q39K, Q105K, S183E in anti-FZD Fab) each for proper paring with their own partner light chains, which also contain three complementary amino acid mutations (Q38K, A/S43K, S176E in anti-LRP6 light chain; Q38D, A/S43D, S176K in the anti-FZD light chain). The order of the anti-LRP6 and anti-FZD Fabs could be reversed, where the anti-FZD binder is a Fab and is fused to anti-LRP binder which is in IgG format (Fig. 15A).
2. HC-LC cross over approach for Fab-on-IgG format: The light chain (VL-CL) domains of anti-LRP6 binder was, through a linker of 5, 10, or 15-mer amino acids, fused in tandem with the N-terminus of the heavy chain

(VH-CH1-CH2-CH3) of an anti-FZD binder. The second construct was VH-CH1 of the anti-LRP6 binder and the third construct was VL-CL of the anti-FZD binder. Similar to the example above, the order of the anti-LRP6 and the anti-FZD binders could be reversed, where anti-FZD binder Fab is
5 fused to the N-terminus of the anti-LRP binder which is in IgG format (Fig. 15A).

Several different pairs of LRP and FZD binders were assembled in these formats and tested in a Wnt responding 293 reporter cell line (293STF). As an example, the anti LRP6E1E2 binder 421.1 (as described in PCT Publication
10 WO2009/064944) was fused to the N-terminus of anti-FZD binder, R2M3, using the charge paring approach to generate, 421.1-R2M3 cp. 421.1-R2M3 cp dose-dependently activated Wnt signaling in the 293 reporter assay (Fig. 15B). An anti-FZD binder, 1RC07, was fused to the N-terminus of an anti-LRP binder, 10SA7, with 5, 10, or 15-mer linkers. All three fusion proteins activated Wnt
15 signaling (Fig. 15C). The anti-FZD binder, 1RC07, was further fused with the anti-LRP binder, 10SG7, either with 1RC07 in the Fab format fused to the N-terminus of 10SG7 in IgG format, or in the reverse order where 10SG7 as Fab fused to the N-terminus of 1RC07 as IgG with either 5, 10, or 15-mer amino acid linkers. All fusion molecules activated Wnt signaling while some preference of
20 orientation and linker length was observed (Fig. 15D and 15E).

The HC-LC crossover Fab-IgG format was also tested. The anti-FZD binder 1RC07 LC was fused to the N-terminus of the anti-LRP6 binder 10SA7 HC to generate 1RC07-5: 10SA7 L->H. The LC of anti-LRP6E1E2 binder 1115.3 (as described in PCT Publication WO2009/064944) was fused to the N-
25 terminus of the anti-FZD binder R2M3 HC with 5 or 10-mer linkers to generate 1115.3:5:R2M3 L->H or 1115.3:10:R2M3 L->H, respectively. These molecules also activated Wnt signaling (Fig. 15F and 15G).

Example 16

30 **Characterization of R2M3-26 in the F(ab')₂ Format**

R2M3-26 IgG1 was digested by IDES (Promega, WI) at 37°C for 2 hours. Vast majority of the digested product was R2M3-26F(ab')₂ (Fig. 16A), some partially digested product with one Fab still attached to Fc (designated as R2M3-26F(ab')₂-Fc here) was also detected, and no uncleaved R2M3-26 was detected. The cleaved product was purified by anti-Lambda resin to remove the Fc fragment, then a SEC polishing was followed to separate the R2M3-26F(ab')₂ from R2M3-26F(ab')₂-Fc. The SDS-PAGE gel of the final purified protein is shown in Fig.16B. The R2M3-26F(ab')₂ activity was measured in STF assay in HEK293 cells. R2M3-26F(ab')₂ was able to activate Wnt signaling (Fig. 16C).

10

Example 17

Characterization of Additional Wnt Surrogate Molecules

The FZD binders were fused to LRP binders. The LRP5 or 6 binders were Nabs (or VHHs) in this example and were fused to the N-terminus of FZD binders LC with a 5-amino acid linker (as represented in Fig. 17A). These proteins were purified by Protein A affinity column followed by a SEC step. The purified proteins were tested in Wnt dependent reporter assay in 293 cells (Fig. 17B, C, D, H), or 293 cells co-transfected with FZD4 expression construct (Fig. 17E, F), or 293 cells co-transfected with FZD9 expression construct (Fig. 17G) in the presence of 20nM R-spondin. These molecules activated Wnt signaling with varying levels of potency and efficacy.

20

Example 18

Characterization of 10SG11-1RC07 in the 2Fv-Ig Format

The molecule 10SG11-1RC07 consists of an N-terminal LRP binder (10SG11) and a Fzd binder (1RC07). The Fv of 10SG11 was fused to the N-terminus of 1RC07 with a 5-amino acid linker as depicted in Fig. 18A. 1RC07 was in the form of an IgG1 with the Fc mutations L234A/L235A/P329G. The protein was purified by a Protein A affinity column followed by an SEC step. The fusion protein was tested in Wnt dependent reporter assays in 293 cell lines and demonstrated the ability to activate Wnt signaling (Fig. 18B-C)

30

Example 19

In Vivo PK/PD Characterization of R2M3-26

Six-week old C57Bl/6J male mice were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and were housed 3 per cage. 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 12/12-hour light/dark cycle in a 30% to 70% humidity environment and room temperature ranging from 20°C to 26°C.

For the pharmacokinetic (PK) study (Fig. 20A), n=3 per group was used. Mice were dosed with R2M3-26 (with effectorless Fc mutations) at 1 mg/kg (10ml/kg in saline) either using intravenous (IV) or intraperitoneal (i.p.) injections. Mice were anesthetized with isoflurane and blood was removed from the retro-orbital plexus, tail vein or heart at 10 minutes, 30 minutes, 1, 4, 24, 72 or 144 hours after injection. Blood was allowed to coagulate at room temperature, followed by centrifugation for 7 minutes at 8,000 g. The serum was removed and stored at -20° C until the measurement of serum R2M3-26 concentrations by ELISA with Anti Human IgG Fc Fragment (Jackson Immuno Research Labs NC9747692).

For the pharmacodynamic (PD) study (Fig. 20B), n=6 per group was used. Mice were injected i.p. with R2M3-26 at the indicated doses (10ml/kg in saline). Control mice received saline only. Eight hours later, mice were anesthetized with isoflurane and the blood was collected by cardiac puncture. Blood was allowed to coagulate at room temperature, followed by centrifugation for 7 minutes at 10,000 g. The serum was removed and stored at -20°C until the measurement of serum R2M3-26 concentrations by ELISA.

A portion of the left liver lobe was snap-frozen in liquid nitrogen and stored at -80°C for RNA analysis. RNA was extracted from liver samples 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). Axin2 mRNA expression was measured by using
5 TaqMan® Fast Advanced Master Mix (ThermoFisher, 4444963) and the Mm00443610_m1 Axin2 Probe (Thermofisher, 4331182).

These studies showed that R2M3-26 was stable, highly bioavailable and active in vivo, as shown by the induction of Axin2 mRNA
10 expression.

Example 20

In Vivo Bone Model and Characterization of AAV-Delivered Wnt Surrogates

15 In vivo experiments were conducted by infecting mice with an AAV vector that expressed Flag- and His-tagged 18R5-DKK1c protein (AAV-18R5- DKK1c-FlagHis). 18R5-DKK1c is a fusion protein containing the frizzled binding antibody, 18R5, in scFv format, fused to DKK1c, as described in PCT Publication WO2016/040895, e.g., Fig. 5. Control mice were treated with
20 vehicle only, romosozumab, an AAV vector that expressed green fluorescent protein (GFP) (AAV-CAG-GFP), or an AAV vector that expressed a fusion protein comprising an anti-GFP scFv fused to a mutant DKK1c (AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His). 28 days after infection, animals were sacrificed and bone mineral density, bone volume and other characteristics
25 were measured. As shown in Figs. 21A-21E, systemic expression of 18R5-DKK1c resulted in significantly increased bone mineral density as early as 14 days of 18R5-DKK1c systemic expression, as determined by dual X-ray absorptiometry (DEXA) scan. Systemic expression of 18R5-DKK1c increased bone mineral density (BMD) as measured by DEXA scan (FIG. 21A) and
30 increased levels of the serum P1NP bone formation marker in naïve mice (FIGS. 21C). Serum levels of AAV-ScFv (anti-GFP)-DKK1cF234K and 18R5-

DKK1c were detected in the serum and found to be well above the in vitro determined EC50 (FIG. 21B). AAV-CAG-GFP and AAV-ScFv (anti-GFP)-DKK1cF234K were negative controls. Romosozumab was a positive control, and vehicle only was a negative control. 18R5-DKK1c also increase bone density in lumbar vertebra and whole body, as shown in FIGS. 20D and 20E, wherein * indicates P value <0.05 and ** indicates P value <0.0001. 18R5-DKK1c expression through AAV also increased bone volume in tibia and femur and cortical thickness in femur mid-diaphysis at 28 days after treatment in naïve mice as measured by micro CT, as shown in Figs. 22A-22D, wherein **** indicates P value <0.0001.

Systemic expression of 18R5-DKK1c resulted in significantly increased mineral apposition rate from baseline to single label in last 8 days, as shown in FIGS 23A and 23B.

Systemic expression of 18R5-DKK1c also resulted in increased osteoblast numbers and decreased osteoclast numbers, as shown in FIGS. 24A-24D.

18R5-DKK1c treatment increased bone stiffness and ultimate load to fracture in biomechanical testing, suggesting improved resistance to fracture, as shown in FIGS. 25A-25C.

These studies demonstrated that systemic expression of 18R5-DKK1c using AAV increased bone mineral density (BMD) as measured by DEXA, and also showed that 18R5-DKK1c increased bone volume as measured by micro CT as early as 14 days of treatment. 18R5-DKK1c also increased cortical thickness 28 days after treatment. Systemic expression of 18R5-DKK1c resulted in significantly increased mineral apposition rate, increased osteoblast numbers, and decreased osteoclast numbers. It also increased bone stiffness and ultimate load to fracture, suggesting improved resistance to fracture.

Example 21

In Vivo Bone Model and Characterization of Wnt Surrogates Produced as Recombinant Proteins

In vivo experiments were conducted by treating mice with
5 recombinantly produced R2M3-26 protein at various dosages via i.p. injection. Control mice were treated with vehicle only (negative control), romosozumab (positive control), anti-Beta-Galactosidase (negative control), or IgG2-anti-GFP (negative control). Bone mineral density (BMD) measured by DEXA and bone volume measured by micro CT were monitored longitudinally at indicated time
10 points. Four weeks after treatment, animals were sacrificed and bone characteristics were measured. For single injection of R2M3-26, the experimental data was monitored and is shown for two weeks after treatment.

Treatment with recombinant R2M3-26 induced rapid and sustained increase of bone mineral density (BMD) and bone volume in naive
15 mice, as shown in FIGs. 26A-26D. Both bone volume and BMD increased rapidly, suggesting resistance to fracture.

The ovariectomy induced osteoporosis model is a well-established high-hurdle model for determining the ability of an anabolic therapy to overcome the bone loss associated with hormone ablation (Zhou, S. et. al., Journal of Cellular Biochemistry, PMID: 11455579). Treatment with
20 recombinant R2M3-26 treatment reversed bone loss in an ovariectomy-induced osteoporosis mouse model, as shown in FIGS. 27A-27C. Increased cortical thickness was observed in the trabecular regions, suggesting increased compressive strength. R2M3-26 treatment increased femur mid-
25 diaphysis cortical bone thickness after 42 days as measured by micro CT, as shown by FIG. 27D. BMD was also increased by R2M3-26 as measured by DEXA, shown in FIG. 27E.

A single injection of R2M3-26 was sufficient to induce rapid bone formation and bone volume within one week, as shown in FIGS. 28A-28C,
30 wherein * indicates P value <0.05.

High dose treatment with R2M3-26 and 1R-C07-26 rapidly and significantly increased bone volume and bone mineral density, and improved biomechanical strength of the bone (ultimate load to failure and stiffness), as shown in FIGS. 29A-29D. 1R-C07-26 showed a robust and significant effect on bone accrual that persisted through 28 days. Both R2M3-26 and 1R-C07-26 significantly increased the resistance to fracture after 28 days of treatment by biomechanical testing.

High dose treatment with R2M3-26 and 1R-C07-3 rapidly and significantly increased bone volume, bone mineral density, and cortical thickness after only 14 days of treatment, as shown in FIG. 30A-E. 1R-C07-3 at 10 mpk appeared more effective at increasing bone mass than any other treatment tested in this preclinical model.

These studies demonstrate that recombinant protein treatment can induce rapid and sustained increase of bone mineral density and bone volume in naïve mice and mouse osteoporosis model. Both bone volume and bone mineral density (BMD) increased rapidly, suggesting resistance to fracture. IgG2-anti-GFP is a negative control. Anti-Beta Galactosidase (anti- β gal) was a negative control.

An additional experiment was done to determine systemic skeletal effects of Wnt surrogate molecules in an ovariectomy-induced model of osteoporosis. C57BL/6 females, 4 weeks old at time of ovariectomy, (n=8/group) were compared to sham surgery operated as well as age-matched naïve mice. Animals were injected i.p. with recombinant Wnt surrogate molecules 7 months after surgery and when the onset of osteoporosis was confirmed. Experimental groups included R2M3-26, 1RC07-3, anti-Bgal (Ab control), and vehicle (PBS). Sub-cutaneous injection of romosozumab was done to another cohort of mice for comparison. Animal were treated twice weekly, and followed for 4 weeks.

As shown in FIG. 31, whole body bone mineral density (BMD) was measured weekly using dual-energy X-Ray absorptiometry (DEXA) and treatment with Wnt surrogate molecules can not only reverse but even

surpass the total BMD seen in naïve or non-surgical animals. After 4 weeks of treatment, animals were assessed for the vertebral resistance to compression fracture.

Treatment with Wnt surrogate molecules significantly increased the vertebral resistance to compression fracture, as shown by fracture analysis (FIG. 32). 1RC07-3 most robustly increases the Max Force required to compressively fracture the vertebra.

The Einhorn fracture model (Bonnarens F, Einhorn TA.

J Orthop Res. 1984;2(1):97-101.PMID: 6491805) with delayed treatment with Wnt surrogate molecules was used to determine ability of this therapy to induce fracture healing. Delayed treatment with either 1RC07-3 or R2M3-26 was tested to determine if either molecule was capable of contributing to increased fracture healing after a mid-traverse femoral fracture. C57BL/6 females, 16 weeks old at time of fracture (n=8/group) were used. The presence of a cartilaginous callus 2 weeks after fracture was confirmed in all animals before the start of treatment. With delayed treatment to allow for callus formation, a pure osteogenic signal could be elicited, with rapid mineralization of the already existing callus.

Animals were injected i.p. with recombinant Wnt surrogate molecules with the following experimental groups: R2M3-26, 1RC07-3, anti-Bgal (Ab control), and vehicle (PBS). Sub-cutaneous injection of romosozumab was done to another cohort of mice for comparison. Animals were treated twice weekly, and followed for 6 weeks. Radiography was used to visualize changes in mineralization of the callus throughout the experiment (FIGs 33A and B). An increase in the mineralization and size of the resulting callus with Wnt surrogate treatment is apparent at both 1 and 6 weeks of treatment. One week was sufficient to induce rapid mineralization that is predictive of rapid bone fracture healing and resistance to fracture. 1RC07-3 appeared to induce mineralization to a greater extent than R2M3-26. Radiographs taken after 6 weeks of treatment show the persistence of the

highly mineralized callus in the 1RCO7-3 group, while some of the fracture callus in the R2M3-26 group has diminished (FIGs 33B and D).

Whole body DEXA was measured throughout the experiment to examine bone mineral density in not only the fractured femur, but also the
5 contralateral, non-fractured, femur where the expected increases in bone mineral density occurred after treatment (FIGs 33C and D). This provides reduced risk of secondary fracture in the already fractured limb and the appendicular skeleton. BMD of contralateral femur at 42 days are shown in Figure 33C.

10 Following 6-weeks of treatment after the confirmation of callus, we scanned the femurs with micro-computed tomography and determined multiple parameters which have been associated with an increased resistance to fracture after healing. Callus tissue volume, the bone volume within that callus, and especially bone mineral content are all significantly
15 increased within the region of interest examined (Figure 33D). Qualitatively, the reconstructions show the prevalence of thick osteoid and mineral within the treated fracture. These parameters suggest a robust resistance to fracture and indicate that delayed treatment with Wnt surrogate molecules, after the spontaneous cartilaginous callus formation, can initiate a rapid and
20 significant increase in bone formation.

In another experiment, the dosing schedule was tested to determine whether Wnt surrogate molecule therapy can induce a significant bone anabolic effect, how long that effect persists, and after washout, to determine how the bone responds to additional treatment. Systemic skeletal
25 effects were compared with variable dosing of 1RCO7-3 on anabolic effect, washout, and redosing after establishing baseline. C57BL/6 females, 12 weeks old (n=8/group) were injected i.p. with recombinant Wnt surrogate molecules with the following experimental groups: two groups with 1RCO7-3, one with anti- β gal (Ab control), and one with vehicle (PBS) on day 0 of the
30 experiment. Sub-cutaneous injection of romosozumab was done to another cohort of mice on day 0 for comparison (romosozumab is an anti-sclerostin

antibody (Saag et al., N Engl J Med. 2017 Oct 12;377(15):1417-1427; PMID:28892457) that may reverse the bone loss associated with osteoporosis). Animals in 1RC07-3 treated groups had significant and rapid induction of bone formation by 14 days (FIG 34). One group received a
5 second injection at day 14 to determine if the bone anabolic effect could be further enhanced. Interestingly, regardless of treatment, all treatment effects were reversed and normalized after 35 days. A 2-week period was allowed to return to baseline levels prior to a second round of treatment. On day 49, a second round of treatment was done to all experimental groups. The Wnt
10 surrogate treated animals responded rapidly, however not to the same magnitude as with the initial treatment (FIG. 34). For all groups, 5 weeks after the last injection, new bone formation ceased. This indicates that a single injection is capable of significantly increasing bone formation, however the anabolic effect is rapidly lost. This suggests that an anti-resorptive agent
15 may be required in combination with Wnt surrogate therapy to maintain the anabolic effect.

The mechanism of action of romosozumab relies upon the stimulation of bone formation by removing an inhibitor (sclerostin) of endogenous Wnt signaling. An experiment was done treating animals with
20 Wnt surrogate molecules plus romosozumab to determine if Wnt surrogate molecule treatment was capable of synergizing with romosozumab in a combination study.

C57BL/6 males, 10 weeks old (n=8/group) were injected i.p. with recombinant Wnt surrogate molecules in combination with romosozumab in
25 the following experimental groups: 1RC07-3 (0.1 mpk), 1RC07-3 (1 mpk), 1RC07-3 (10 mpk), 1RC07-3 (0.1 mpk) + romosozumab (25 mpk), 1RC07-3 (1 mpk) + romosozumab (25 mpk), 1RC07-3 (10 mpk) + romosozumab (25 mpk), romosozumab (25 mpk) alone, anti-Bgal (Ab control), and vehicle (PBS). Animals were treated twice weekly and followed for 3 weeks.

30 Whole body BMD was measured weekly and results are presented in FIG 35. Conclusions from this study are that endogenous

romosozumab can stimulate additional bone growth in the presence of high dose 1RCO7-3. These data further suggest that peak anabolic action has not yet been reached with 10 mpk 1RCO7-3 treatments. These data also show that romosozumab can stimulate bone formation even in the presence of 1RCO7-3. Overall, This study shows that Wnt surrogate molecule treatment can synergize with romosozumab to enhance the bone anabolic effect after only 21 days of twice weekly treatment.

Changes in gene expression in whole bone were measured in a time course after Wnt surrogate molecule therapy in mice to assess how this therapy regulates expression of genetic markers related to proliferation and osteogenesis. C57BL/6 females, 13 weeks old (n=5/group) were injected i.p. with 1RCO7-3 or anti-Bgal (Ab control) once. Sub-cutaneous injection of romosozumab was done to another cohort of mice for comparison. Cohorts of animals were sacrificed at 8, 24, 48 and 120 hours after treatment, and tibia bones and serum were isolated and flash frozen for RNA extraction. ELISA was used to measure levels of therapeutic molecules in serum over the course of the experiment as described above (Figure 36).

For purification of RNA from bone, the excised tibia from freshly sacrificed animals were processed as follows: the ends of the tibia were clipped to expose marrow cavity and marrow cavity was flushed with ice cold saline through 30 gauge needle, Steps were taken to ensure all muscle tissue and cartilage has been removed; bone appeared completely white with no red marrow component residual. Tibias were placed in 1.5 mL Eppendorf tubes and flash frozen in liquid nitrogen. To lyse, a single tissue lyser bead was placed in the tube with bone and Trizol was added directly to frozen bone and bead. Tissue lyser at high speed was used to completely homogenize. Homogenates were then subject to chloroform extraction to separate the nucleic acid phase. Further isolation and purification was carried out using an RNeasy mini kit (Qiagen).

RNA Isolated from tibias was tested for relative transcript levels of Runt Related Transcription Factor 2 (RunX2), Collagen Type I Alpha 1

Chain (Col1A1), Dentin Matrix Acidic Phosphoprotein 1 (Dmp1), Alkaline phosphatase (Alp), Receptor activator of nuclear factor kappa-B ligand (RankL), Dickkopf WNT Signaling Pathway Inhibitor 1 (Dkk1), sclerostin (Sost), Cyclin D1 (Ccnd1), Axin2, and Ki67.

5

Table 4. Changes in gene expression in bone with Wnt surrogate molecule (1RC07-3) and romosozumab (Rxmab) Therapy in mice

gene	Time(hr)	Fold Induction +/- SEM relative to Bgal mean value		
		Bgal	Rzmab	1RC073
RunX2	24	1.0+/-0.3	8.8+/-4.4	9.6+/-3.6 **
	48	1.0+/-0.7	1.9+/-1.0	1.5+/-0.5
ColA1	24	1.0+/-0.2	3.9+/-2.0	3.0+/-1.0
	48	1.0+/-0.5	7.0+/-3.3	2.7+/-1.5
Dmp1	24	1.0+/-0.2	2.7+/-1.1	4.8+/-2.9
	48	1.0+/-0.6	1.6+/-0.7	3.8+/-1.8
Alp	24	1.0+/-0.4	18.3+/-11.7	16.5+/-6.4 *
	48	1.0+/-0.6	4.0+/-1.8	5.0+/-1.9
RankL	24	1.0+/-0.3	8.6+/-4.5	8.7+/-3.3
	48	1.0+/-0.7	1.5+/-0.6	4.3+/-1.4
Dkk1	24	1.0+/-0.2	10.5+/-5.1	17.9+/-6.0 **
	48	1.0+/-0.5	4.3+/-2.5	2.8+/-1.3
Sost	24	1.0+/-0.2	2.1+/-1.0	2.5+/-0.9
	48	1.0+/-0.6	5.1+/-2.3	9.0+/-4.2 **
Ccnd1	24	1.0+/-0.4	3.3+/-0.8	3.4+/-1.8
	48	1.0+/-0.6	2.5+/-1.2	2.4+/-1.2
Axin2	24	1.0+/-0.5	3.2+/-1.1	6.1+/-1.8 **
	48	1.0+/-0.8	3.6+/-2.3	4.6+/-1.6 *
Ki67	24	1.0+/- 0.3	7.7+/-4.3	10.0+/-3.2
	48	1.0 +/-0.5	1.0+/-0.5	25.5+/-12.2 ***

* p<0.05, ** p<0.005, 2-way ANOVA comparison with Bgal control

*** p<0.001, 2-way ANOVA comparison with both Bgal and romosozumab

In comparison to anti-sclerostin antibody (romosozumab) treatment, gene expression signatures over the time points were distinct with Wnt surrogate molecule therapy, with induction of more robust Axin2 and Ki67 expression than
5 that caused by romosozumab treatment.

Example 22

In Vivo Liver Regeneration Model and Characterization of AAV-Delivered Wnt Surrogates

10 In vivo experiments were conducted by infecting approximately 8-weeks old C57BL/6J mice with an AAV vector that expressed Flag- and His-tagged 18R5-DKK1c protein (AAV-18R5-DKK1c-FlagHis). 18R5-DKK1c is a fusion protein containing the frizzled binding antibody, 18R5, in scFv format fused to DKK1c, as described in PCT Publication WO2016/040895, e.g., Fig. 5.

15 Control mice were either injected sub-cutaneously with phosphate-buffered saline (PBS) only or romosozumab (10mg/kg), or injected intravenously (IV) with an AAV vector that expressed green fluorescent protein (GFP) (AAV-CAG- GFP), or an AAV vector that expressed a fusion protein comprising an anti-GFP scFv fused to a mutant DKK1c (AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His). 28

20 days after infection, animals were weighed and sacrificed. The liver was weighed, and the liver to body weight ratio calculated. The content of the small intestine and colon was removed by flushing with phosphate-buffered saline and gentle pressure to expel the content. The small intestine and colon were then weighed.

25 Systemic expression of 18R5-DKK1c-FlagHis resulted in a significant liver weight increase (FIG. 37A). Systemic expression of the negative controls, eGFP or anti-eGFP-Dkk1cF234K, did not affect the liver to body weight ratio. Administration of the romosozumab recombinant protein or vehicle control, did not affect the liver to body weight ratio.

30 None of the treatments affected the small intestine (FIG. 37B) or colon (FIG. 37C) to body weight ratio.

These studies showed that 18R5-DKK1c-FlagHis increases liver weight, but not that of the small or large intestines. This suggests that 18R5-DKK1c-FlagHis can promote liver regeneration.

20

5

Example 23

In Vivo Liver Regeneration Model and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted by treating mice with recombinantly produced anti-eGFP, R2M3-26, 1R-C07-26, romosozumab or
10 Rspo2 proteins at various dosages. The Rspo2 protein is a fusion protein between a short splice variant of the Rspo2 gene and a human Fc fragment.

In one study, mice were housed 4 per cage and n=8 per treatment group were used. Approximately 8-weeks old C57BL6/J mice were administered recombinant proteins, anti-eGFP (1 mg/kg), R2M3-26 (1 or 10 mg/kg) or 1R-C07-
15 26 (1, 5 or 10 mg/kg), twice weekly intra-peritoneally (i.p.) for four weeks. In addition, groups of mice were administered romosozumab (30 mg/kg) or PBS vehicle control, subcutaneously.

Mice were weighed at the beginning and throughout the treatment. None of the treatment with recombinant proteins affected total body weight
20 significantly (FIG. 38A). On day 28, the liver was weighed, and the liver to body weight ratio calculated (FIG. 38B). The highest dose of R2M3-26 (10 mg/kg) resulted in a significant increase in liver to body weight ratio. None of the other treatment affected the liver weight significantly.

The increase in liver weight in response to R2M3-26 suggest that
25 this recombinant protein can promote liver regeneration.

In another study, mice were housed 5 per cage and n=10 per treatment group were used. Approximately 8-weeks old C57BL/6J mice received a single i.p. injection containing anti-eGFP (0.56 mg/kg), R2M3-26 (0.3 mg/kg) or Rspo2 (0.46 mg/kg) alone, or with a combination of R2M3-26 (0.1 mg/kg) and
30 Rspo2 (0.46mg/kg).

24 or 48 hours after injection, mice were euthanized. A portion of the left liver lobe was snap-frozen in liquid nitrogen and stored at -80oC for RNA analysis. Cyclin D1 and Ki67 expression were measured by performing qPCR using the Mm00432359_m1 Ccnd1 probe and the Mm01278617_m1 Ki67 probe (Thermofisher, 4331182). An additional portion of the left liver lobe was fixed in formalin and embedded in paraffin for immunohistochemistry analysis. Sections were stained with the anti-proliferating cell nuclear antigen (PCNA) (Abcam, ab18197) or anti-phospho-histone H3 (pH3) rabbit antibodies (Abcam, ab47297). The number of positive nuclei were counted using the image processing software, Image J.

Rspo2 alone increased Ki67 (FIG. 39A) and CyclinD1 (FIG. 39B) mRNA expression. In combination with R2M3-26, Rspo2 increased Ki67 and CyclinD1 expression further than with Rspo2 alone at 24 and 48 hours after treatment with recombinant proteins. Rspo2 alone increased the number of PCNA (FIG. 39C) and pH3 (FIG. 39D) positive nuclei in liver sections. In combination with R2M3-26, Rspo2 increased the number of PCNA and pH3 positive nuclei further than with Rspo2 alone at 48 hours after treatment with recombinant proteins.

These studies show that the proliferation markers, Ki67 mRNA, CyclinD1 mRNA and PCNA-positive nuclei, and the pH3 mitotic marker are induced by the R2M3-26 and Rspo2 recombinant proteins and suggest that these recombinant proteins can promote liver regeneration.

Example 24

25 In Vivo Chronic Liver Injury Model and Characterization of AAV-Delivered Wnt Surrogates

Two in vivo experiments were conducted in two, thioacetamide (TAA)- and CCl4-induced, liver cirrhosis mouse models, thioacetamide (TAA)- and CCl4-induced, to test the effect of AAV vectors expressing 18R5-DKK1c-FlagHis or Rspo2 protein on chronic liver injury. TAA was added to the drinking water of 6 weeks old C57BL/6J mice at a concentration of 300 mg/L throughout

the TAA treatment duration. Mice were housed 5 per cage and groups of n=10 were used, except for the control groups without TAA treatment where n=5 per group was used.

In Study 1 (FIGS. 40A, 40C, 40E, 40G-H), mice with (n=10) or
5 without (n=5) TAA treatment were weighed and sacrificed after 9 weeks of TAA addition into the drinking water, to measure baseline values. Livers were weighed and liver samples were collected for mRNA and histological analysis. TAA supplementation was maintained in the drinking water of the remaining mice and they were injected IV with AAV vectors that expressed an enhanced green
10 fluorescent protein (eGFP) (3e10 genomic particles (GC)), 18R5-DKK1c- FlagHis (3e10 or 1e11 GC) or Rspo2 protein (1e11 GC) or a combination of 18R5-DKK1c-FlagHis (3e10 GC) and Rspo2 (1e11 GC). 5 age-matched naïve animals (no TAA) were kept as a negative control. Three weeks after AAV injection, all mice were weighed and euthanized. Livers were weighed and liver samples were
15 collected for mRNA and histological analysis.

Treatment with 18R5Dkk1FH or Rspo2 resulted in a significant increase of liver weight (FIG. 40C) and liver to body weight ratio (FIG. 40E) in mice undergoing a continuous exposure to TAA. Treatment with a combination of 18R5Dkk1FH and Rspo2 resulted in a further increase in liver weight and liver to
20 body weight ratio beyond that observed with either treatment alone. The combination 18R5Dkk1FH and Rspo2 treatment resulted in a decrease of the fibrosis marker Col1a1 mRNA expression (FIG. 40G). Histological liver sections were stained with Sirius red to visualize the accumulation of collagen in fibrotic area (FIG. 40H). Quantification of the percentage of red area, using Image J
25 analysis software, showed a significant increase of fibrotic area in TAA-treated mice. A combination of 18R5Dkk1FH and Rspo2 resulted in a reversal of fibrotic area increase when compared to mice treated with the eGFP negative control. Treatment with Rspo2 alone also resulted in a significant but smaller reversal than the combination treatment.

30 In Study 2, (FIGS. 40B, 40D, 40F), mice were exposed to TAA-supplemented water for 11 weeks, and were returned to standard drinking

thereafter, two days prior to AAV treatment. At the start of AAV treatment, mice exposed to TAA (n=10) or not (n=5) were weighed and sacrificed to collect liver samples for baseline measurements. The remaining mice were injected with AAV vectors that expressed an enhanced green fluorescent protein (eGFP) (1.3e11 genomic particles (GC)), 18R5-DKK1c-FlagHis (3e10 or 1e11 GC) or Rspo2 protein (1e11 GC) or a combination of 18R5-DKK1c-FlagHis (3e10 GC) and Rspo2 (1e11 GC). 5 age-matched naïve animals (no TAA) were kept as a negative control. Three weeks after AAV injection, all mice were weighed and euthanized. Livers were weighed and liver samples were collected for mRNA and histological analysis.

A similar liver weight and liver to body weight increase was observed in mice treated with 18R5-Dkk1c-FlagHis and Rspo2 either alone or in combination than what was observed in Study 1 (FIGS. 40D, 40F).

These studies show that 18R5-Dkk1c-FlagHis and Rspo2 can increase liver weight in a TAA-induced liver cirrhosis model and reduce fibrosis markers. These results suggest that 18R5-Dkk1c-FlagHis and Rspo2 can promote liver tissue repair after chronic liver injury.

Example 25

In Vivo Chronic Liver Injury Models and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted in thioacetamide (TAA)-induced and CCl₄-induced mouse models of liver cirrhosis by treating mice with recombinantly produced anti-eGFP, R2M3-26 and Rspo2 proteins.

In the TAA-induced cirrhosis model, six weeks old male mice were exposed to TAA-supplemented drinking water (300 mg/L) for approximately 22 weeks (FIG. 41A). TAA exposure was removed two days prior to beginning of treatment with recombinant proteins and mice were provided with fresh drinking water. Mice were housed 5 per cage and n=10 per treatment group were used. In a mono treatment study (FIGS. 41B, 41D, 41F, 41H, 41J, 41L), mice were injected i.p. with anti-eGFP (1 mg/kg) or Rspo2 (1 mg/kg) twice weekly. In a

combination treatment study (FIGS. 41C, 41E, 41G, 41I, 41K, 41M), mice were injected i.p. with anti-eGFP (1.3mg/kg) or a combination of R2M3-26 (0.3 mg/kg) and Rspo2 (1 mg/kg) twice weekly. Mice were then weighed and sacrificed at day 3, 7 or 14 days after beginning of treatment. Groups of control mice without exposure to TAA (n=5 per group) were euthanized at day 0 and day 14 in both studies.

Treatment with Rspo2 protein alone or in combination with R2M3-26 resulted in an increase in liver to body weight ratio (FIGS. 41B and 41C) and a transient stimulation of the Wnt signaling pathway as shown by an increase in Axin2 expression (FIGS. 41D and 41E). Treatment with Rspo2 protein alone or in combination with R2M3-26 induced the following proliferation markers: cyclinD1 (FIGS. 41F, 41G) and Ki67 (FIGS. 41H and 41I) mRNA expression, PCNA (FIGS. 41J, 41K) and pH3 (FIGS. 41L, 41M) positive nuclei.

In an additional study, plasma was collected for prothrombin time measurement. Coagulation time is impaired in TAA-induced cirrhosis model as exemplified by an increase in pro-thrombin (PT) test to normal value ratio in mice exposed to TAA when compared to normal mice without TAA exposure (FIG. 41N). Treatment with Rspo2 (1 mg/kg) and R2M3-26 (0.3 mg/kg) reversed the prolongation in PT time as shown by the decrease in $PT_{\text{test}}/PT_{\text{normal}}$ ratio at day 7 and day 14 after biweekly Rspo2 and R2M3-26 treatment.

These studies show that Rspo2 and R2M3-26 can stimulate liver cell proliferation and improve hepatocytes functional activity such as pro-thrombin time in a TAA-induced liver cirrhosis model. These results suggest that Rspo2 and R2M3-26 can promote liver tissue repair in chronic liver disease.

In the CCl₄-induced cirrhosis model, six-weeks old C57BL/6J male mice were injected i.p. with 2 ml/kg CCl₄ in mineral oil, twice weekly for 8 weeks (FIG. 42A). 3 days after the last CCl₄ injection, mice were injected i.p. twice weekly with the following recombinant proteins: anti- β -galactosidase (10mg/kg), Rspo2 (1 or 10 mg/kg), or a combination of R2M3-26 (0.3mg/kg) and Rspo2 (1 mg/kg). Three additional control groups were included: one group injected with CCl₄ but no proteins, one group injected with mineral oil, and one untreated age-

matched naïve group. n=8 were used for each group. After two weeks of treatment with recombinant proteins, mice were weighed and sacrificed. Plasma was collected for pro-thrombin time measurement. Livers were weighed and liver samples were collected for histological analysis.

5 Treatment with R2M3-26 and Rspo2 resulted in a significant increase in liver to body weight ratio when compared to treatment with anti- β -galactosidase negative control (FIG. 42B). Treatment with Rspo2 (10 mg/kg) or a combination of R2M3-26 and Rspo2 resulted in a significant decrease in prothrombin time (FIG. 42C). Treatment with Rspo2 (10 mg/kg) or a combination
10 of R2M3-26 and Rspo2 resulted in a significant reversal in fibrotic area, induced by CCl₄ (FIG. 42D).

 This study showed that Rspo2 and R2M3-26 can induce an increase in liver weight, improve hepatocytes functional activity such as pro-thrombin time and reduce fibrosis markers in a CCl₄-induced liver cirrhosis
15 model. These results suggest that Rspo2 and R2M3-26 can promote liver tissue repair in chronic liver disease.

Example 26

20 **In Vivo Acute Liver Injury Model and Characterization of Recombinantly Produced Wnt Surrogates**

 In vivo experiments were conducted using acetaminophen- induced mouse models of acute liver injury by treating mice with recombinantly produced anti-eGFP, R2M3-26 and Rspo2 proteins.

 Eight-week old C57BL/6 male mice were housed 5 per cage. n=10
25 were used per group. Mice were fasted overnight for 12 hours. Acetaminophen (APAP) was administered i.p. at a sublethal dose (300 mg/kg).

 In a first study, anti-eGFP (0.3 mpk) or R2M3-26 (0.3 mpk) were injected i.p. either immediately after or 3 or 6 hours after APAP injection (FIG.43). Serum samples were collected at 24 and 48 hours after APAP injection for ALT
30 measurements. Mice were sacrificed 48 hours after APAP injection and liver samples were collected for mRNA analysis.

R2M3-26 treatment did not affect ALT level significantly (FIG. 43B). Treatment with R2M3-26 induced cyclinD1 (FIG. 43C) and Ki67 (FIG. 43D) mRNA significantly, beyond the level induced by APAP treatment alone.

In a second study, human Fc (0.46 mg/kg) or Rspo2 (0.46 mg/kg) were injected i.p. either immediately after or 3 or 6 hours after APAP injection (FIG. 44). Serum samples were collected at 24 and 48 hours after APAP injection. Liver samples were collected at 48 hours after APAP injection. Rspo2 treatment did not affect ALT serum level significantly (FIG. 44B). Treatment with Rspo2 induced cyclinD1 (FIG. 44C) and Ki67 (FIG. 43D) mRNA significantly, beyond the level induced by APAP treatment alone.

In a third study, anti-eGFP (0.56 mg/kg) or a combination of R2M3-26 (0.1 mg/kg) and Rspo2 (0.46 mg/kg) were injected i.p. 3 hours after APAP administration. Serum and liver samples were collected at 24, 36, 48 and 60 hours after APAP injection for ALT measurements and mRNA analysis.

R2M3-26 and Rspo2 combination treatment did not affect ALT level significantly (FIG. 45B). Treatment with R2M3-26 and Rspo2 induced cyclinD1 (FIG. 45C) and Ki67 (FIG. 45D) mRNA significantly, beyond the level induced by APAP treatment alone.

An additional study was performed to evaluate the effect of Rspo2 and R2M3-26 on the survival of mice treated with a dose of 600 mg/kg of acetaminophen (FIG. 46). Anti-eGFP (0.3 mg/kg), R2M3-26 (0.3 mg/kg), Rspo2 (0.46mg/kg) or a combination of R2M3-26 (0.1 mg/kg) and Rspo2 (0.46 mg/kg) were injected i.p. 3 hours after APAP administration. Mice were monitored several times daily over the next 96 hours. A consistent trend in improving survival was observed in groups treated with R2M3-26 (FIG. 46B), Rspo2 (FIG. 46C) or a combination of R2M3-26 and Rspo2 (FIG. 46D).

These studies show that Rspo2 and R2M3-26 can induce proliferation markers beyond that induced spontaneously in APAP-induced acute injury model. These results suggest that Rspo2 and R2M3-26 can enhance liver tissue repair after an acute liver injury.

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 applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the

5 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, applications and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description.

10 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.

15

CLAIMS

What is claimed is:

1. A soluble, multivalent, multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises: (i) one or more region that specifically binds to one or more Frizzled (Fzd) receptor (a Fzd binding region); and (ii) one or more region that specifically binds to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) (a LRP5/6 binding region).
2. The Wnt surrogate molecule of claim 1, comprising one or more Fzd binding regions and one or more LRP5/6 binding regions.
3. The Wnt surrogate molecule of claim 1, wherein the one or more Fzd binding regions comprise one or more antigen-binding fragments of an antibody.
4. The Wnt surrogate molecule of claim 3, wherein the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and VHH or single domain antibodies (sdAb).
5. The Wnt surrogate molecule of any of claims 3-4, wherein the one or more Fzd antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Tables 1A or 1B; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Tables 1A or 1B, or a variant of said Fzd binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.
6. The Wnt surrogate molecule of any of claims 3-5, wherein the one or more Fzd binding regions comprise an amino acid sequence having at least 90% identity

to any of the sequences set forth in SEQ ID NOs:1-65 or 129-132, or an antigen-binding fragment thereof.

7. The Wnt surrogate molecule of any of claims 1-6, wherein the one or more Fzd binding regions bind to one or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

8. The Wnt surrogate molecule of claim 7, wherein the one or more Fzd binding region binds to two or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

9. The Wnt surrogate molecule of claim 8, wherein the one or more Fzd binding region binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii) Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8.

10. The Wnt surrogate molecule of any of claims 1-9, wherein the one or more LRP5/6 binding regions comprise one or more antigen-binding fragments of an antibody.

11. The Wnt surrogate molecule of claim 10, wherein the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and VHH or sdAb.

12. The Wnt surrogate molecule of any of claims 1-11, wherein the one or more LRP5/6 binding regions or antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2,

or a variant of said LRP5/6 binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

13. The Wnt surrogate molecule of any of claims 10-12, wherein the one or more LRP5/6 binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:66-88 or 133, or an antigen-binding fragment thereof.

14. The Wnt surrogate of any of claims 1-13, wherein the Fzd binding region and the LRP5/6 binding region comprise the sequences set forth in Table 3 for any of the Wnt surrogates disclosed therein.

15. The Wnt surrogate molecule of any of claims 1-14, wherein the Fzd binding region comprises a Fab, and the LRP5/6 binding region comprises a VHH or sdAb or a scFv.

16. The Wnt surrogate molecule of claim 15, wherein the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.

17. The Wnt surrogate molecule of claim 16, wherein the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain.

18. The Wnt surrogate molecule of claim 17, wherein the LRP5/6 binding region is fused to the heavy chain or the light chain via one or more linker moiety.

19. The Wnt surrogate molecule of any of claims 1-14, wherein the Fzd binding region comprises a VHH or sdAb or scFv, and the LRP5/6 binding region comprises a Fab.

20. The Wnt surrogate molecule of claim 19, wherein the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.
21. The Wnt surrogate molecule of claim 20, wherein the Fzd binding region is fused to the N-terminus or the C-terminus of the heavy chain.
22. The Wnt surrogate molecule of claim 20, wherein the Fzd binding region is fused to the N-terminus or the C-terminus of the light chain.
23. The Wnt surrogate molecule of claim 21 or claim 22, wherein the Fzd binding region is fused to the heavy chain or the light chain via one or more linker moiety.
24. The Wnt surrogate molecule of any of claims 1-14, wherein the Fzd binding region comprises a Fab or Fv, and the LRP5/6 binding region comprises a Fab or Fv.
25. The Wnt surrogate molecule of claim 24, wherein the Fab of the Fzd binding region or the Fab of the LRP5/6 binding region is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.
26. The Wnt surrogate molecule of claim 25, wherein only one of the Fab of the Fzd binding region or the Fab of the LRPp5/6 binding region is present within the full immunoglobulin (Ig).
27. The Wnt surrogate molecule of claim 26, wherein the Fab of the Fzd binding region is present within the full Ig.
28. The Wnt surrogate molecule of claim 27, wherein the Fab or Fv of the LRP5/6 binding region is fused to the N-terminus of the Ig, optionally the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig.

29. The Wnt surrogate molecule of claim 27, wherein the Fab of the LRP5/6 binding region is fused to the C-terminus of the Ig, optionally the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig.
30. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig.
31. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable light chain region of the full IgG.
32. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable light chain region of the full IgG.
33. The Wnt surrogate molecule of claim 27, wherein the variable heavy chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable light chain region of the LRP5/6 binding Fv is fused to the N-terminus of the variable light chain region of the full IgG.
34. The Wnt surrogate molecule of claim 26, wherein the Fab of the LRP5/6 binding region is present within the full Ig.
35. The Wnt surrogate molecule of claim 34, wherein the Fab or Fv of the Fzd binding region is fused to the N-terminus of the Ig, optionally the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig.

36. The Wnt surrogate molecule of claim 34, wherein the Fab or Fv of the Fzd binding region is fused to the C-terminus of the Ig, optionally the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig.
37. The Wnt surrogate molecule of claim 34, wherein the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig.
38. The Wnt surrogate molecule of claim 34, wherein the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fab is fused to the N-terminus of the variable light chain region of the full IgG.
39. The Wnt surrogate molecule of claim 34 or claim 35, wherein the variable light chain region of the Fzd binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fv is fused to the N-terminus of the variable light chain region of the full IgG.
40. The Wnt surrogate molecule of claim 34 or claim 35, wherein the variable heavy chain region of the Fzd binding Fv is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable light chain region of the Fzd binding Fv is fused to the N-terminus of the variable light chain region of the full IgG.
41. The Wnt surrogate molecule of any of claims 1-14, wherein the Fzd binding region comprises a VHH or sdAb or scFv, and the LRP5/6 binding region comprises a VHH or sdAb or scFv.
42. The Wnt surrogate molecule of claim 41, wherein the Fzd binding region is fused to the Lrp5/6 binding region, and wherein the Fzd binding region or the LRP5/6 binding region is fused to an Fc region.

43. The Wnt surrogate molecule of claim 41, wherein the Fzd binding region is fused to the N-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the C-terminus of an Fc region.
44. The Wnt surrogate molecule of claim 41, wherein the Fzd binding region is fused to the C-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the N-terminus of an Fc region.
45. The Wnt surrogate molecule of any of claims 1-14, wherein the surrogate molecule has a structure set forth in Figs. 1A-D, 10A, 15A., 16A or 18A.
46. The Wnt surrogate molecule of any of claims 1-45, wherein the one or more antigen-binding fragment thereof, is humanized.
47. The Wnt surrogate molecule of any of claims 1-46, which binds to the one or more Fzd receptor with a KD of 50 μ M or lower.
48. The Wnt surrogate molecule of any of claims 1-47, which binds to the one or more LRP5/6 receptor with a KD of 50 μ M or lower.
49. The Wnt surrogate molecule of any of claims 1-48, which modulates a Wnt signaling pathway in a cell, optionally wherein the cell is a mammalian cell.
50. The Wnt surrogate of claim 49, wherein the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway.
51. The Wnt surrogate molecule of claim 49 or claim 50, which increases signaling via the Wnt signaling pathway in the cell.

52. An isolated polynucleotide encoding a polypeptide sequence comprising one or more of the Fzd binding regions and/or one or more of the LRP5/6 binding regions of a Wnt surrogate molecule of any of claims 1-51.
53. An expression vector comprising the isolated polynucleotide of claim 52.
54. An isolated host cell comprising the expression vector of claim 53.
55. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the Wnt surrogate molecule according to any of claims 1-51, the polynucleotide of claim 52, the expression cell of claim 53, or the host cell of claim 54.
56. A method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell the Wnt surrogate molecule according to any of claims 1-51, the polynucleotide of claim 52, the expression cell of claim 53, or the host cell of claim 54, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.
57. 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 the Wnt surrogate molecule according to any of claims 1-51, the polynucleotide of claim 52, the expression cell of claim 53, the host cell of claim 54, or the pharmaceutical composition of claim 55, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.
58. The method of claim 57, wherein the disease or disorder is a bone disease or disorder.
59. The method of claim 58, wherein the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6.

60. The method of claim 59, wherein the Wnt surrogate molecule also binds Fzd5 and Fzd8.

61. The method of claim 57, wherein the disease or disorder is selected from the group consisting of: bone fractures, stress fractures, vertebral compression fractures, osteoporosis, osteoporotic fractures, non-union fractures, delayed union fractures, spinal fusion, pre-operative optimization for spine surgeries, osteonecrosis, osseointegration of implants or orthopedic devices, osteogenesis imperfecta, bone grafts, tendon repair, tendon-bone integration, tooth growth and regeneration, maxillofacial surgery, dental implantation, periodontal diseases, maxillofacial reconstruction, osteonecrosis of the jaw, hip or femoral head, avascular necrosis, alopecia, hearing loss, vestibular hypofunction, macular degeneration, age-related macular degeneration (AMD), vitreoretinopathy, retinopathy, diabetic retinopathy, diseases of retinal degeneration, Fuchs' dystrophy, cornea diseases, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, muscular dystrophy, muscle atrophy caused by sarcopenia or cachexia, diseases affecting blood brain barrier (BBB) integrity, spinal cord injuries, spinal cord diseases, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), metabolic syndrome, diabetes, dyslipidemia, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, pressure sores, venous leg ulcers, epidermolysis bullosa, dermal hypoplasia, myocardial infarction, coronary artery disease, heart failure, hematopoietic cell disorders, immunodeficiencies, graft versus host diseases, acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases including alcoholic hepatitis, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, 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, livery 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.

62. A method for increasing bone mineral density, increasing bone volume, increasing bone cortical thickness, increasing bone mineral apposition rate, increasing bone stiffness, increasing bone biomechanical strength, increasing resistance to bone fracture, or decreasing bone loss associated with osteoporosis, comprising providing to a subject an effective amount of the pharmaceutical composition of claim 55, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

63. The method of claim 62, wherein the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6.

64. The method of claim 63, wherein the Wnt surrogate molecule also binds Fzd5 and Fzd8.

65. 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 55, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

66. The method of any of claims 57-65, further comprising providing to the subject an antiresorptive agent.

67. The method of claim 66 for the treatment of osteoporosis, optionally postmenopausal osteoporosis.

68. A method for inhibiting or reducing bone resorption in a subject in need thereof, comprising providing to the subject an effective amount of the Wnt surrogate molecule according to any of claims 1-51, the polynucleotide of claim 52, the expression cell of claim 53, the host cell of claim 54, or the pharmaceutical composition of claim 55, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

69. The method of claim 68, further comprising providing to the subject an antiresorptive agent.

70. The method of claim 68 or claim 69, wherein the subject has been diagnosed with or is at risk for osteoporosis, optionally postmenopausal osteoporosis.

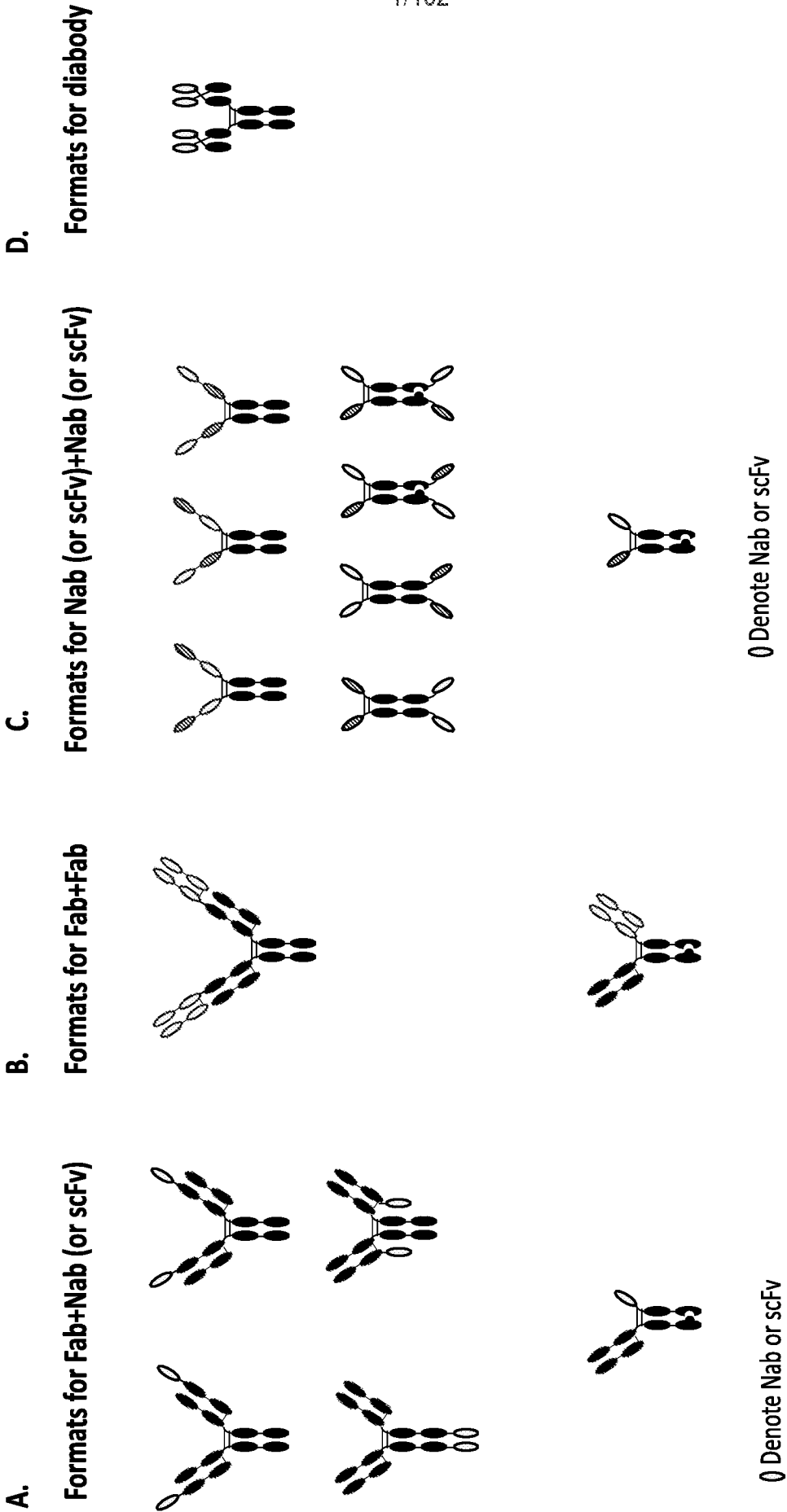


FIG. 1

B. SEC chromatography-protein and 293STF activity traces

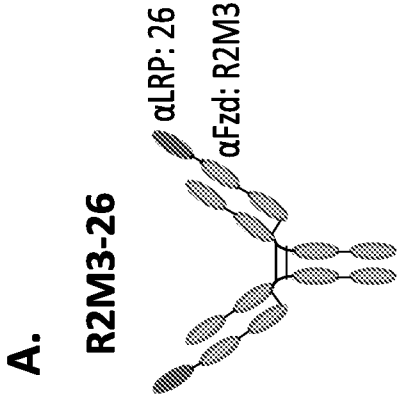
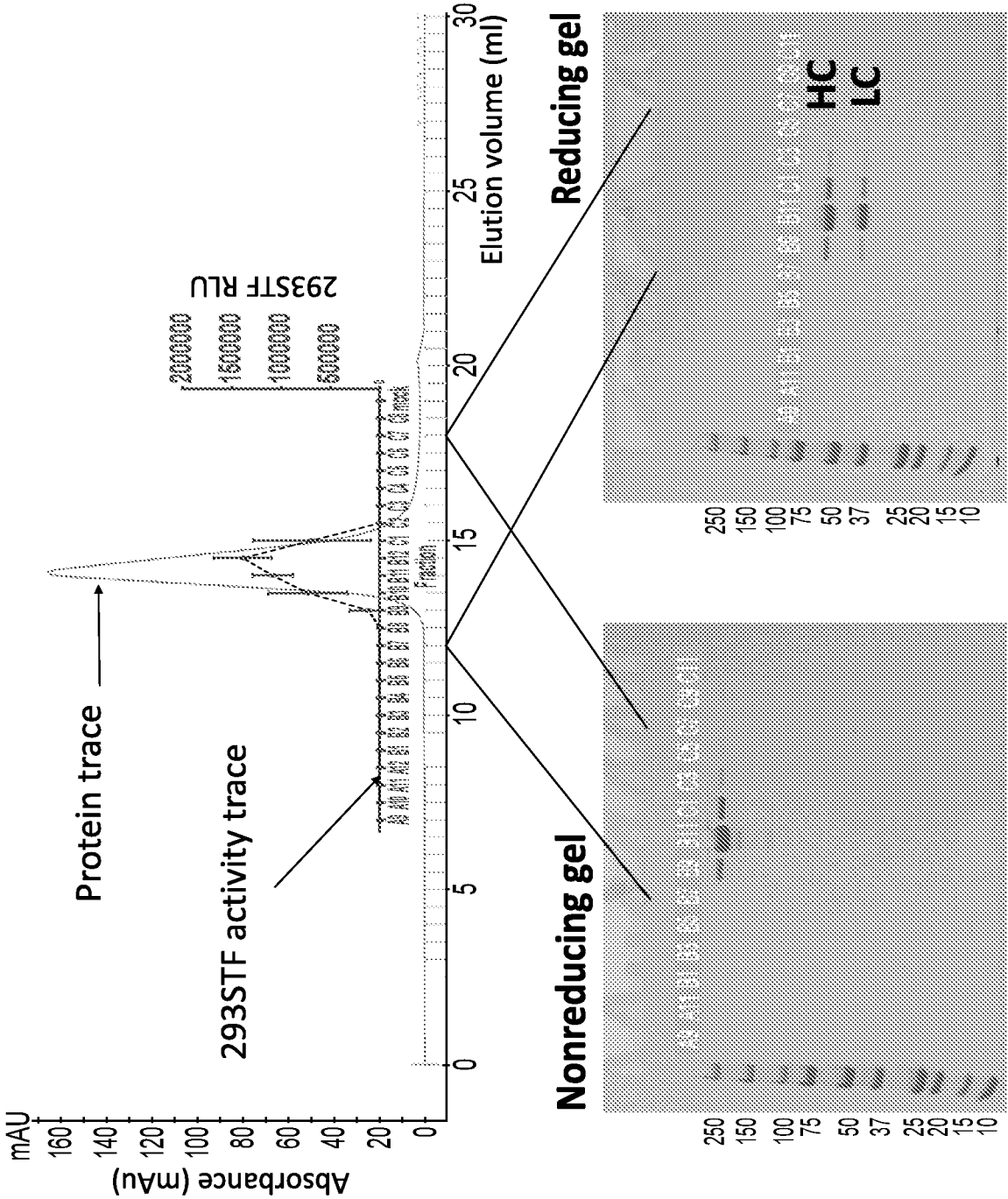
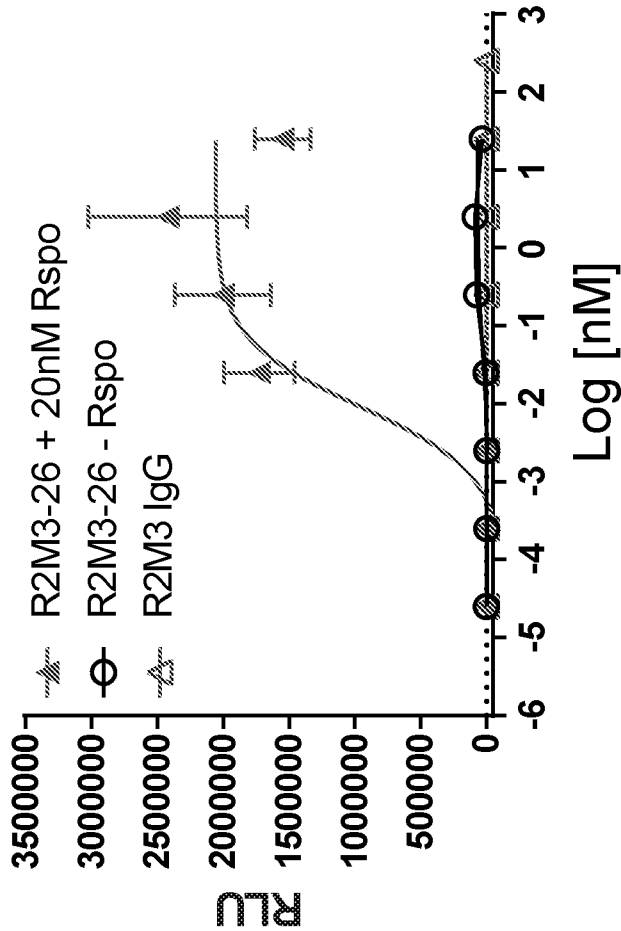


FIG. 2

D.

293STF



C.
Affinity determination (Octet)

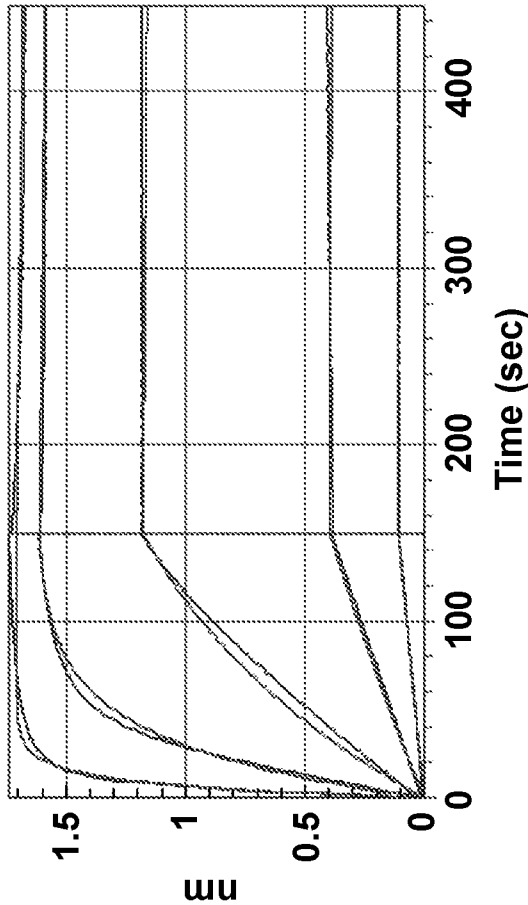
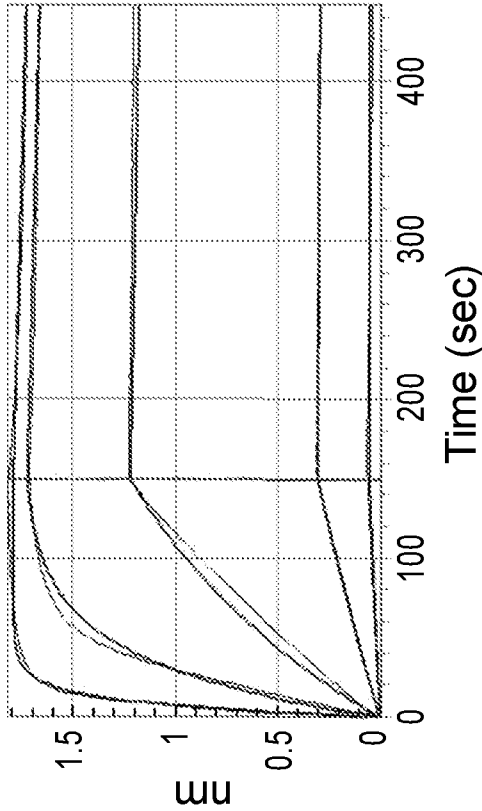


FIG. 2 (contd.)



C.

Affinity determination (Octet)



D.

293STf

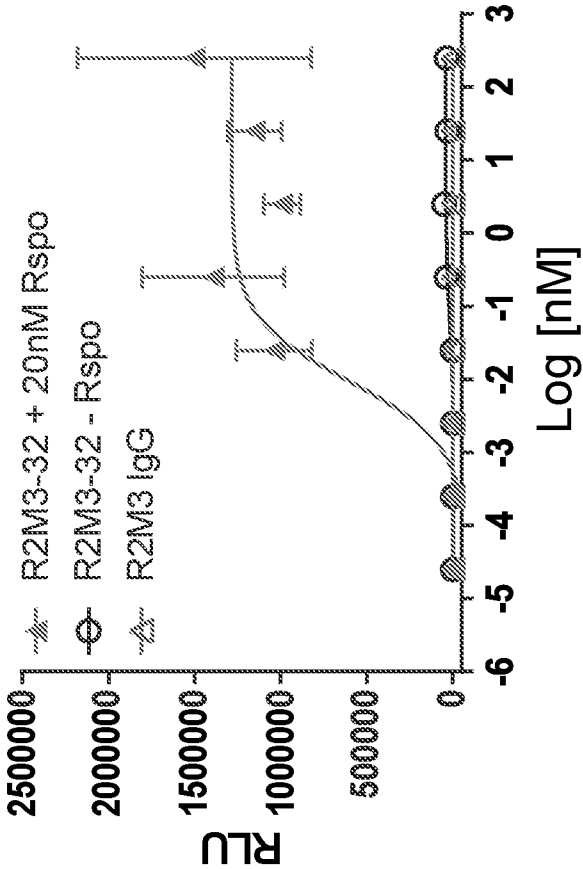


FIG. 3 (contd.)

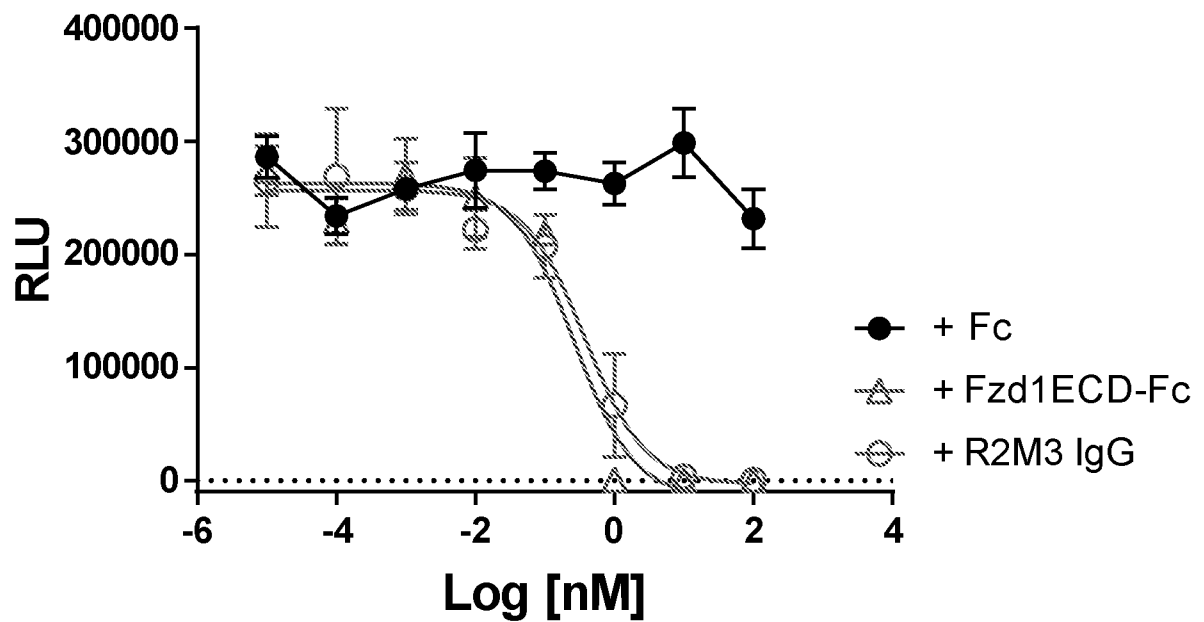
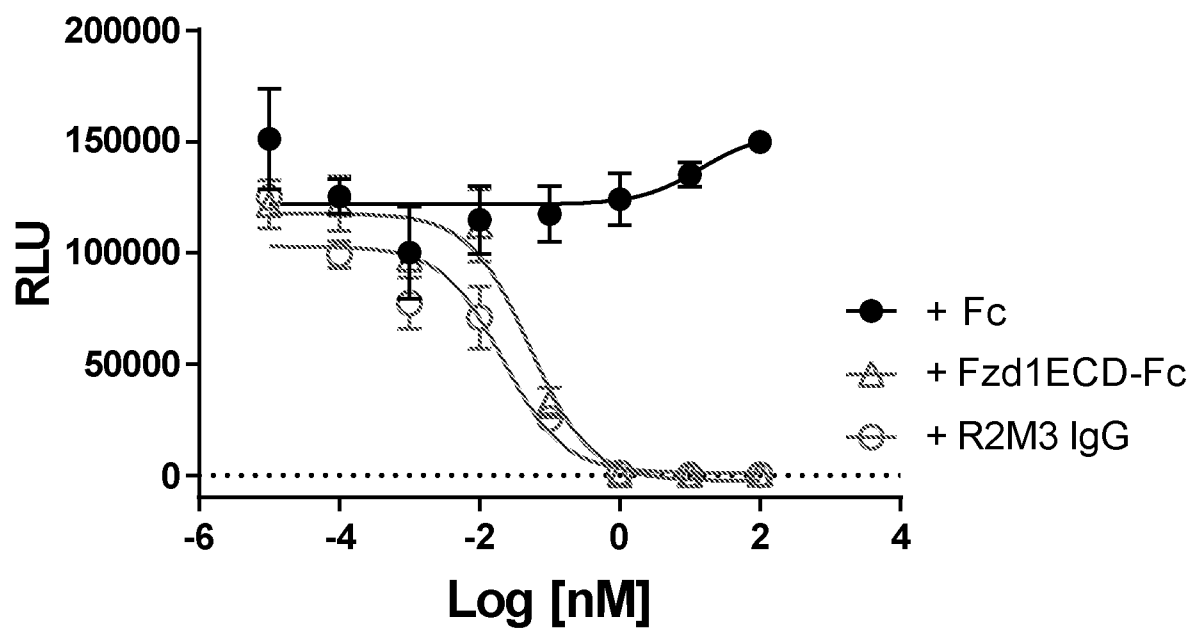
A.**B.**

FIG. 4

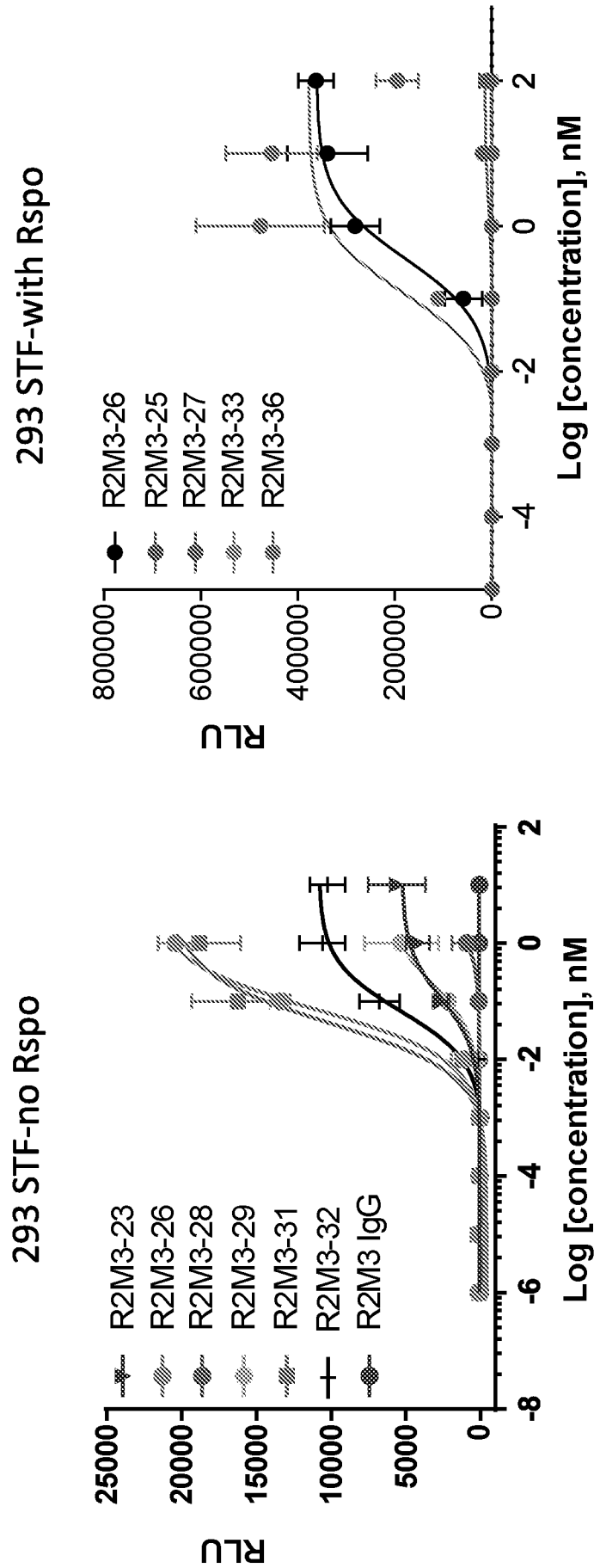


FIG. 5

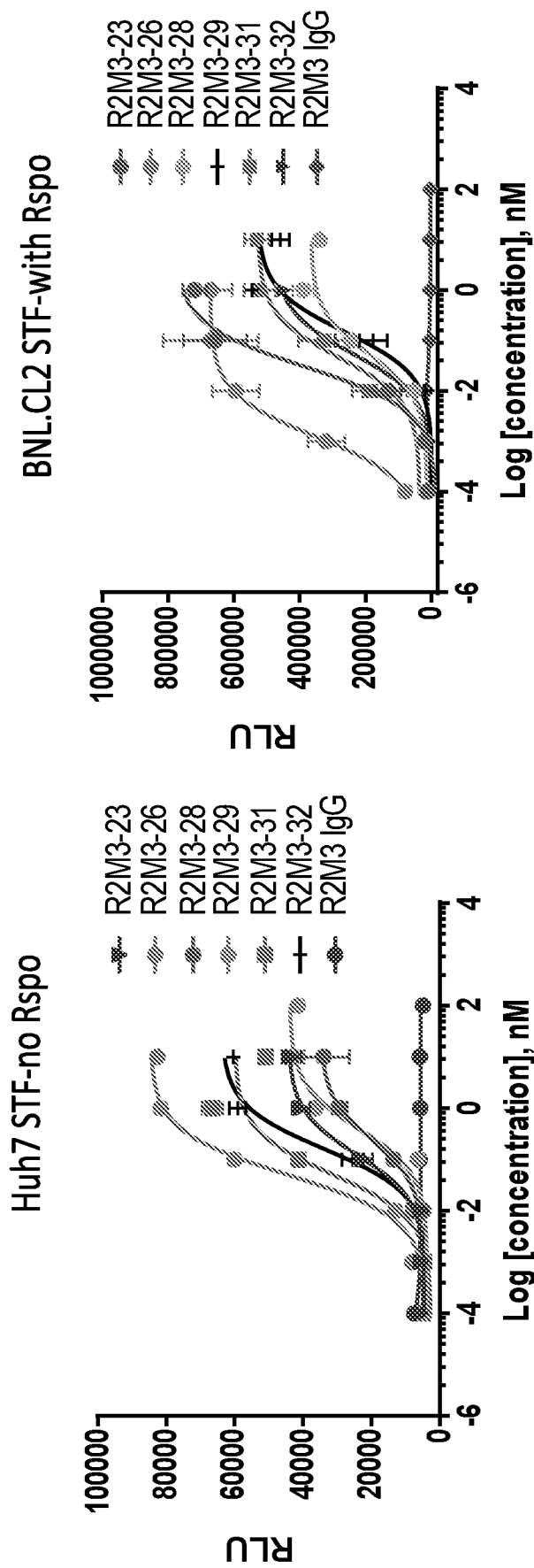


FIG. 5 (contd.)

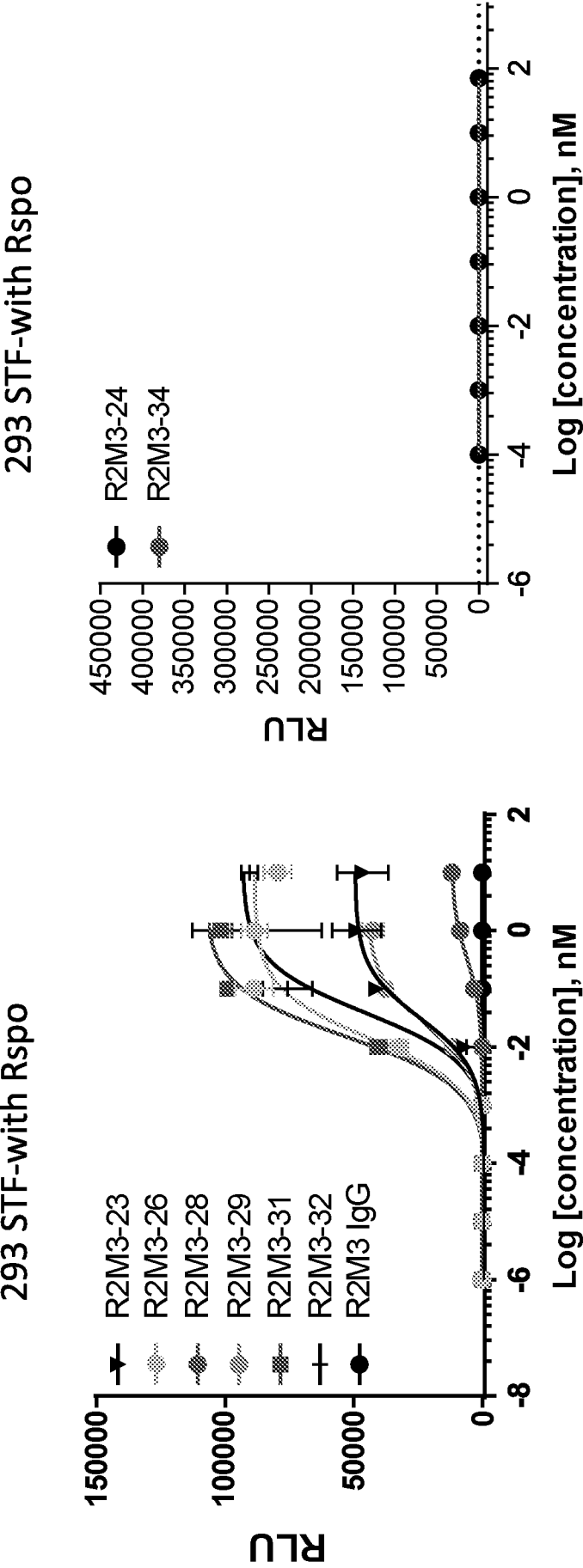


FIG. 5 (contd.)

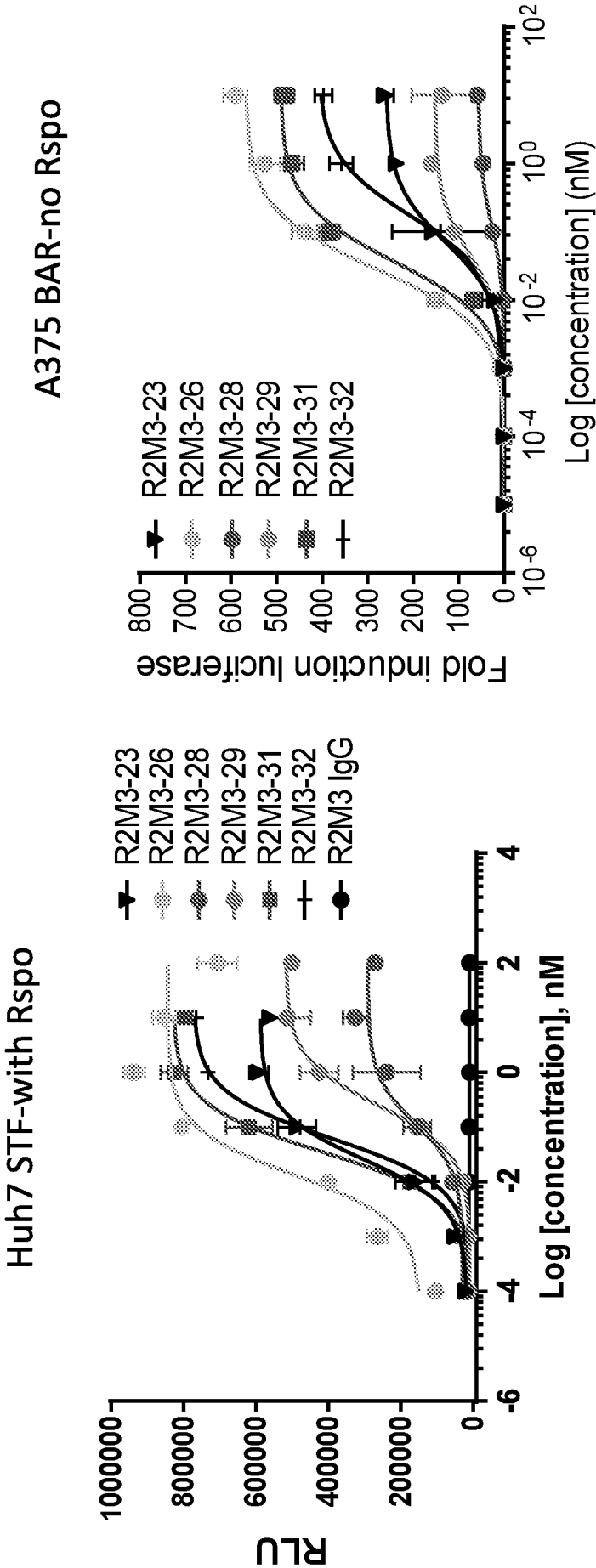


FIG. 5 (contd.)

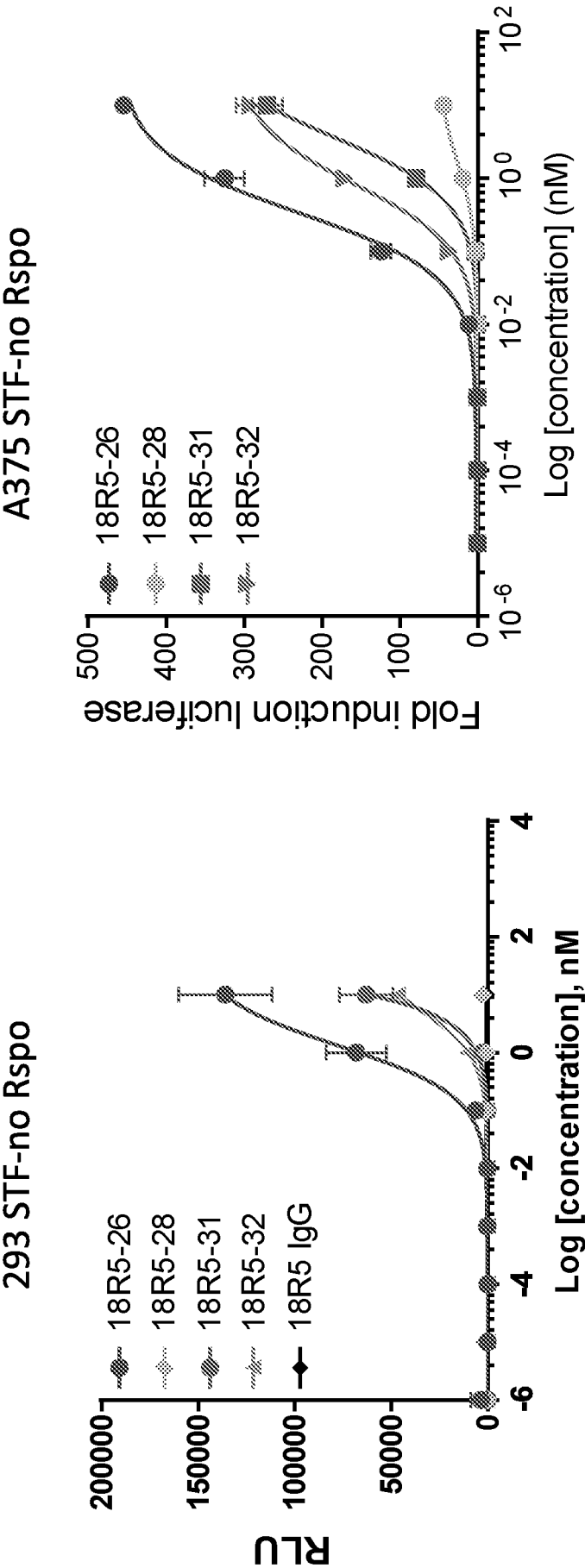


FIG. 6

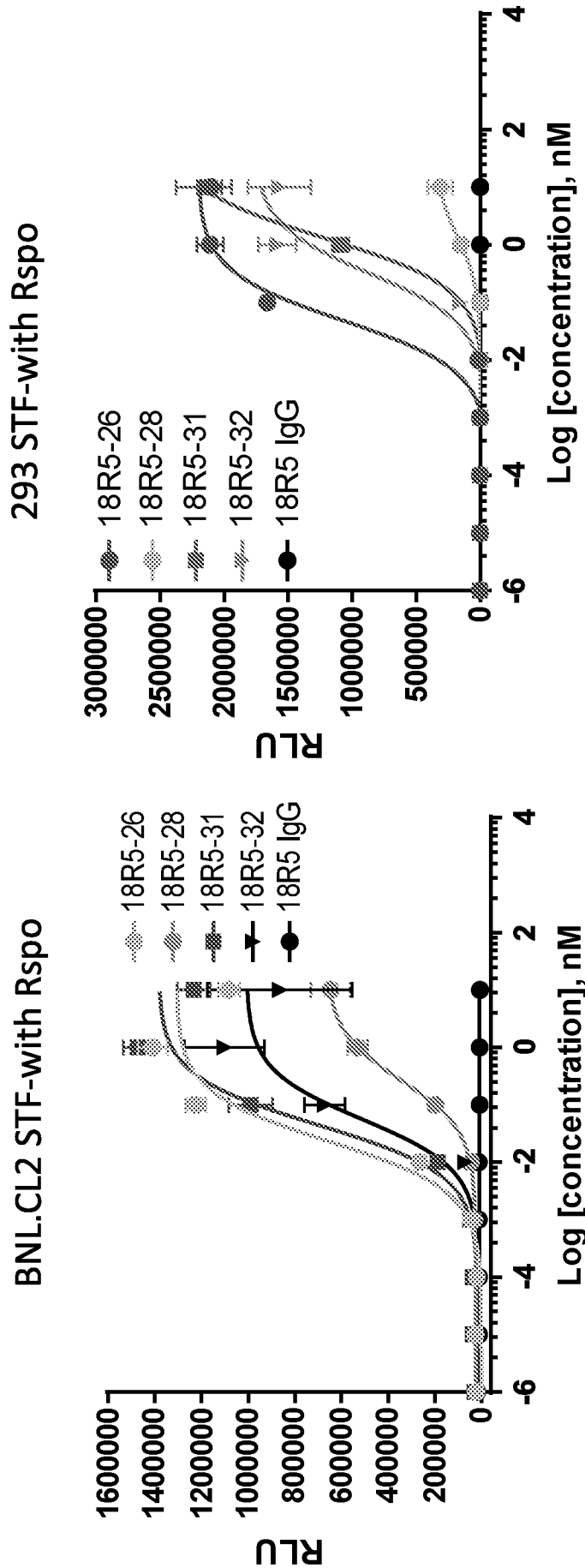


FIG. 6 (contd.)

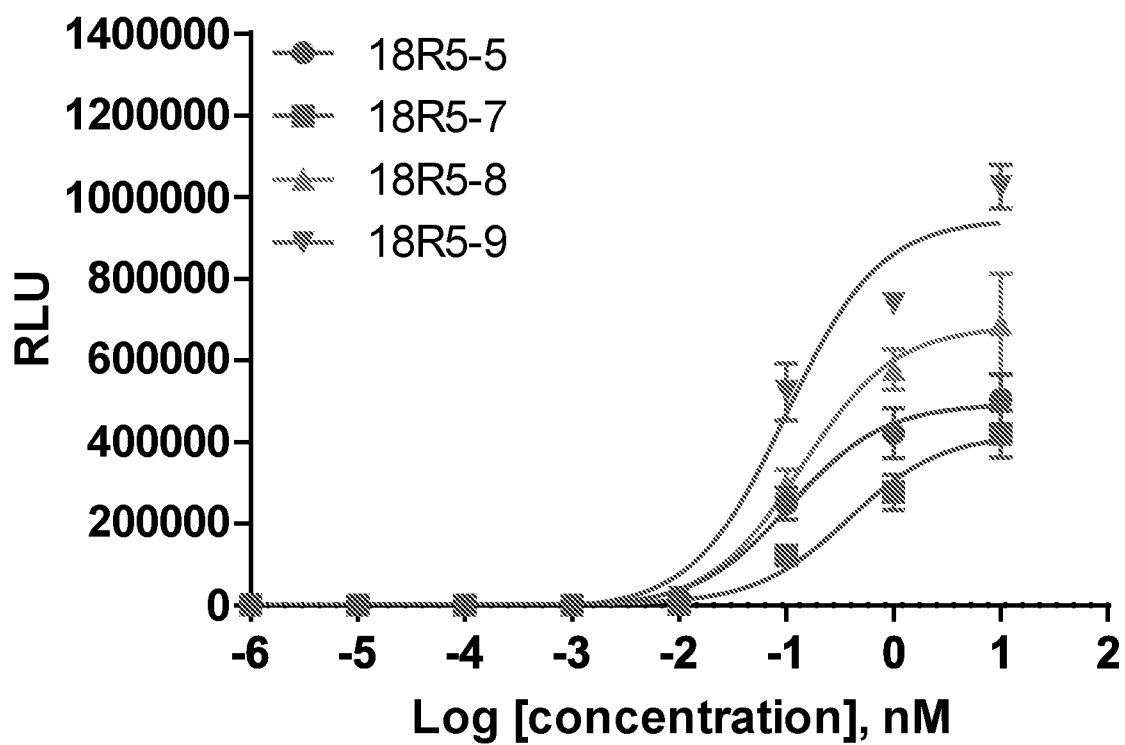
293 STF (with Rspo)

FIG. 7

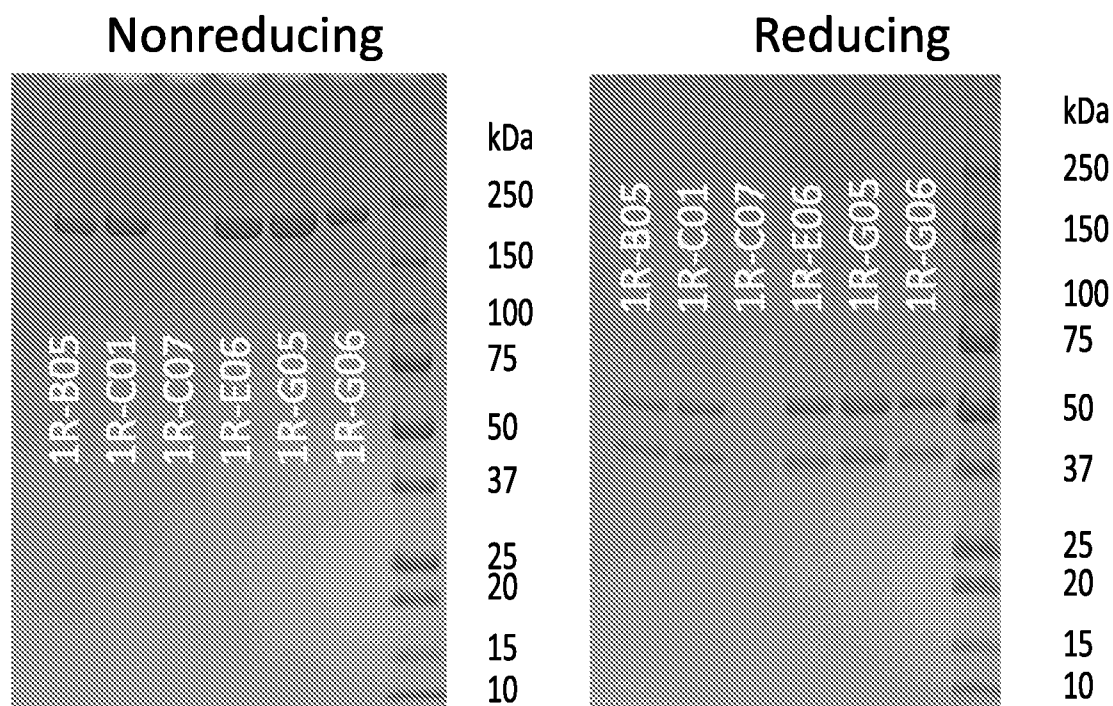
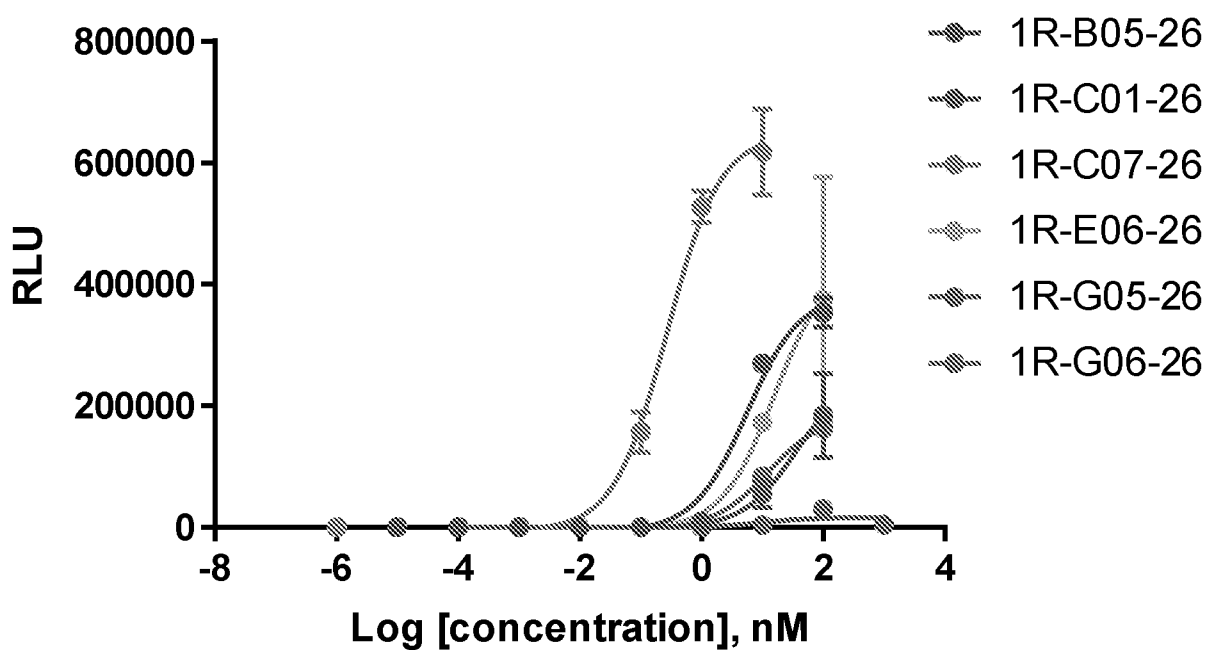
A.**B.**

FIG. 8

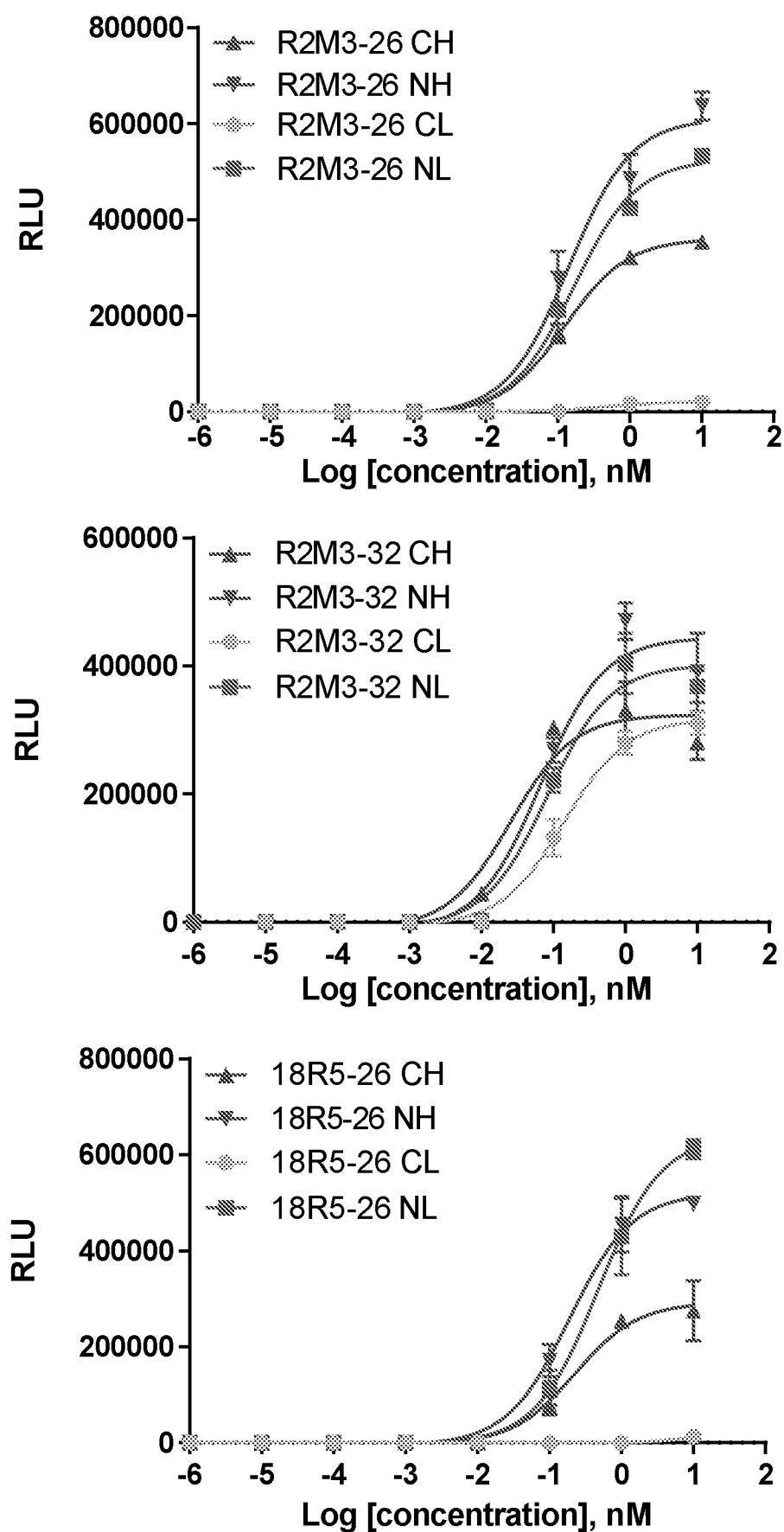


FIG. 9

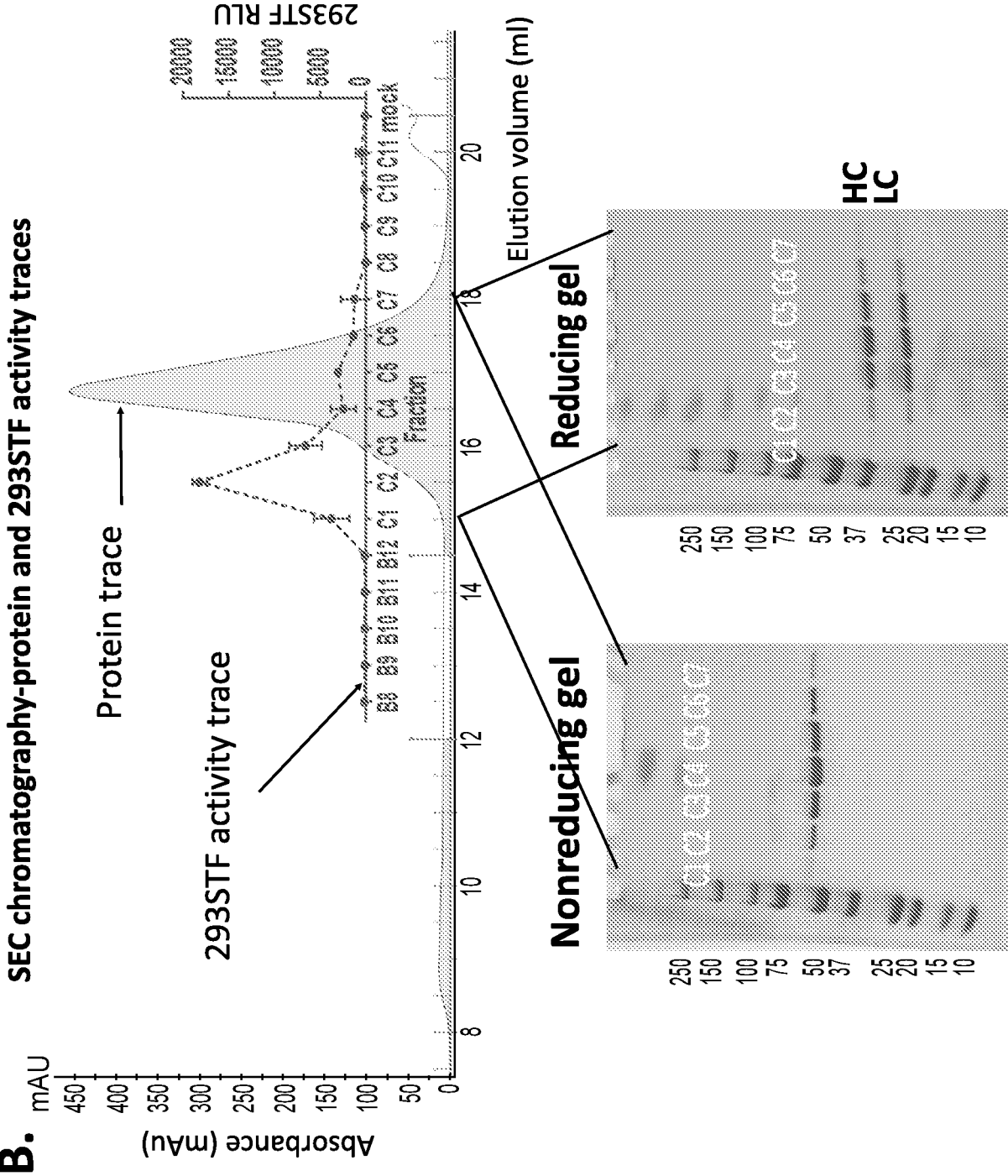
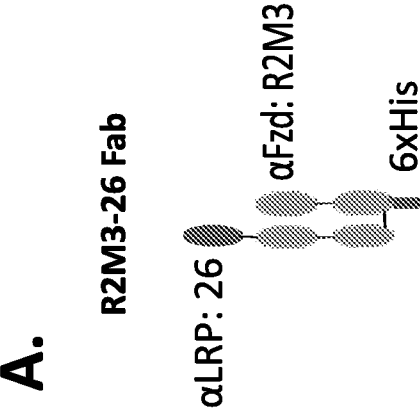


FIG. 10

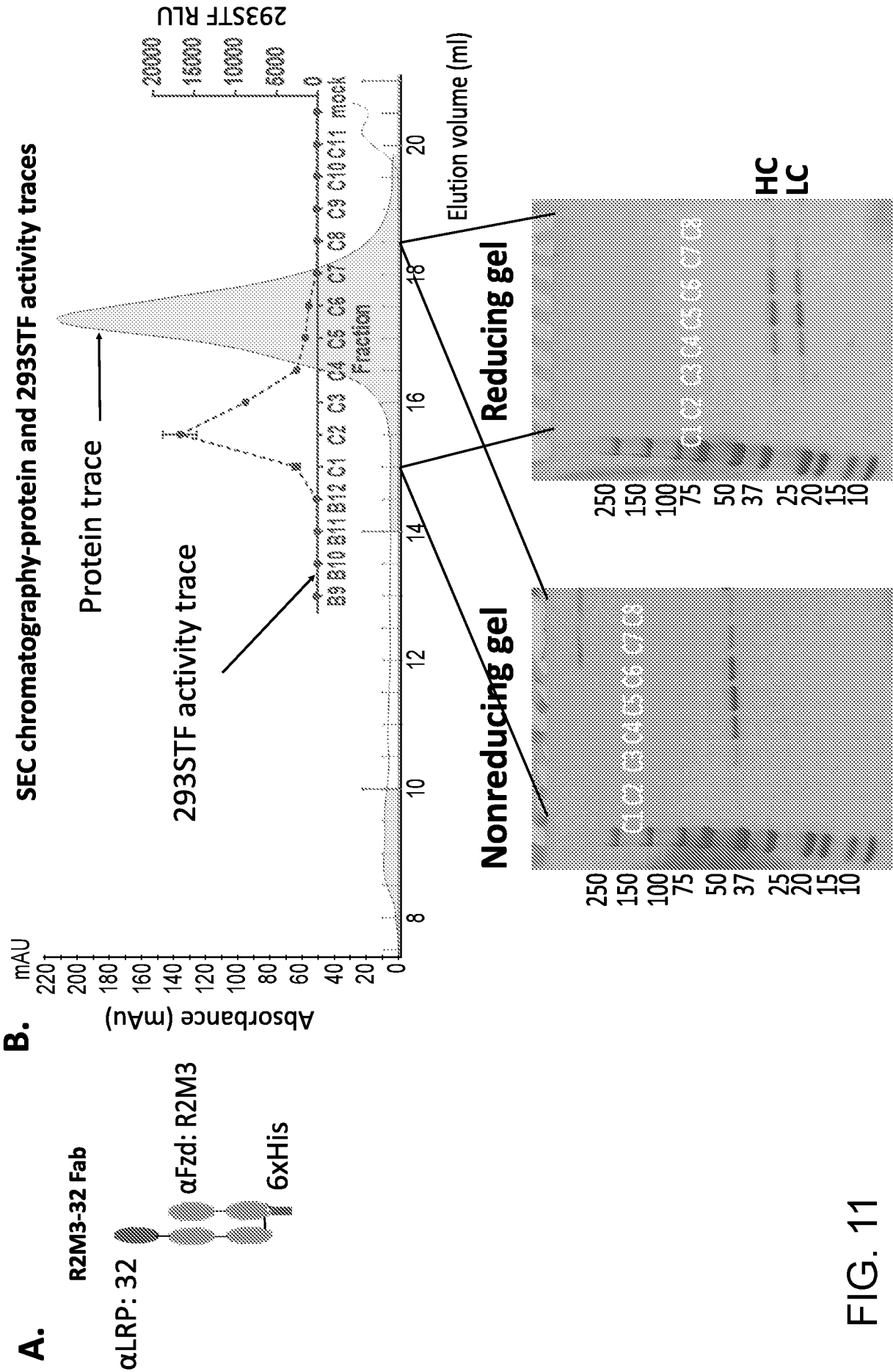
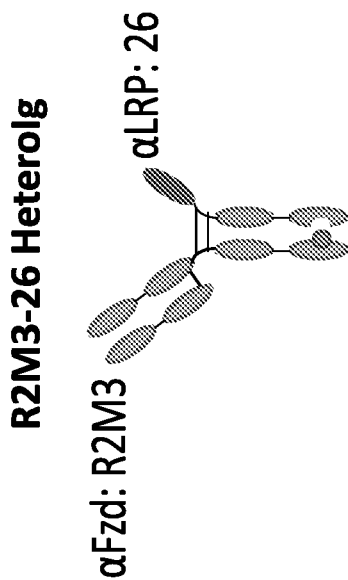


FIG. 11

A. **293 STF reporter assay with Rspo**



B.

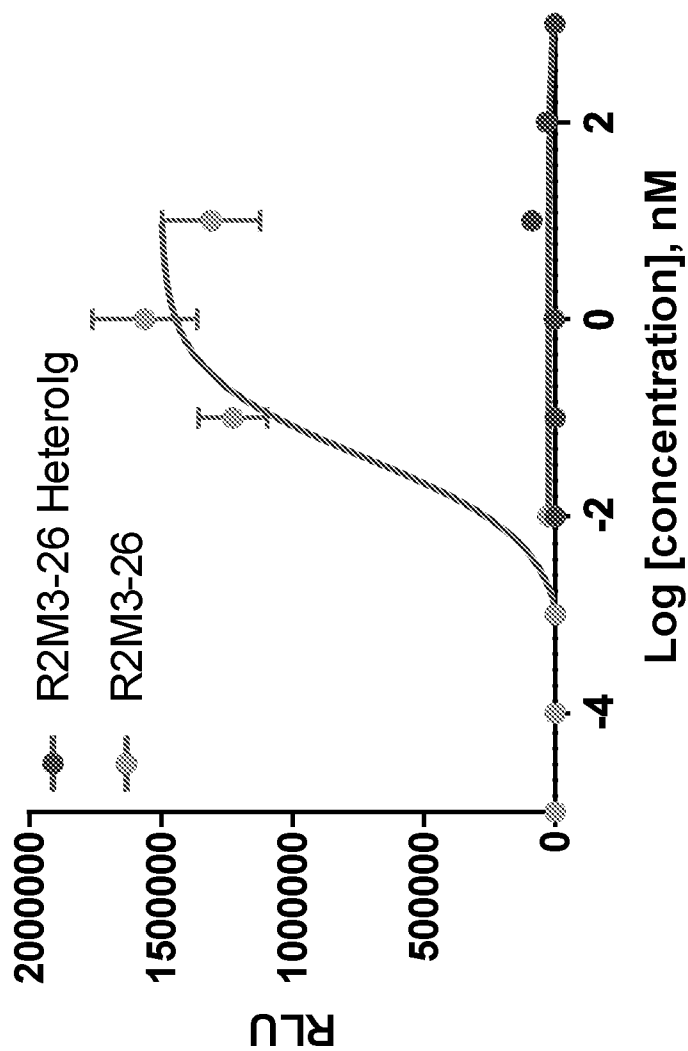


FIG. 12



FIG. 13

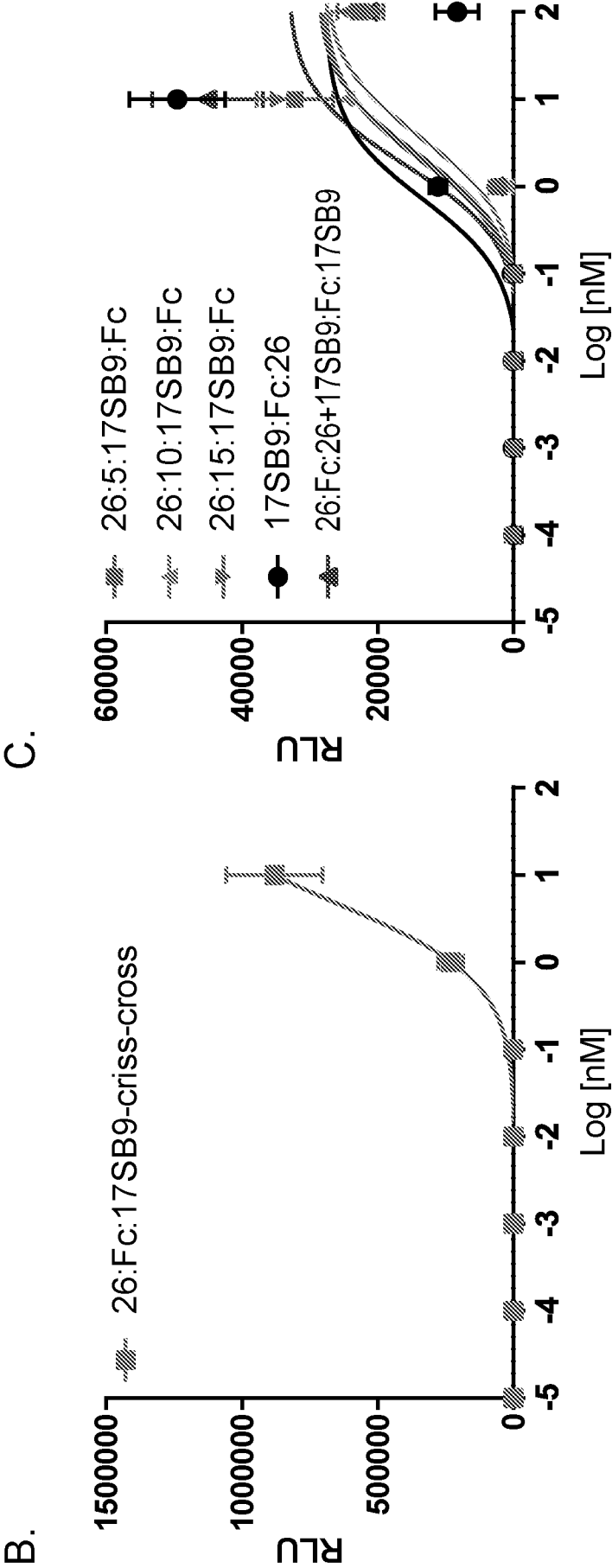
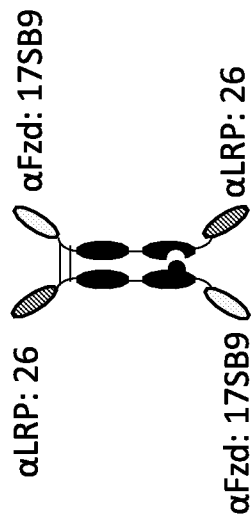


FIG. 13 (contd.)

D.

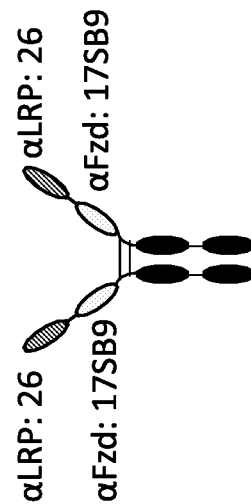
26:Fc:17SB9-criss-cross



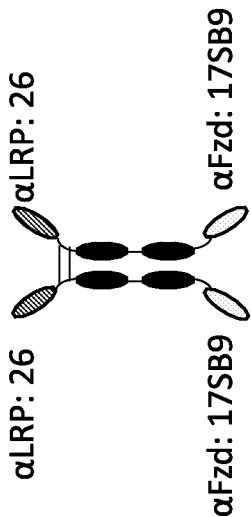
26:5:17SB9:Fc

26:10:17SB9:Fc

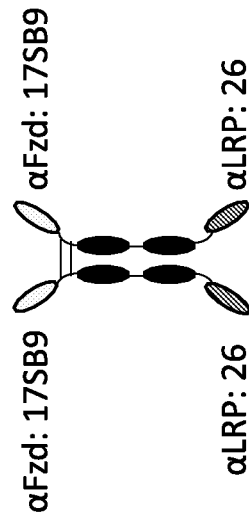
26:15:17SB9:Fc



26:Fc:17SB9



17SB9:Fc:26



26:Fc:26+17SB9:Fc:17SB9

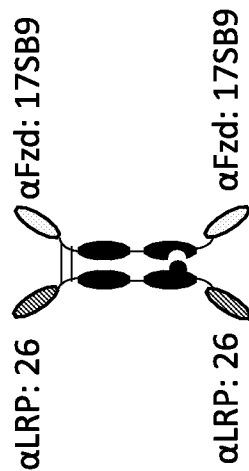


FIG. 13 (contd.)

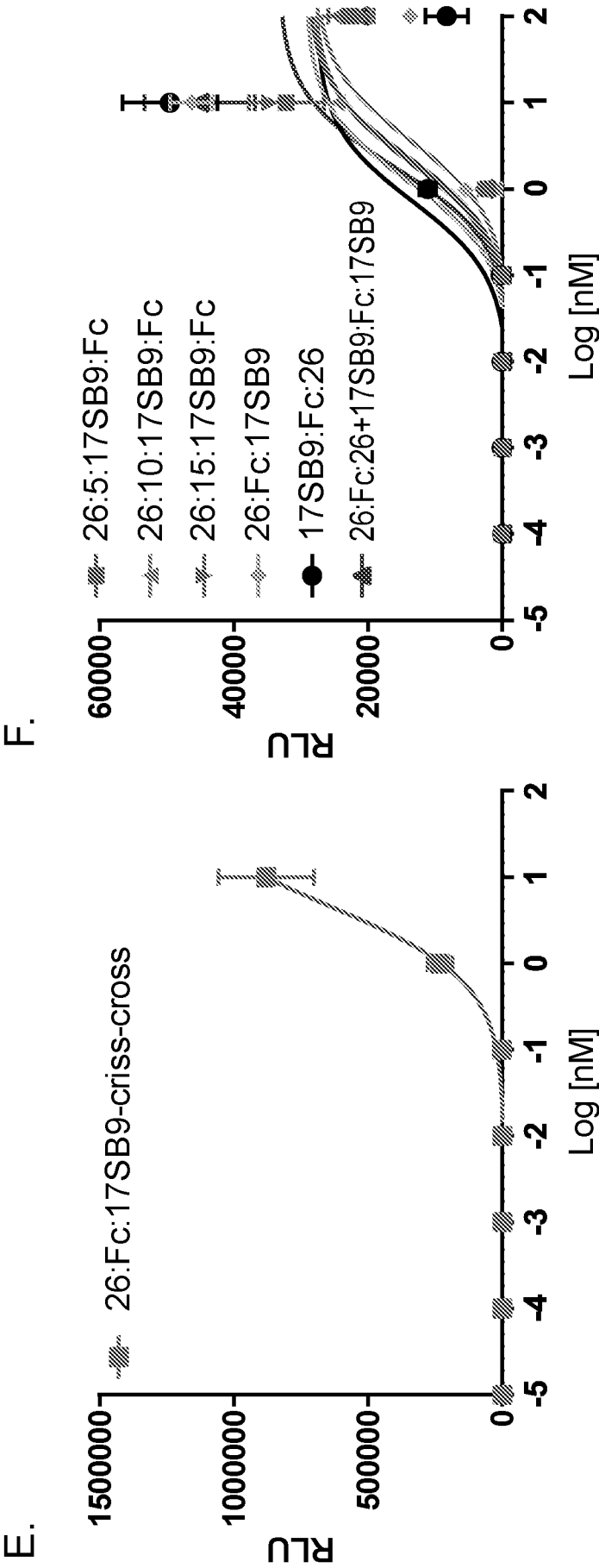


FIG. 13 (contd.)

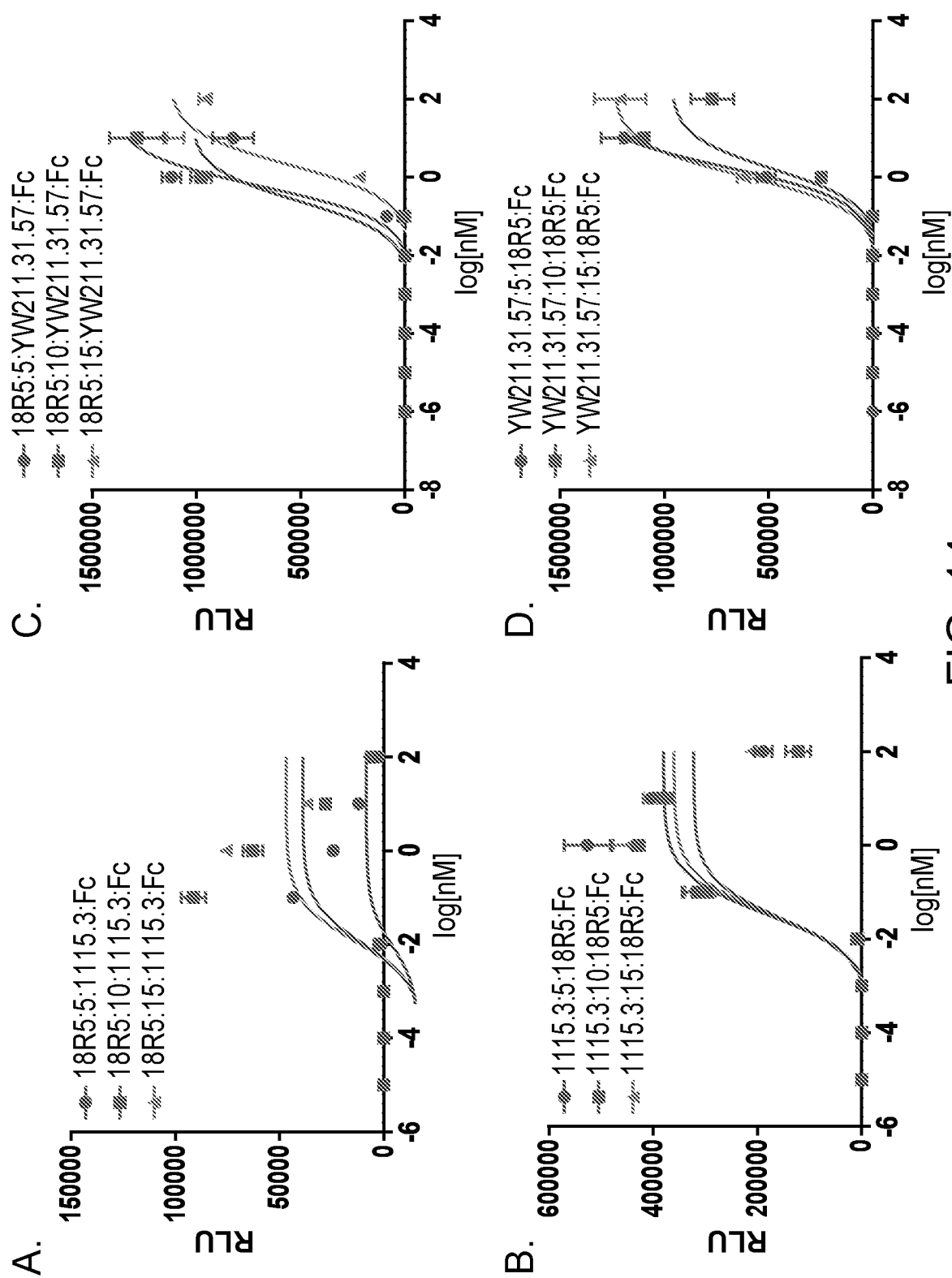


FIG. 14

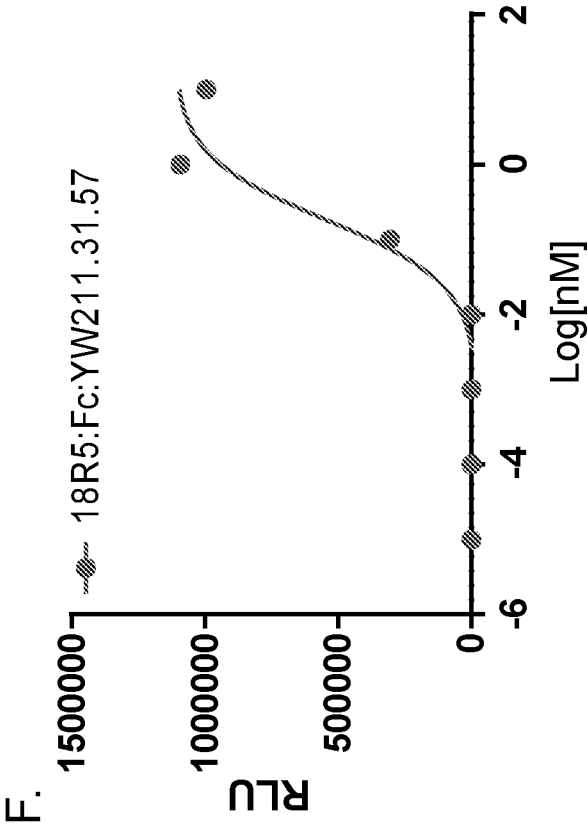
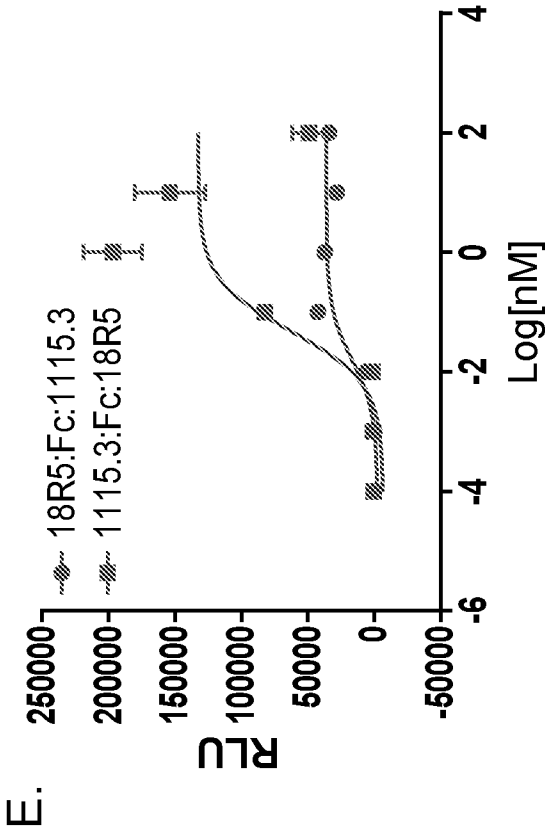
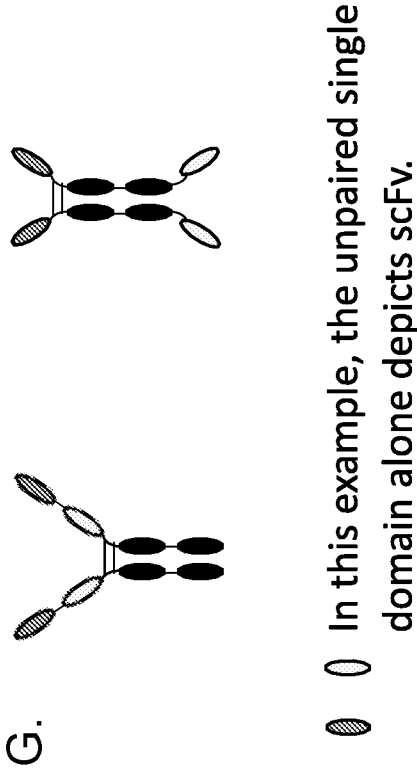


FIG. 14 (contd.)

H.

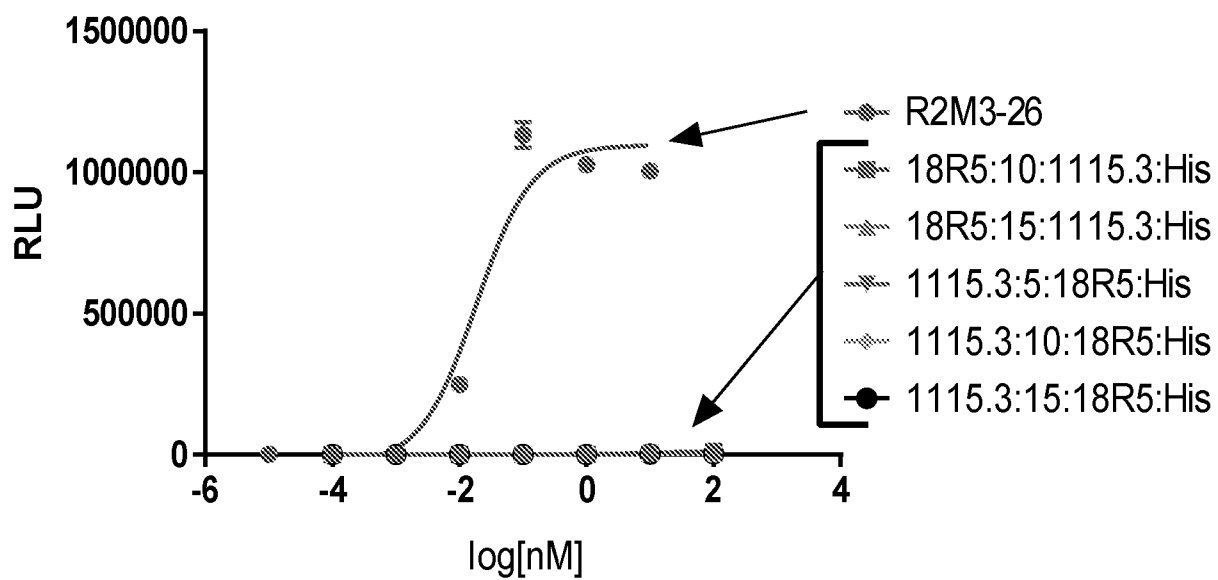


FIG. 14 (contd.)

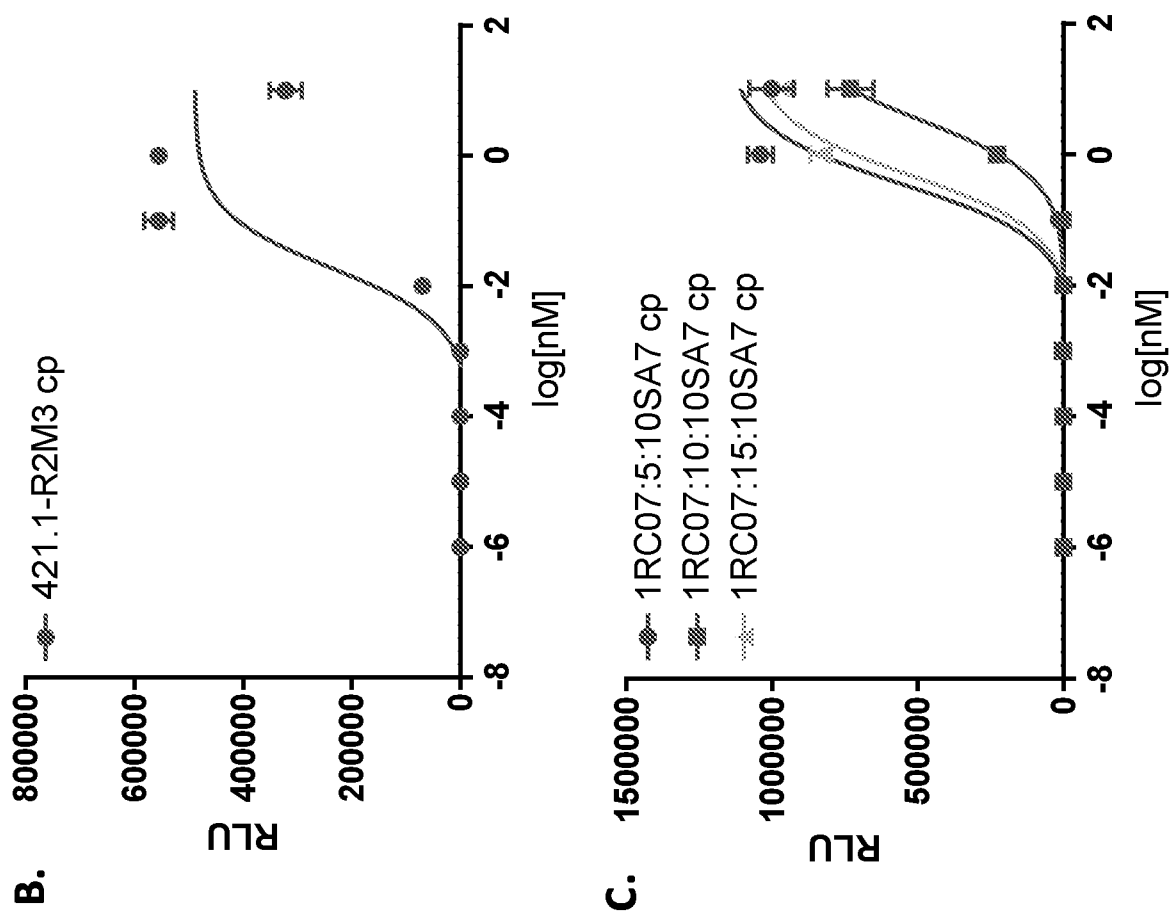


FIG. 15

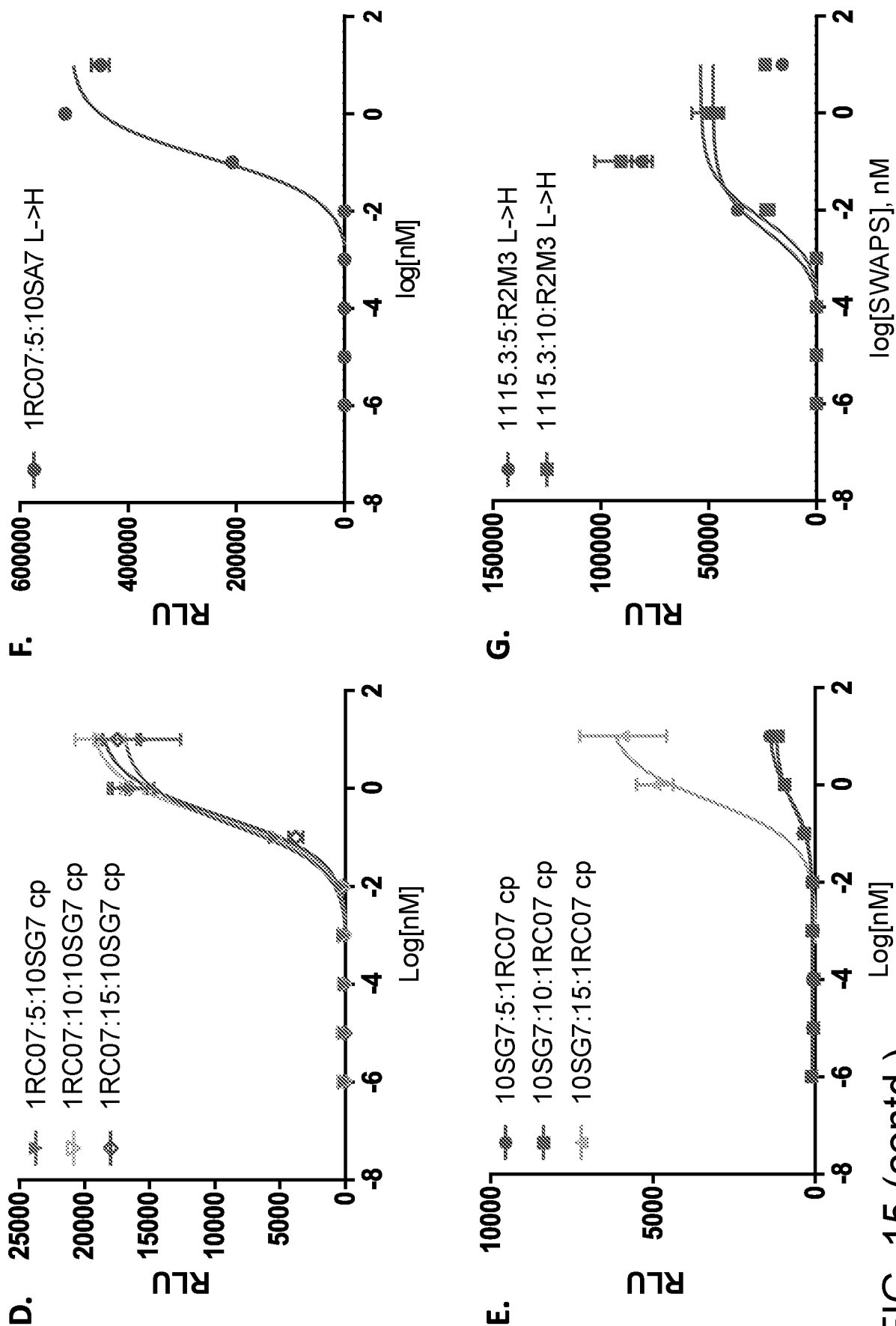


FIG. 15 (contd.)

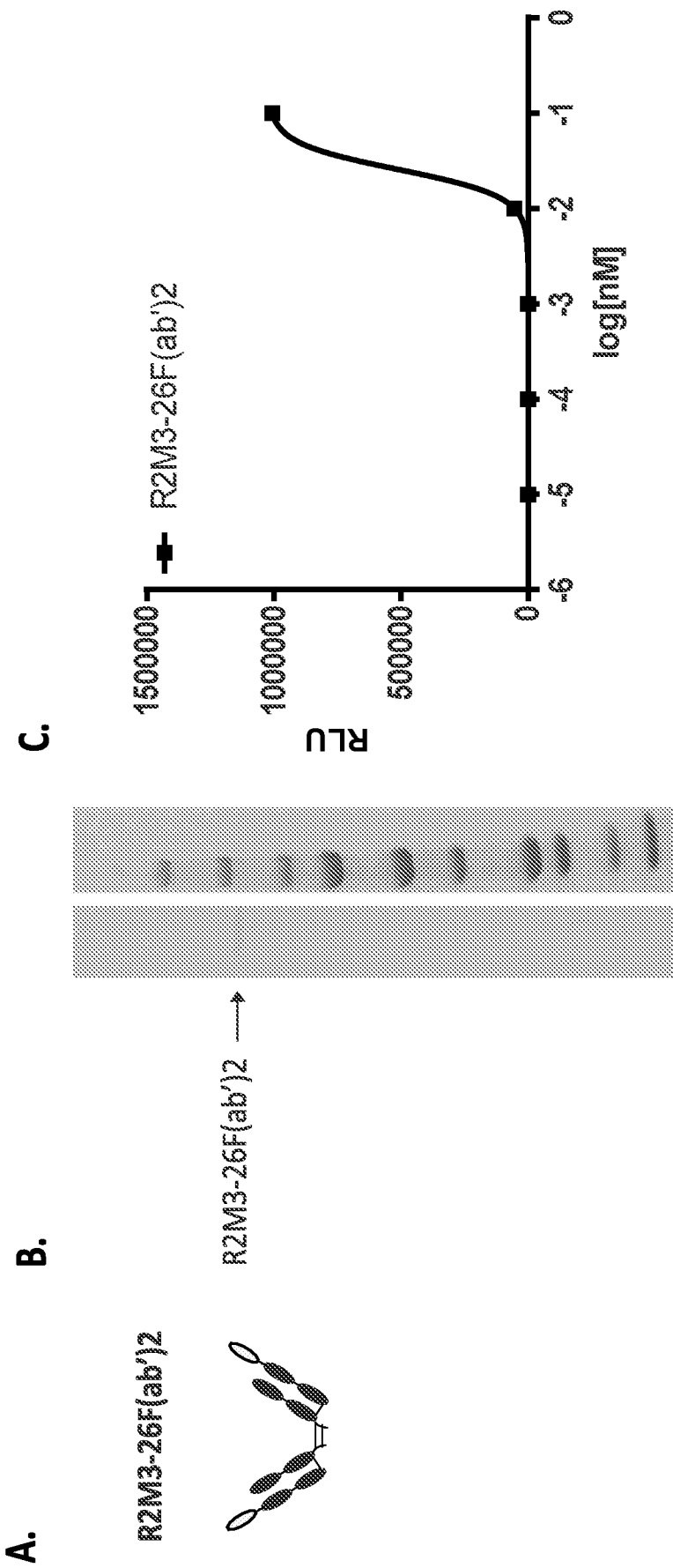
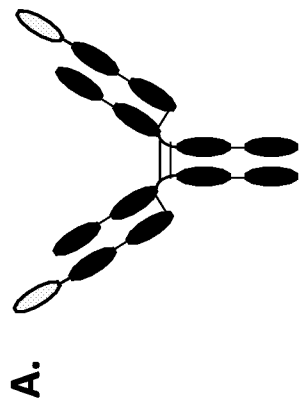


FIG. 16



B.

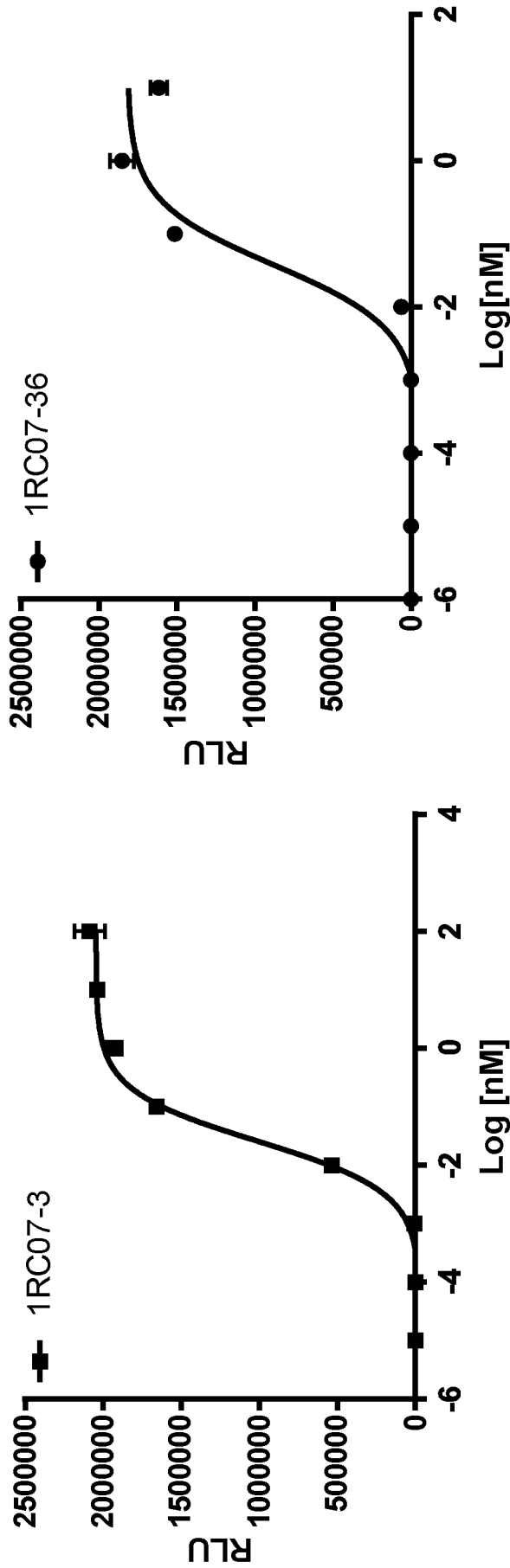


FIG. 17

C.

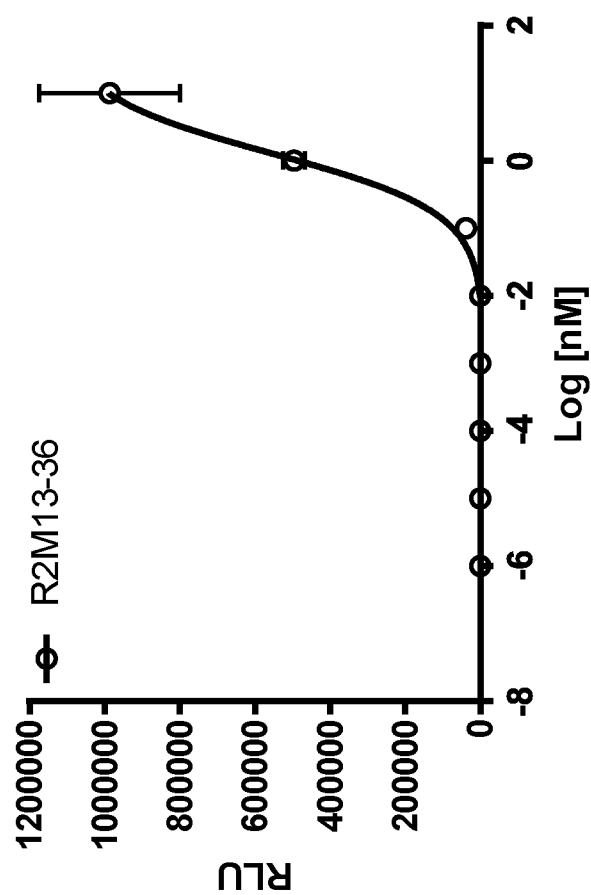
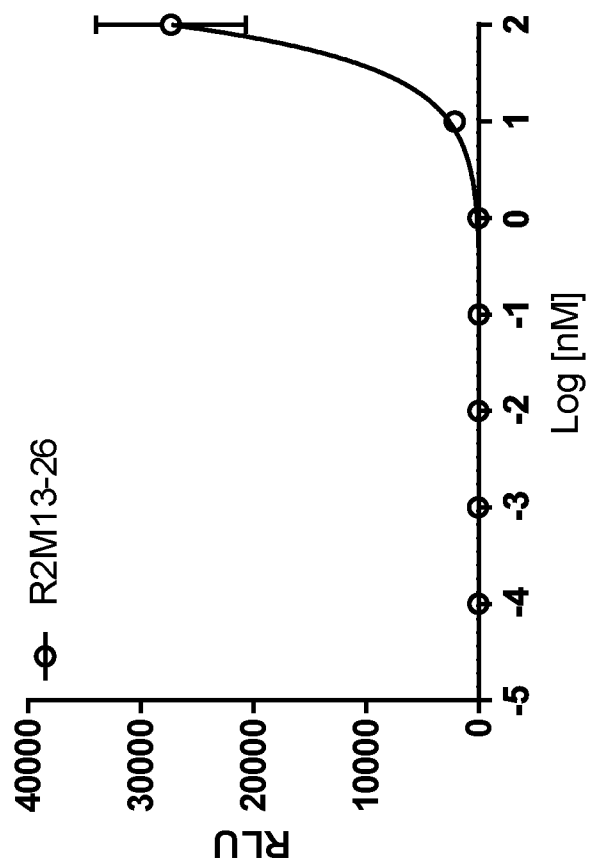
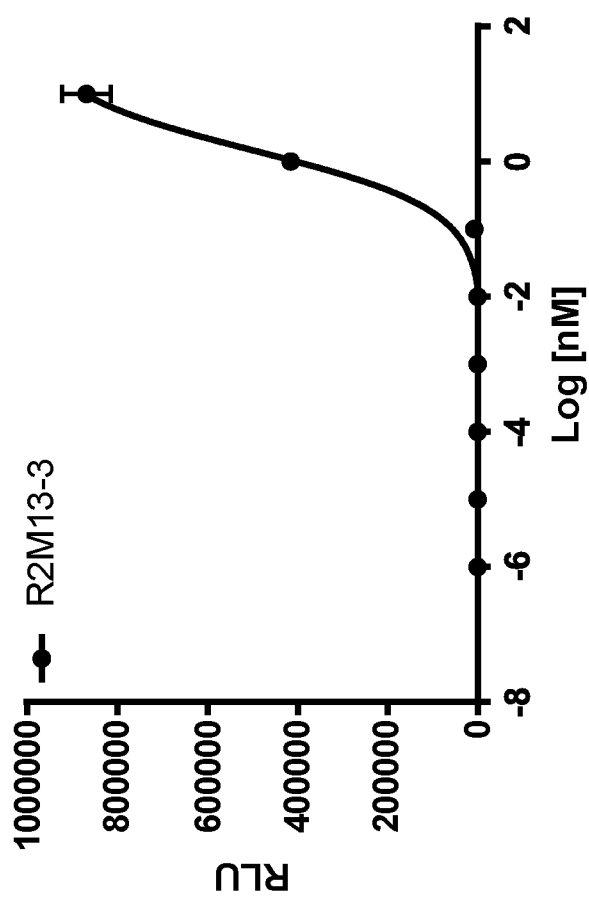


FIG. 17 (contd.)

D.

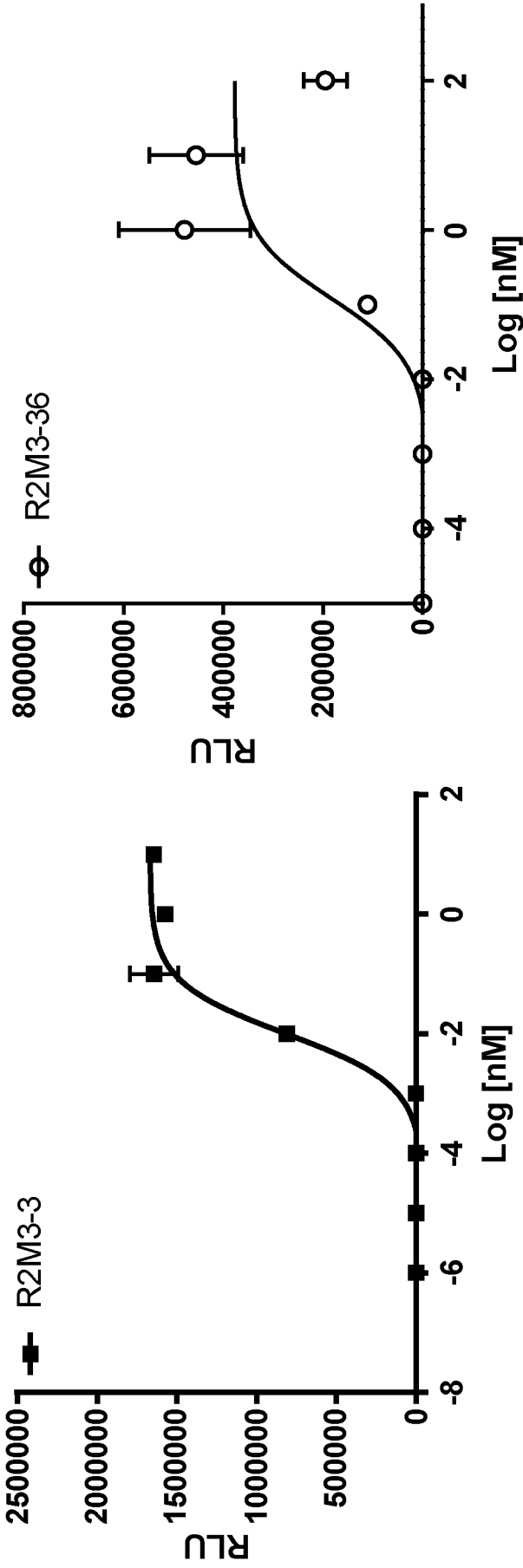


FIG. 17 (contd.)

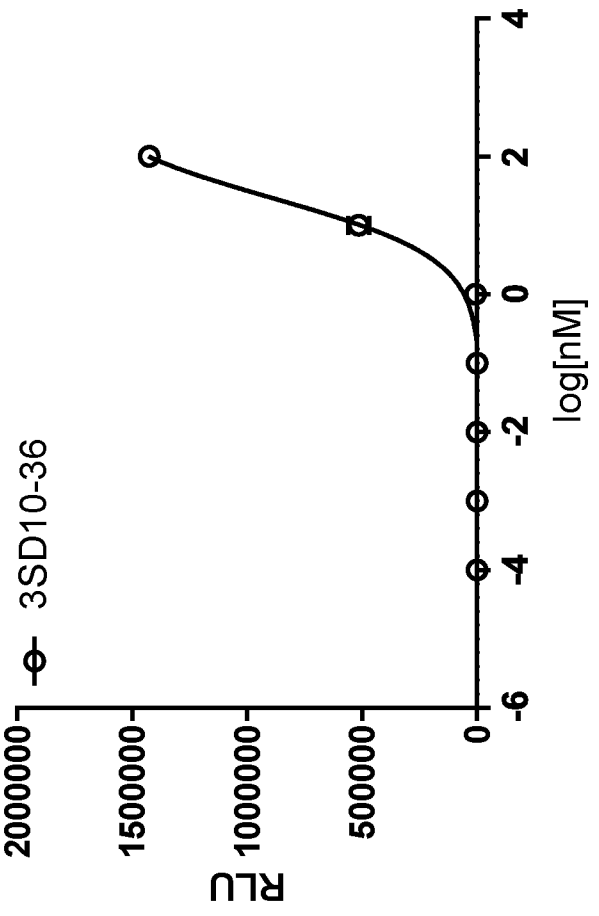
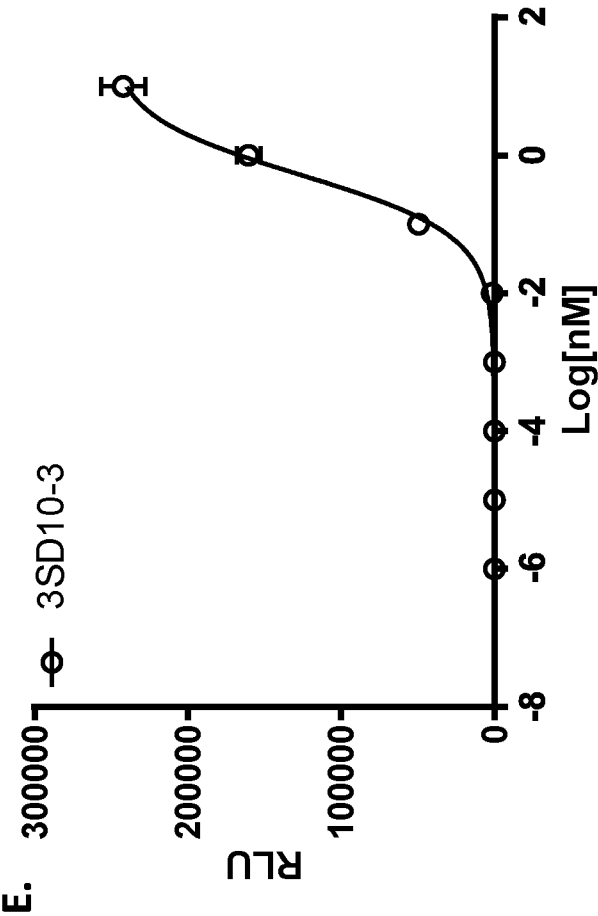
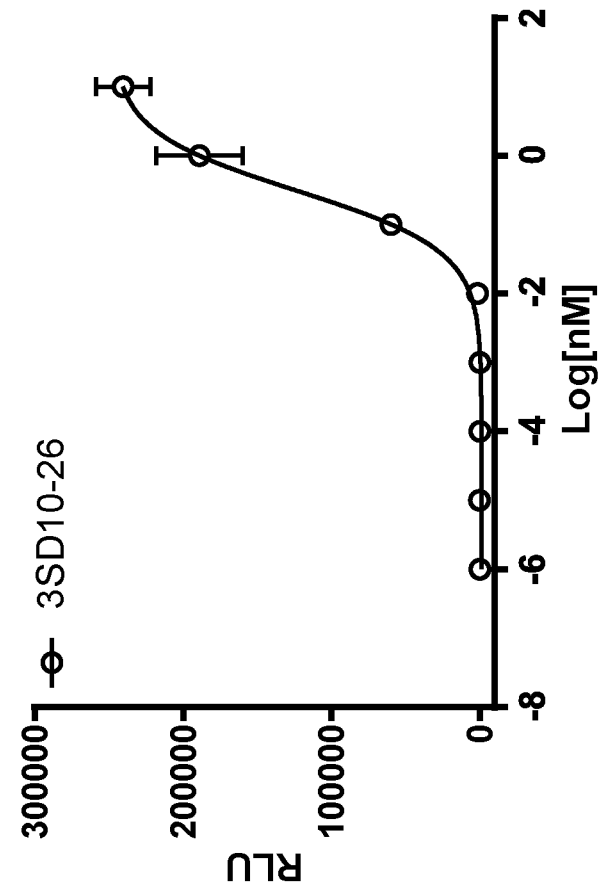


FIG. 17 (contd.)

E.

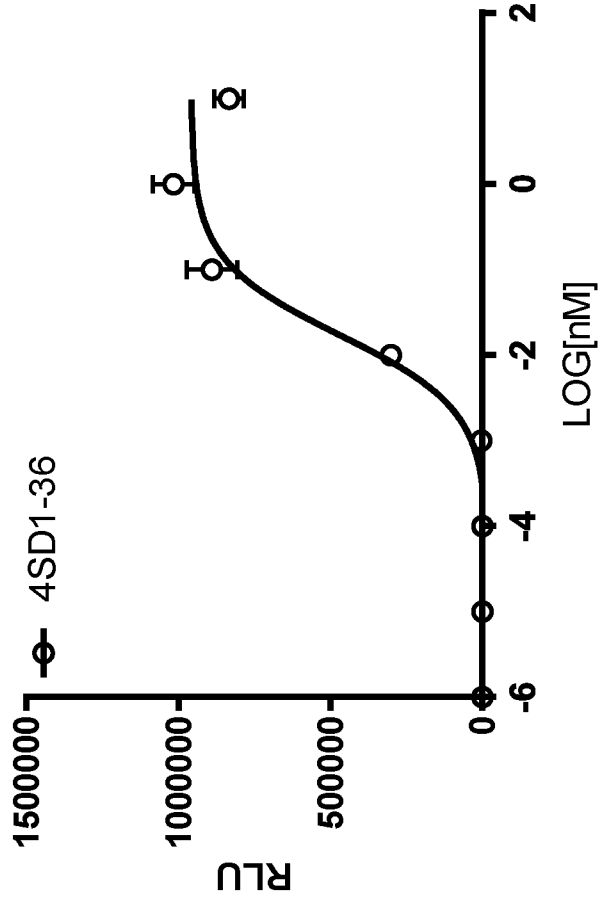
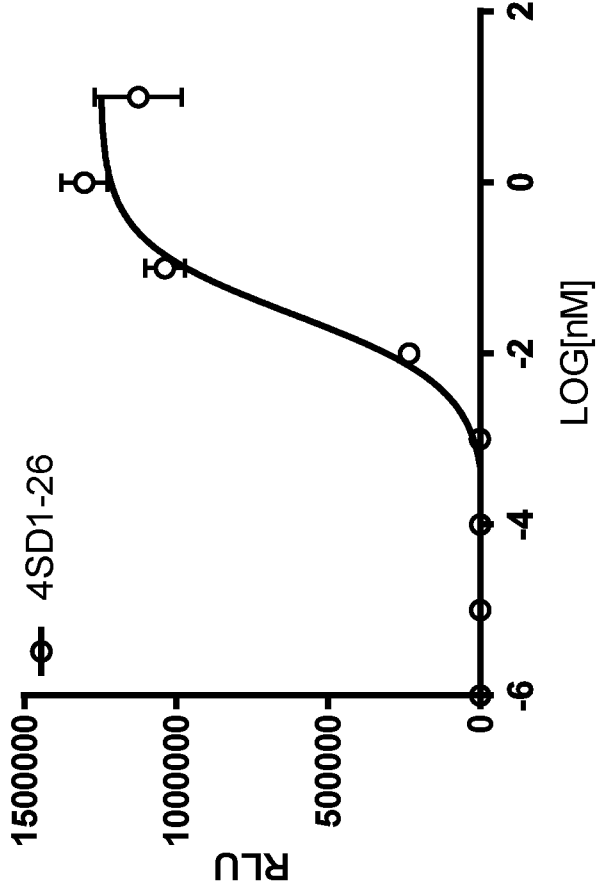
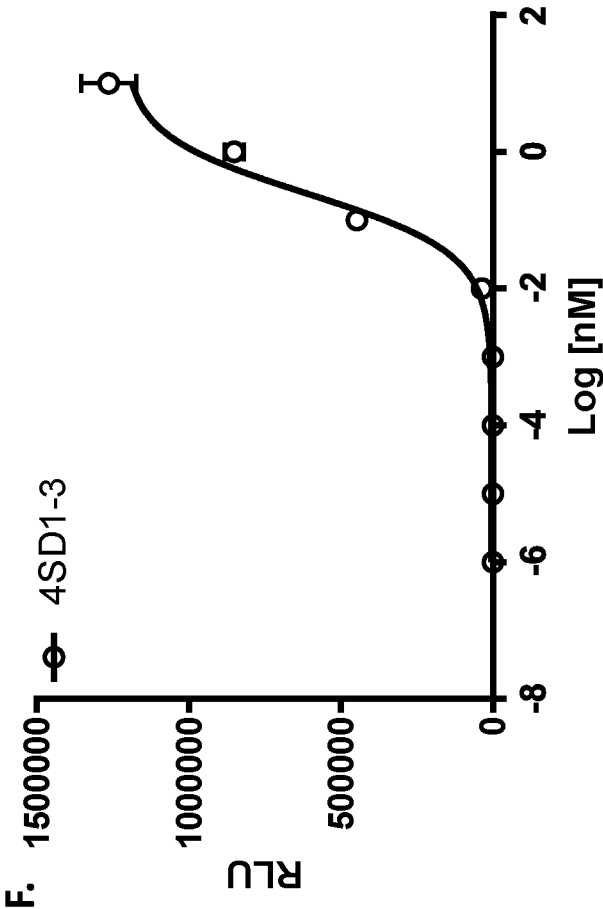


FIG. 17 (contd.)

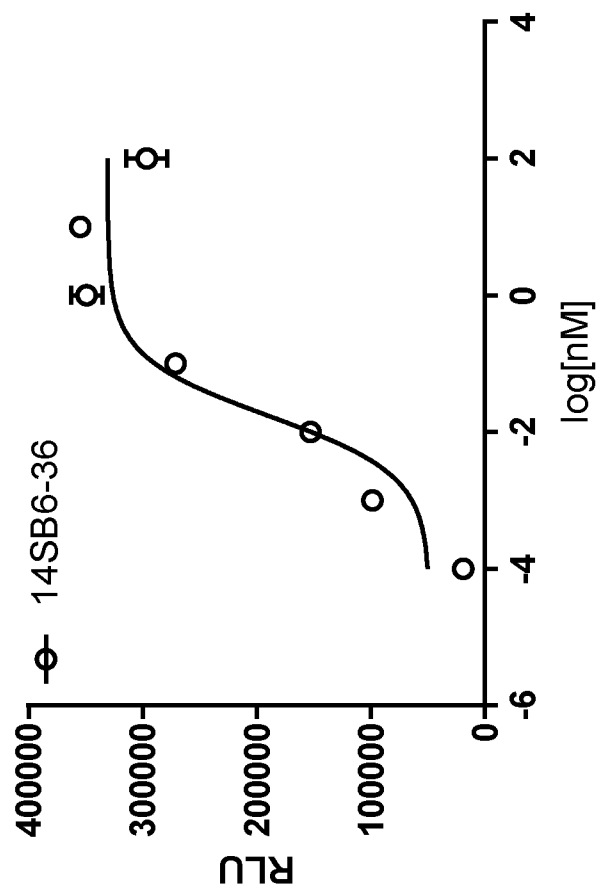
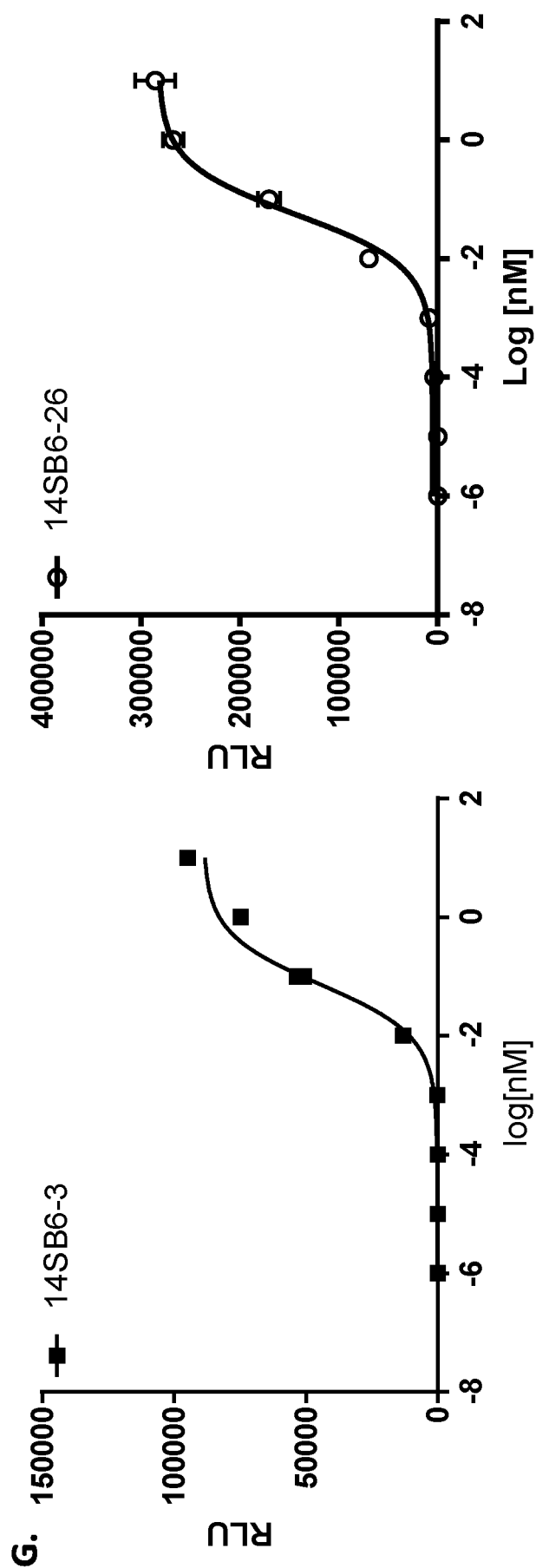


FIG. 17 (contd.)

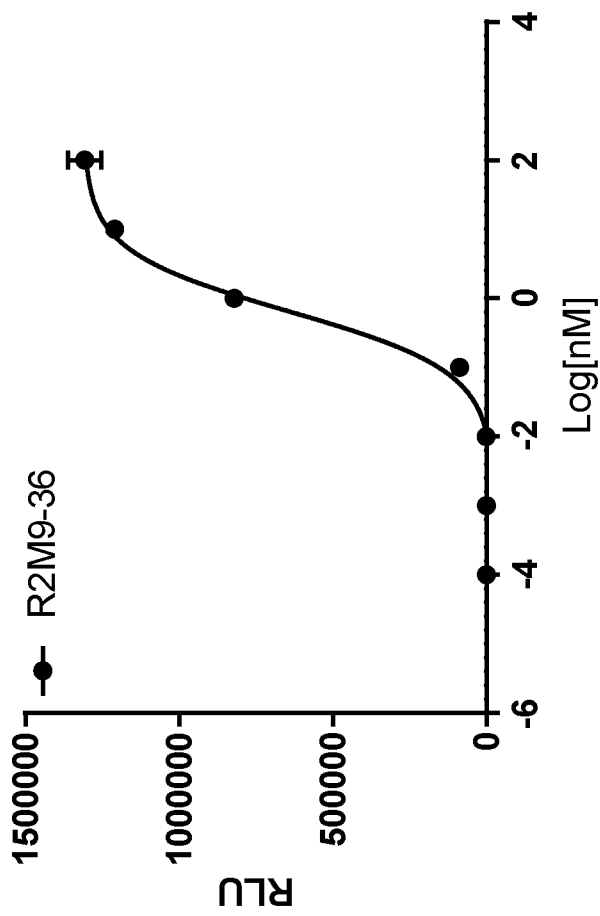
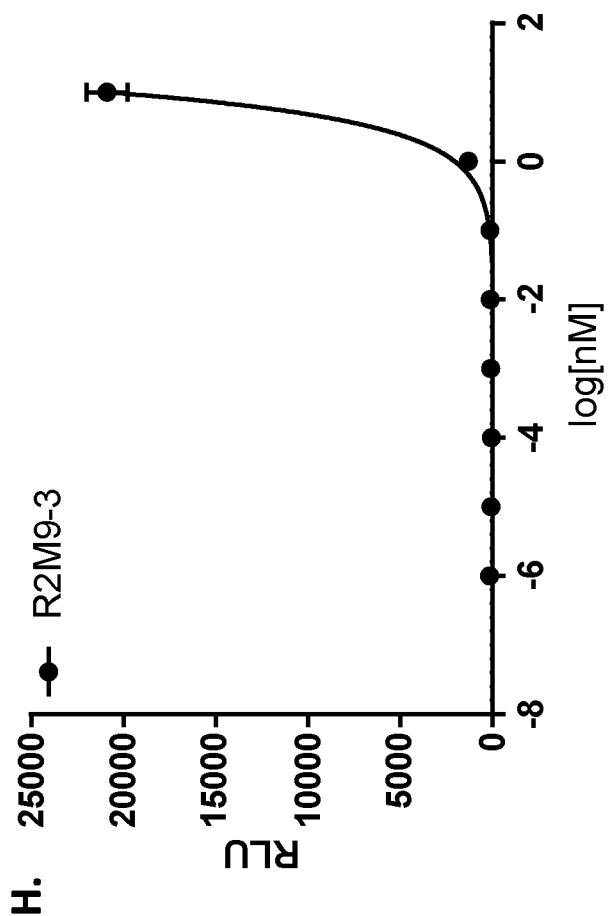
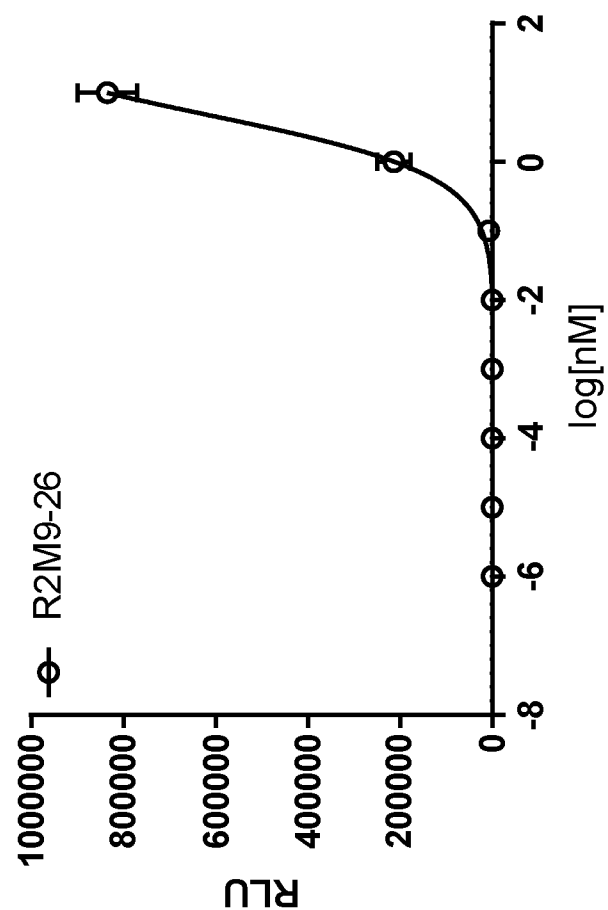


FIG. 17 (contd.)

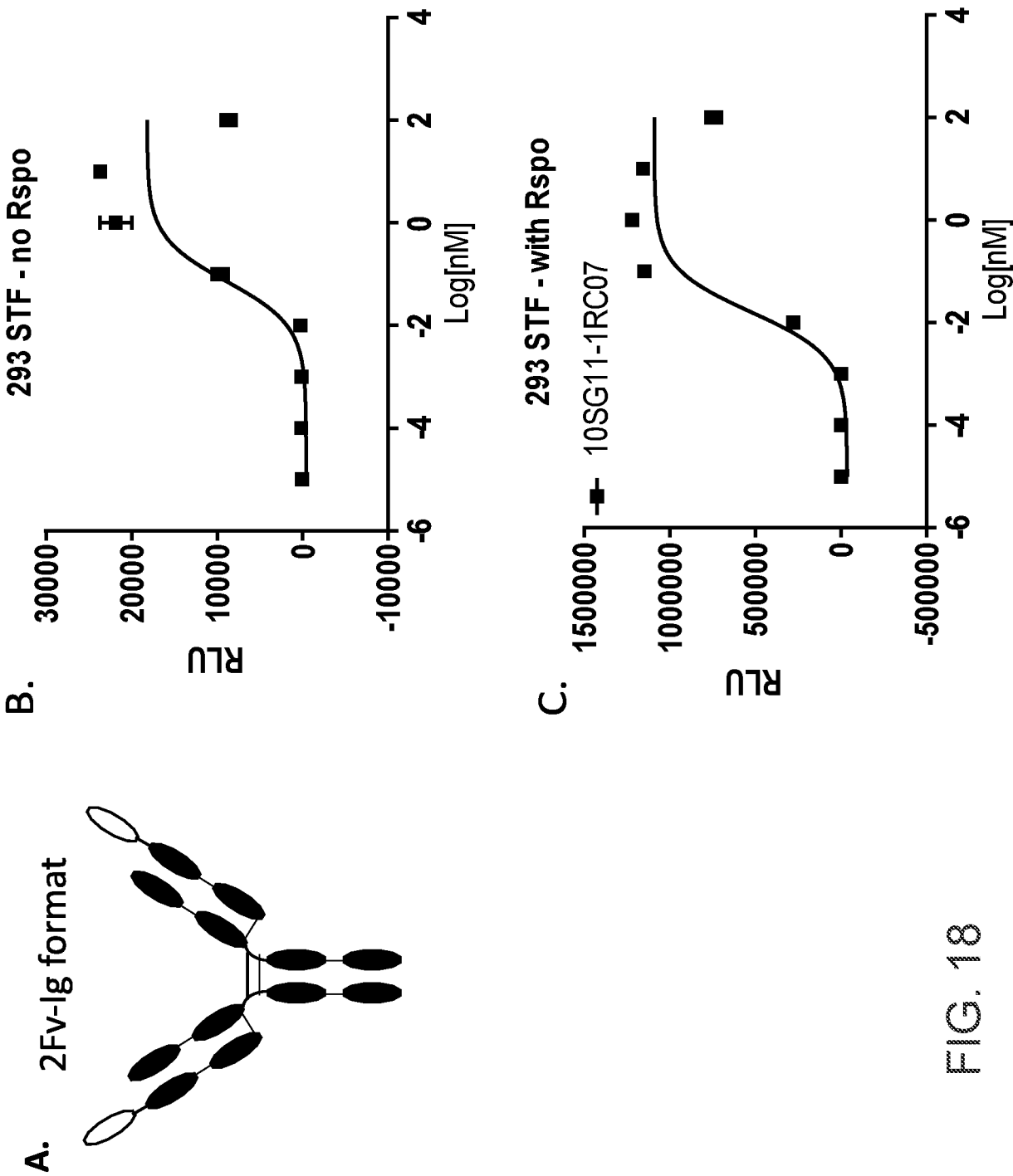


FIG. 18

FIG. 19

Leader = italics

Linker = underlined

VHH/sdAb or VH or VL = bold

*MYRMQLLS***SCIALSLALVTNSDVQLVESGGGLVQPGGSLRLSCAASG***SIFMINTMAWYRQAPGNQRE*
LVATIRPVVSETTYADAVKGRFTISR*DN***AKNTVYLQMN****SLK***SEDTAIYYCNAKRPWGTRDEYWGQG*
TLTVVSSGSGGSQT*TVVLQEP***SLSVSPGGTVTLT***CG***LSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNT**
RSSDVPERFSGSIVGNKAALTITGAQPDD*ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLF*
P*PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT***PSKQSNNKYAASSYLSLTPEQWK**
SHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:89)

*MYRMQLLS***SCIALSLALVTNSDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQREL**
VAMIRPVVTEIDYADSVKGRFTISR*NNAMKTVYLQMN***NLKPEDTAVYYCNAKRPWGSRDEYWGQG**
TQVTVSSGSGGSQT*TVVLQEP***SLSVSPGGTVTLT***CG***LSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNT**
RSSDVPERFSGSIVGNKAALTITGAQPDD*ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLF*
P*PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT***PSKQSNNKYAASSYLSLTPEQWK**
SHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:90)

*MYRMQLLS***SCIALSLALVTNSEVQLVESGGGLVQAGGSLRVSCAASGGTFSRYHMGWFRQAPGKER**
EFVSAITWSSGRTYYADFVKGRFTISR*DDARNTVYLQMS***SLKPEDTAVYYCALTWAPTPTNRRSDY**
AYWGQGTQVT*VSSGSGGSQT***TVVLQEP***SLSVSPGGTVTLT**CG***LSSGSVSTNYYPSWYQQTPGQAPR**
TLIYYTNT*RSSDVPERFSGSIVGNKAALTITGAQPDD**ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAA*
P*SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT***PSKQSNNKYAASSYLSL**
TPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:91)

*MYRMQLLS***SCIALSLALVTNSEVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDMAWYRQAPGNQRE**
LVATIRPVVSETTYADAVKGRFTISR*S***NAMKTVYLQMN****SLK***SEDTAIYYCNAKRPWGTRDEYWGQG*
TLTVVSSGSGGSQT*TVVLQEP***SLSVSPGGTVTLT***CG***LSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNT**
RSSDVPERFSGSIVGNKAALTITGAQPDD*ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLF*
P*PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT***PSKQSNNKYAASSYLSLTPEQWK**
SHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:92)

*MYRMQLLS***SCIALSLALVTNSAVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRQAPGNQREL**
VATIRPVVSETTYADAVKGRFTISR*S***NAMKTVYLQMN****SLK***SEDTAIYYCNAKRPWGTRDEYWGQGT*
LVT*VSSGSGGSQT***VVLQEP***SLSVSPGGTVTLT**CG***LSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNT**
SSDVPERFSGSIVGNKAALTITGAQPDD*ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLF*
P*PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT***PSKQSNNKYAASSYLSLTPEQWKS**
HRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:93)

*MYRMQLLS***SCIALSLALVTNSAVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKER**
EFVASIRWSSGNTWYADSMKGRFTISR*DN***AKNTVYLQMN****SLKPEDTAVYYCYANIYYTRRAPEEYW**
GQGT*LVTVSSGSGGSQT***VVLQEP***SLSVSPGGTVTLT**CG***LSSGSVSTNYYPSWYQQTPGQAPRTLIY**
YTNT*RSSDVPERFSGSIVGNKAALTITGAQPDD**ESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSV*
TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT**PSKQSNNKYAASSYLSLTPE**
QWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:94)

*MYRMQLLS***SCIALSLALVTNSEVQLVQSGAEVKKPGASVKVSCKASGYFTSYGISWVRQAPGQGLEW**
MGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVW
GQGT*TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL*
QSSGLYSLSSVTV*PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPPCPAPPELLGGPSVFL*
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLN*NGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI*
AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK* (SEQ ID NO:95)

FIG. 19 (contd.)

MYRMQLLSICIALSLALVTNSEVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELI
ANMRGGGYMKYAGSLKGRFTMSTESAKNTLYLQMNSLKPEDTAVYYCYARTQRMGVVNSYWGG
GTLVTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRP
 SGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPS
 SEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS
 RSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:96)

MYRMQLLSICIALSLALVTNSQVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQREL
IANMRGGGYMKYAGSLKGRFTMSTESAKNTLYLQMNSLKPEDTAVYFCNAVYDGYTIRGQGT
VSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPER
 FSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA
 NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS
 VTHEGSTVEKTVAPTECS* (SEQ ID NO:97)

MYRMQLLSICIALSLALVTNSEVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELI
ANMRGGGYMKYADSVQGRFTISRDNKNTVYLQMNSLKPEDTAVYYCAAQFRNDYGLRYQSTNN
YWGGGTLTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDK
 SNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTL
 FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQ
 WKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:98)

MYRMQLLSICIALSLALVTNSQVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQREL
IANMRGGGYMKYAGSLKGRFTMSTESAKNTVYLQMNSLKPEDSAVYYCNANYRGNRYWGQGT
TVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPE
 RFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQ
 ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS
 QVTHEGSTVEKTVAPTECS* (SEQ ID NO:99)

MYRMQLLSICIALSLALVTNSDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQREL
VAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGGG
TQVTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPS
 GIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSS
 EELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS
 SYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:100)

MYRMQLLSICIALSLALVTNSEVQLVESGGGLVQAGGSLRVSCAASGGTFSRYHMGWFRQAPGKER
EFVSAITWSSGGRYYADFVKGRFTISRDDARNTVYLQMSSLKPEDTAVYYCALTWAPTPTNRRSDY
AYWGGGTQVTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIY
 DKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSV
 TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPE
 QWKS
 QVTHEGSTVEKTVAPTECS* (SEQ ID NO:101)

MYRMQLLSICIALSLALVTNSAVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRQAPGNQREL
VATIRPVVSETTYADAVKGRFTISRSNAMKTVYLQMNSLKS EDTAIYYCNAKRPWGTRDEYWGGGT
LTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGI
 PERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEE
 LQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS
 SCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:102)

MYRMQLLSICIALSLALVTNSAVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKER
EFVASIRWSSGNTWYADSMKGRFTISRDNKNTVYLQMNSLKPEDTAVYYCYANIYYTRRAPEEYW
GQGT
GGT
LTVSSGSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSN
 RPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFP
 PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQW
 KSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:103)

FIG. 19 (contd.)

**MYRMQLLSIALSLALVTNSEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGKGLE
WVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKVFANWQGQT
LVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K* (SEQ ID NO:104)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGDVMTQSPSLPVTGPASISCRSSQSLHNGYNYLDWYLQKPGQSPQLLI
YLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHTWPTYFGQGTKEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:105)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGDIVMHTPLSLSVTPGEPASISCRSSRSLDDTDDGNTYLDWYLQKPGQSPQLLI
HTLSHRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSIQLPWTFGQGTKEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:106)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQ
RPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQW
KSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:107)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGQSVVTQPPSVSGAPGQRTVITSTRSSSNIGAGYDVHWYQQHPGTAPKLLIFG
NSIRPSGVPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSLSAWVFGGGKLTVLGQPKAAPSV
VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLT
EQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:108)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGEIVLTQSPATLSLSPGEGATLSCRASQSVGYLTWYRQKPGQAPRLLIYDASN
RATGIPARFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFPLTFGQGTKEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEK
KVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:109)**

**MDMRVPAQLLGLLLLWLRGARC DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGDIQLTQSPSSLSASVGDRVITCRASRSISSYFNWYQQKPGKAPKLLIYAASSL
QSGVPSRFSGSRSGTDFTLTISLQPEDFATYYCQQAADTFPTFGQGTREIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEK
KVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:110)**

**MDMRVPAQLLGLLLLWLRGARCQVQLQESGPGLVKPSSETLSLTCTVSGGSISGNNYYWGWIQQPPG
KGLEWIGSIYFTGGTYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARVMLITDAFDIWGQ
GTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV**

FIG. 19 (contd.)

EWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GKGSGSGHHHHH** (SEQ ID NO:111)

MDMRVPAQLLGLLLLWLRGARCQLQLQESGSLVKPSQTLSLTCAVSGGSISSGGYSWSWIRQPP
GKGLEWIGSIYHSGSTYYNPSLKSRLTISVDTSKNQFSLKLSSVTAADTAVYYCARFYDILTGYSYF
DYWGQGTLTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK153HHHHH** (SEQ ID NO:112)

MDMRVPAQLLGLLLLWLRGARCQVQLQWAGALLKPSETLSLTCAVSGASFSGHYWTWIRQPPGK
GLEWIGEIDHTGSTNYEPLSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGGGGYDWGHHYH
GLDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
SVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
FYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGKGSGSGHHHHH* (SEQ ID NO:113)

MDMRVPAQLLGLLLLWLRGARCQVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWRQHPG
KGLEWIGIYYSGSTYYNPSLKSRLTISVDTSKNQFSLKLNSVTAADTAVYYCARATYGGDAFDIWG
QGTMTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
PGKGSGSGHHHHH** (SEQ ID NO:114)

MDMRVPAQLLGLLLLWLRGARCQVQLQESGPGLVKPSETLSLTCTVSGGAISGTSYFWGWIRQPPG
KGLEWIGSIYYTGNTYYNPSLKSRLTVSVDTSKNQFSLNLNSVTAADTATYYCARIGIAVAAPVDHW
GQGTLTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGKGSGSGHHHHH* (SEQ ID NO:115)

MDMRVPAQLLGLLLLWLRGARCQLQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPG
KGLEWIGIYYSGSTYYNPSLKSRLTISVDKSKNQFSLKLSSVTAADTAVYYCARVRDYDSSGGYY
DYFDYWGQGTLTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGSGSGHHHHH** (SEQ ID NO:116)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQAPGQG
LEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMD
VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK
SLSLSPGKGS~~SGSDVQLVESGGGLVQAGGSLRLACAGS~~GRIFAIYDIAWYRHPPGNQRELVAMIRP
VVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGTQVTVS
S* (SEQ ID NO:117)

MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGS~~GRIFAIYDIAWYRHPPGNQ~~
RELVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSS~~SGSGSEVQLVQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQAPGQGLEWMGW~~
SAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWGQGT
TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPEAAGGPSVFLFPPK
KDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQQDWL
NGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*
(SEQ ID NO:118)

MDMRVPAQLLGLLLLWLRGARCAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQ
APRTLIYYTNRSSDVPERFSGSIVGNKAALTITGAQPDDSVYFCLLYLGRGIWVFGGGTKLTVLGQP
KAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSQCQTVEGSTEKTVAPTECS~~SGSGSDVQLVESGGGLVQAGGSLRLACAGS~~
GRIFAIYDIAWYRHPPGNQRELVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAV
YYCNAKRPWGSRDEYWGQGTQVTVSS* (SEQ ID NO:119)

MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGS~~GRIFAIYDIAWYRHPPGNQ~~
RELVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSS~~SGSGSQAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIY~~
TNRSSDVPERFSGSIVGNKAALTITGAQPDDSVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSV
TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPE
QWKSHRSYSQCQTVEGSTEKTVAPTECS* (SEQ ID NO:120)

MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQAPGQ
GLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYG
MDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC~~SGSGSGHHHHHH~~* (SEQ
ID NO:122)

MYRMQLLSIALSLALVTNSAVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKER
EFVASIRWSSGNTWYADSMKGRFTISRDNANTVYLMNLSLKPEDTAVYYCYANIYYTRRAPEEYW
GQGT~~LVTVSSGSGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIY~~
YTNRSSDVPERFSGSIVGNKAALTITGAQPDDSVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSV
TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPE
QWKSHRSYSQCQTVEGSTEKTVAPTECS* (SEQ ID NO:123)

MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQAPGQ
GLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYG
MDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC~~SGSGSGHHHHHH~~* (SEQ
ID NO:124)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCQAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPG
QAPRTLIIYTNTRSSDVPERFSGSIVGNKAALTITGAQPDDESIFYCLLYLGRGIWVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:125)

**MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQ
GLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYG
MDVWGGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVK
GFYPDSIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
TQKSLSLSPGK*** (SEQ ID NO:126)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTIVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLSCAVKGFYPDSIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKSGSGSHHHHHH*** (SEQ ID NO:127)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTIVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPDSIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGSGSAVQQVESGGGLVQPGGSLRLSCAA
SGFTLDYYAISWFRQAPGKKRELVADITSGGSTNYADSVKGRFTISRDNAKNTIYLQMNSLKPEDTA
VYFCNAVITYNGYTIWGGGTQVTVSS*** (SEQ ID NO:128)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQ
GTQVTVSSGSGSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQR
PSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQPKAAPSVTLFPP
PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWK
SHRSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:134)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGTSYADSVKGRFTISKDNKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGSGSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQRPSGIPVR
FSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQPKAAPSVTLFPPSSEELQ
ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSC
QVTHEGSTVEKTVAPTECS*** (SEQ ID NO:135)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQ
GTQVTVSSGSGSGSGDIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAA
SSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGGGKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVCLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYE
KHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:136)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTIVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGSGDIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSL
QSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGGGKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVCLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:137)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVT
HQLSSPVTKSFNRGEC*** (SEQ ID NO:138)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDDYVYRGQ
GTQVTVSSGSGSGQAVVLQEPSSLVSPGGTVTLTCLSSGVSSTNYPPSWYQQTPGQAPRTLIIYTT
NTRSSDVPERFSGSIVGNKAALTITGAQPDDSVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQ
WKSHRSYSQCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:139)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGSGSGQAVVLQEPSSLVSPGGTVTLTCLSSGVSSTNYPPSWYQQTPGQAPRTLIIYTTNTRSSDV
PERFSGSIVGNKAALTITGAQPDDSVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKSHRSYS
CQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:140)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDDYVYRGQ
GTQVTVSSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLL
GGVPSRFSGSGSGTDFLTITSLQPEDFATYYCQQTYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:141)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTIVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLL
LGGVPSRFSGSGSGTDFLTITSLQPEDFATYYCQQTYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:142)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLLGGVPSR
FSGSGSGTDFLTITSLQPEDFATYYCQQTYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC*** (SEQ ID NO:143)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDDYVYRGQ
GTQVTVSSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:144)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTIVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSL
QSGVPSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:145)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVT
HQLSSPVTKSFNRGEC*** (SEQ ID NO:146)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNLSLKPEDTAVYYCYVKLRDDDYVYRGQ
GTQVTVSSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:147)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTYYLQMNLSLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
YACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:148)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVT
HQLSSPVTKSFNRGEC*** (SEQ ID NO:149)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQ
RELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNLSLKPEDTAVYYCYVKLRDDDYVYRGQ
GTQVTVSSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:150)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELAMIRPVVTEIDYADSVKGRFTISRNNAMKTYYLQMNLSLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
YACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:151)

**MDMRVPAQLLGLLLLWLRGARCQVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGK
EREFVSGIRWSSGGSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGLTVTV
SSGGSGSDIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVT
HQLSSPVTKSFNRGEC*** (SEQ ID NO:152)

**MDMRVPAQLLGLLLLWLRGARCEVQLLQSGAEVKKPGSSVKVSKASGGTFTYRYLHWVRQAPGQ
GLEWMGGIPIFGTGNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCASSMVRVPYYPYGM
VWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK
SLSLSPGK*** (SEQ ID NO:153)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVKPGGSLRLSCAASGFNFGIYSMTWVRQAPGK
GLEWISYISGDSGYTNYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARVGPGGWFDPWG
QGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
PGK* (SEQ ID NO:154)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVKPGGSLRLSCAASGFTFTNYAMSWVRQAPGK
GLEWVSAISGSGGSTYYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARATGFGTVVFDY
WGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSV
FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
SDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK* (SEQ ID NO:155)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPG
KGLEWVSYIENDGSITTYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARAPYYYGSGSLF
RLDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK* (SEQ ID NO:156)**

**MDMRVPAQLLGLLLLWLRGARCQVQLVQSGAEVKKPGSSVKVSCKASGYTFTNFMHWVRQAPG
QGLEWMGWINPNSGGTKYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARSVGEVGATM
LGIGVWYWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC
PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK* (SEQ ID NO:157)**

**MDMRVPAQLLGLLLLWLRGARCQVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
REL VAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSGSAVQQVESGGGLVQPGGSLRLSCAA
SGFTLDYYAISWFRQAPGKKREL VADITSGGSTNYADSVKGRFTISRDNANTYILQMNSLKPEDTA
VYFCNAVTYNGYTIWGQGTQVTVSSGSGSGHHHHHH* (SEQ ID NO:2192)**

**MDMRVPAQLLGLLLLWLRGARAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGKK
REL VADITSGGSTNYADSVKGRFTISRDNANTYILQMNSLKPEDTAVYFCNAVTYNGYTIWGQGTQ
VTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSGSDVQLVESGGGLVQAGGSLRLACAGSGRIF
AIYDIAWYRHPPGNQREL VAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYC
NAKRPWGSRDEYWGQGTQVTVSS* (SEQ ID NO:2193)**

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGGSAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGKKRELVADI
TSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYFCNAVITYNGYTIWGQGTQVTVSSDK
THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2194)**

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGGSGGSAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGKKR
ELVADITSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYFCNAVITYNGYTIWGQGTQV
TVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVY
TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2195)**

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSGSGSGGSGGSGGSAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQA
PGKKRELVADITSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYFCNAVITYNGYTIWG
QGTQVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2196)**

**MDMRVPAQLLGLLLLWLRGARCAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGK
KRELVADITSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYFCNAVITYNGYTIWGQGT
QVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSGSDVQLVESGGGLVQAGGSLRLACAGSGR
IFAIYDIAWYRHPPGNQRELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYY
CNAKRPWGSRDEYWGQGTQVTVSS* (SEQ ID NO:2197)**

**MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQ
RELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTAVYYCNAKRPWGSRDEYWG
QGTQVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSGSDVQLVESGGGLVQAGGSLRLACAG
SGRIFAIYDIAWYRHPPGNQRELVAMIRPVTEIDYADSVKGRFTISRNNAMKTVYLMNNLKPEDTA
VYYCNAKRPWGSRDEYWGQGTQVTVSS* (SEQ ID NO:2198)**

**MDMRVPAQLLGLLLLWLRGARCAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGK
KRELVADITSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYFCNAVITYNGYTIWGQGT
QVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSGSAVQQVESGGGLVQPGGSLRLSCAASGF
TLDYYAISWFRQAPGKKRELVADITSGGSTNYADSVKGRFTISRDNANKNTIYLMNSLKPEDTAVYF
CNAVITYNGYTIWGQGTQVTVSSGSGHHHHHH* (SEQ ID NO:2199)**

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMSWVRQTPEKRELVAAINLNGGSTYYS
DTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGT~~PFAYWGQGT~~LVTVSAGSAAAGS
SGSSSGADIVLTQSPATLSVTPGDSVSLCKASQSSYNLHWYQQKSHESPRLLIKYTSQSISGIPS
RFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKGSGSGDKTHTCPPCPAPEA
AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVS~~LT~~TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK* (SEQ ID NO:2200)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMSWVRQTPEKRELVAAINLNGG
STYYS~~DTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGT~~PFAYWGQGT~~LVTVSAGS~~
AASGSSGGSSSGADIVLTQSPATLSVTPGDSVSLCKASQSSYNLHWYQQKSHESPRLLIKYTSQSI
SGIPSRFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKGSGSGDKTHTCPPC
PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVS~~LT~~TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK* (SEQ ID NO:2201)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGSGGSSGGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMSWVRQTPEKRELVAAI
NLNGGSTYYS~~DTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGT~~PFAYWGQGT~~LV~~
VSAGSAAAGSSSGSSSGADIVLTQSPATLSVTPGDSVSLCKASQSSYNLHWYQQKSHESPRLLIK
YTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKGSGSGDKTH
TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVS~~LT~~TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2202)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAINLNGGSTYYS~~DTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGT~~PFAYW
GQGT~~LVTVSAGSAAAGSSSGSSSGADIVLTQSPATLSVTPGDSVSLCKASQSSYNLHWYQQKSH~~
ESPRLLIKYTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~GLEWVSVISGDGSYTYAD
SVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGT~~LVTVSSGGGGSGGGG~~
SGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERF
SGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGDKTHTCPPCPAPEAA
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSV~~LT~~TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK* (SEQ ID NO:2203)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVQLGGSLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAINLNGGSTYYSDTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGTPFAYW
GQGTLVTVSAGSAASGSSGGSSSGADIVLTQSPATLSVTPGDSVLSCKASQSSISYNLHWYQQKSH
ESPRLLIKYTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSGSGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGKGLEWVSVISGDGS
YTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTVSSGGGG
SGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPS
GIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGS~~SGSGDKTHTCPPCP~~
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK* (SEQ ID NO:2204)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVQLGGSLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAINLNGGSTYYSDTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGTPFAYW
GQGTLVTVSAGSAASGSSGGSSSGADIVLTQSPATLSVTPGDSVLSCKASQSSISYNLHWYQQKSH
ESPRLLIKYTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSGSGSGGGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGKGLEWVSVI
SGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTVS
SGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYD
KSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGS~~SGSGDKTH~~
TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2205)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVL
SGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYISWVRQAPGKGLEWVAEISPYSGSTYYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMMDYWGQGTLVTVSSGS
AASGSSGGSSSGADIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASF
LYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYTTPPTFGQGTKEIKGSGSGDKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK* (SEQ ID NO:2206)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVL
SGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYISWVRQAPGKGLEWVAEISPYSG
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMMDYWGQGTLV
TVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLL
IYSASFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYTTPPTFGQGTKEIKGSGSGDKT
HTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2207)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGK
GLEWVSVISGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGSGSSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYIISWVRQAPGKGLEWVAEI
SPYSGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVM DYWG
QGTLVTVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVAWYQQKPG
KAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQGKVEIKGS
GSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2208)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYIISWVRQAPGK
GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRG
SVM DYWGQGTLVTVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQG
TKVEIKGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGKGLEWVSVISGD
GSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTVSSGG
GGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNR
PSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGS GSGDKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK* (SEQ ID NO:2209)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYIISWVRQAPGK
GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRG
SVM DYWGQGTLVTVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQG
TKVEIKGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGKGLEWVS
VISGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTV
SSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIY
DKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGS GSGDKT
HTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2210)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYIISWVRQAPGK
GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRG
SVM DYWGQGTLVTVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQG
TKVEIKGSGSGSGSGSGGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGK
GLEWVSVISGDGSYTTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2211)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLVSWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSGDVKLVESGGGLVKLGSLRLSCAASGFSFS
TSYMSWVRQTPEKRLLELVAAILNNGGSTYYSDTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYC
ASELAGYGTFFAYWGQGLTVTVSAGSAASGSSGSSSGADIVLTQSPATLSVTPGDSVLSCKASQ
SISYNLHWYQQKSHESPRLLIKYTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMFCQQNSWP
LTFGAGTKLEVK* (SEQ ID NO:2212)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGSLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAILNNGGSTYYSDTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYCASELAGYGTFFAYW
GGTLTVTVSAGSAASGSSGSSSGADIVLTQSPATLSVTPGDSVLSCKASQSISYNLHWYQQKSH
ESPRLLIKYTSQSISGIPSRFSGSGSGTDFTLTINNVEDDFGMFCQQNSWPLTFGAGTKLEVKG
SGSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ
QQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFSH
YTLVSWVRQAPGKGLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCA
RNFYKYVFANWGQGLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSF
YVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLV
FGGGTKLTVL* (SEQ ID NO:2213)

MDMRVPAQLLGLLLLWLRGARCAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYPPSWYQDTPG
QDPRTLIYNTNRSSDVPERFSGSIVGNKAALTITGAQPDDESIVFCLLYLGRGIWVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAK
SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2214)

MDMRVPAQLLGLLLLWLRGARQCIVLTQSPAISASPGEKVTISCSANSSVRFMFWYQKKPGSKPK
PLIYRTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQYHSYPWTFGGGKLEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLESTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2215)

MDMRVPAQLLGLLLLWLRGARCVQLQQSGPELVKPGASVRISCKASGYTFTTYYIHWLKDRPGQG
LEWIGWIFPGNVNTKYNAKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFCAREELQYYFDYWGD
GSTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQS
SGLYSLKSVVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGEVQLVQSGAEVKKPGAS
VKVSCKASGYTFTSYGISWVRKAPGGGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTAYME
LRLSRSDDTAVYYCASSKEKATYYYGMDVWGKGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALG
CLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLESVTVTPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2216)

MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAKS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2217)

MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSASVGDRVTITCRASQSISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLESTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2218)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCQVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGEVQLVESGGG
LVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWVASISSTSGSKYYADSVKGRFTISRDN
KNTLYLQMNSLRAEDTAVYSCAKTYYDFWSGYTTFDYWGDGTLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSKVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2219)**

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSPGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2220)**

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSASVGDRVTITCRASQSISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTL
TSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2221)**

**MDMRVPAQLLGLLLLWLRGARCQVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGSGEVQLV
ESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWVASISSTSGSKYYADSVKGRFTI
SRDNKNTLYLQMNSLRAEDTAVYSCAKTYYDFWSGYTTFDYWGDGTLTVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSKVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD
SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2222)**

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSPGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2223)**

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSASVGDRVTITCRASQSISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTL
TSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2224)**

**MDMRVPAQLLGLLLLWLRGARCQVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGSGSGG
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWVASISSTSGSKYYADSVK
GRFTISRDNKNTLYLQMNSLRAEDTAVYSCAKTYYDFWSGYTTFDYWGDGTLTVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSKVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP
VLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2225)**

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:2226)

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSAYVGDRVITITCRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTLT
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:2227)

**MDMRVPAQLLGLLLLWLRGARCVQLQQWGAGLLKPSETLSLTCVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGGEVQLVESVGG
LVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWISTISGSGGSTYYADSVKGRFTISRDNK
NTLYLQMNSLRAEDTAVYYCARAGYGRYYYGMDVWGDGTTTVSSASTKGPSVFPLAPSSKSTSG
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLKSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGGSFFL
YSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*** (SEQ ID NO:2228)

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:2229)

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSAYVGDRVITITCRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTLT
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:2230)

**MDMRVPAQLLGLLLLWLRGARCVQLQQWGAGLLKPSETLSLTCVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGSGGEVQLV
ESVGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWISTISGSGGSTYYADSVKGRFTIS
RDNKNTLYLQMNSLRAEDTAVYYCARAGYGRYYYGMDVWGDGTTTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLKSVTVPSSSLGTQTYIC
NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDS
DGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*** (SEQ ID NO:2231)

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:2232)

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSAYVGDRVITITCRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTLT
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:2233)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCQVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGK
GLEWIGEIDHTGSTNYEPLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDVWGKGTTTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGSGSSGG
EVQLVESVGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGKGLEWISTISGSGGSTYYADSVK
GRFTISRDNKNTLYLQMNSLRAEDTAVYYCARAGYGRYYYGMDVWGDGTTTVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP
PVLDSGGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2234)**

**MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSAYVGDRVTITCRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNFPYFPAKQVQWKVDNALQSGNSQESVTEQDSKSTYSLESTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2235)**

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2236)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVESVGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGK
GLEWISTISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARAGYGRYYYGMD
VWGDGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGGQVQLQQWGAGLLK
PSETLSLTCAVSGASFSGHYWTWIRKPPGKGLEWIGEIDHTGSTNYEPLRSRVTISVDTSKNQFSL
NLKSVTAADTAVYYCARGGQGGYDWGHYHGLDVWGKGTTTVTVSSASTKGPSVFPLAPSSKSTSGG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLESVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLY
SKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2237)**

**MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSAYVGDRVTITCRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNFPYFPAKQVQWKVDNALQSGNSQESVTEQDSKSTYSLESTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:2238)**

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:2239)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVESVGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGK
GLEWISTISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARAGYGRYYYGMD
VWGDGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGGQVQLQQWG
AGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGKGLEWIGEIDHTGSTNYEPLRSRVTISVDTSK
NQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYHGLDVWGKGTTTVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLESVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:2240)**

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSAYVGDRVITICRVSQGISSYLNWYQKKPGKKP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYPFTFGPGTKVDIKRTVAAP
SVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYSLESTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:2241)

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQDKPGQDP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRYSYSCQVTHEGSTVEKTVAPTECS*** (SEQ ID NO:2242)

**MDMRVPAQLLGLLLLWLRGARCEVQLVESVGGLVQPGGSLRLSCAASGFTFSSYAMHWVRDAPGK
GLEWISTISGSGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARAGYGRYYYYGMD
VWGDGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLKSVVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGSGSGSGSGSGGQVQ
LQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRKPPGKGLEWIGEIDHTGSTNYEPLRSRVTIS
VDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYHGLDWGKGTTVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLKSVVTPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALG
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*** (SEQ ID NO:2243)

**MDMRVPAQLLGLLLLWLRGARCVQLQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRQPPGK
GLEWIGEIDHTGSTNYEPLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYH
GLDWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHHHHH***
(SEQ ID NO:2244)

**MDMRVPAQLLGLLLLWLRGARCDIQTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAP
KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTL
TLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*** (SEQ ID NO:2245)

**MDMRVPAQLLGLLLLWLRGARCSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSP
VLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAAS
YLSLTPEQWKSHRYSYSCQVTHEGSTVEKTVAPTECSGSGSGEVQLVESGGGLVQPGGSLRLSCAA
SGFTFSSYAMHWVRQAPGKGLEWVASISSTSGSKYYADSVKGRFTISRDNKNTLYLQMNSLRAE
DTAVYSCAKTYIDFWSGYYTFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGDSFFLYSKLTVDKSRWQ
QGNVFCFSVMHEALHNHYTQKSLSLSPGK*** (SEQ ID NO:2246)

**MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGGSRLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAILNNGSTYYSDTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYCASELAGYGTPTFAYW
GQGTLTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHHHHH*** (SEQ ID
NO:2247)

FIG. 19 (contd.)

**MDMRVPAQLLGLLLLWLRGARCAAADIVLTQSPATLSVTPGDSVSLSCKASQSISYNLHWYQQKSHE
SPRLLIKYTSQSIGIPSRFSGSGSGTDFTLTINNVEDDFGMFCQQSNSWPLTFGAGTKLEVKRTV
AAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSS
TLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSEVQLVQSGAEVKKPGASVKVSCK
ASGYTFTSYGISWVRQAPGGGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRS
DDTAVYYCASSKEKATYYYYGMDVWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMEALHNHYTQKSLSLSPGKGSGSG HHHHHH* (SEQ ID NO:2248)**

**MDMRVPAQLLGLLLLWLRGARCAAADIVLTQSPATLSVTPGDSVSLSCKASQSISYNLHWYQQKSHE
SPRLLIKYTSQSIGIPSRFSGSGSGTDFTLTINNVEDDFGMFCQQSNSWPLTFGAGTKLEVKRTV
AAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSS
TLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSGGGGSEVQLVQSGAEVKKPGASV
KVSCKASGYTFTSYGISWVRQAPGGGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMEL
RSLRSDDTAVYYCASSKEKATYYYYGMDVWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREP
QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGKGSGSGHHHHHH* (SEQ ID NO:2249)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLVSWVRQAPGK
GLEWVSISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMEALHNHYTQKSLSLSPGKGSGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFT
SYISWVRQAPGKGLEWVAEISPYSGSTYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC
ALRARPPIRLHPRGSVMDYWGQGTITVSSGSAASGSSGSSSGADIQMTQSPSSLSASVGDRVTI
TCRASQDVSTAWAYQQKPGKAPKLLIYSASFYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
QQSYTTPPTFGQGTKEIK* (SEQ ID 2250)**

**MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQ
GLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYYG
MDVWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAG*
(SEQ ID 2251)**

**MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCRASQSISSYNLWYQQKPGKAPK
LLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKGSGSGSY
VLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQRPSGIPVRFSGSNSGNT
ATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV
EKTVAPECS* (SEQ ID 2252)**

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCQVQLVQSGAEVKKPGSSVKVSCKASGYTFTYRYLHWVRQAPGQ
GLEWMGRIIPVLKITNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAVDDAFDIWGQGTMT
VTVSSGSGSGQVQLQQWGAGLLKPSETLSLTCVSGASFSGHYWTWIRQPPGKGLEWIGEIDHTGS
TNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYHGLDVWGQGTTVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK*
(SEQ ID 2253)

MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQ
GLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYG
MDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT
QKSLSLSPGK* (SEQ ID NO:2254)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMWSVRQTPEKRELVAAINLNGGSTYY
DTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYCASELAGYGPFPAYWGQGTLVTVSAGSAASGS
SGGSSSGADIVLTQSPATLSVTPGDSVSLSCKASQSYNLHWYQQKSHESPRLLIKYTSQSI
RFGSGSGTDFTLTINNVEDDFGMVFCQQSNSWPLTFGAGTKLEVKGSGSGHHHHHH* (SEQ ID
NO:225)

5

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMWSVRQTPEKRELVAAINLNGG
STYYSDTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYCASELAGYGPFPAYWGQGTLVTVSAGS
AASGSSGGSSSGADIVLTQSPATLSVTPGDSVSLSCKASQSYNLHWYQQKSHESPRLLIKYTSQSI
SGIPSRFGSGSGTDFTLTINNVEDDFGMVFCQQSNSWPLTFGAGTKLEVKGSGSGHHHHHH*
(SEQ ID NO:2256)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGSGGDVKLVESGGGLVKLGGSRLSCAASGFSFSTSYMWSVRQTPEKRELVAAI
NLNGGSTYYSDTVKGRFTISRDNKNTLYLQMSSLKSEDTAFYYCASELAGYGPFPAYWGQGTLV
VSAGSAASGSSSGSSSGADIVLTQSPATLSVTPGDSVSLSCKASQSYNLHWYQQKSHESPRLLIK
YTSQSI
SGIPSRFGSGSGTDFTLTINNVEDDFGMVFCQQSNSWPLTFGAGTKLEVKGSGSGHHHH
HH* (SEQ ID NO:2257)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGGSRLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAILNNGGSTYYSDTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGTPEFAYW
GQGTLTVTVSAGSAASGSSGGSSSGADIVLTQSPATLSVTPGDSVSLSCASQSISYNLHWYQQKSH
ESPRLLIKYTSQSIGIPSRFSGSGSGTDFTLTINNVETEDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGKGLEWVSVISGDGSYTYAD
SVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLTVTSSGGGGSGGGG
SGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERF
SGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGHHHHHH* (SEQ ID
NO:2258)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGGSRLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAILNNGGSTYYSDTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGTPEFAYW
GQGTLTVTVSAGSAASGSSGGSSSGADIVLTQSPATLSVTPGDSVSLSCASQSISYNLHWYQQKSH
ESPRLLIKYTSQSIGIPSRFSGSGSGTDFTLTINNVETEDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSGSGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGKGLEWVSVISGDGS
YTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLTVTSSGGGG
SGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPS
GIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGHHHHHH*
(SEQ ID NO:2259)

MDMRVPAQLLGLLLLWLRGARCDVKLVESGGGLVKLGGSRLRLSCAASGFSFSTSYMSWVRQTPEK
RLELVAAILNNGGSTYYSDTVKGRFTISRDNANTLYLQMSSLKSEDTAFYYCASELAGYGTPEFAYW
GQGTLTVTVSAGSAASGSSGGSSSGADIVLTQSPATLSVTPGDSVSLSCASQSISYNLHWYQQKSH
ESPRLLIKYTSQSIGIPSRFSGSGSGTDFTLTINNVETEDFGMYFCQQSNSWPLTFGAGTKLEVKG
SGSGSGSGGGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGKGLEWVS
SGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLTVT
SGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYD
KSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGHHH
HHH* (SEQ ID NO:2260)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYISWVRQAPGKGLEWVAEISPYSGSTYYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMYDYGQGTLTVTSSGS
AASGSSGGSSSGADIQMTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQKPGKAPKLLIYSAF
LYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQGTKEIKSGSGHHHHHH*
(SEQ ID NO:2261)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLWVRQAPGK
GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWG
QGTLTVTSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
SGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYISWVRQAPGKGLEWVAEISPYSG
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMYDYGQGTLT
TVSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQKPGKAPKLL
IYSAFLYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTTPPTFGQGTKEIKSGSGHHH
HHH* (SEQ ID NO:2262)

FIG. 19 (contd.)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~
 GLEWVSVISGDGSY~~TY~~YADSVKGRFTISSDNSKNTLYLQMN~~SLRAEDTAVYYCARNFIKYVFANWG~~
 QGTLTVTSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
 APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
 SSGSGSGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFTSY~~YISWVRQAPGKGLEWVAEI~~
 SPYSGSTYYADSVKGRFTISADTSKNTAYLQMN~~SLRAEDTAVYYCALRARPPIRLHPRGSVMDYWG~~
 QGTLTVTSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVAWYQQKPG
 KAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYTTPPTFGGQTKVEIKG
 SSGHHHHHHH* (SEQ ID NO:2263)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSY~~YISWVRQAPGK~~
 GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMN~~SLRAEDTAVYYCALRARPPIRLHPRG~~
 SVMDYWGQGTLTVTSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
 WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYTTPPTFGQG
 TKVEIKGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGKGLEWVSVISGD~~
 GSYTYADSVKGRFTISSDNSKNTLYLQMN~~SLRAEDTAVYYCARNFIKYVFANWGQGTLTVTSSGG~~
 GSGSGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNR
 PSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGHHHHHHH*
 (SEQ ID NO:2264)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSY~~YISWVRQAPGK~~
 GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMN~~SLRAEDTAVYYCALRARPPIRLHPRG~~
 SVMDYWGQGTLTVTSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
 WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYTTPPTFGQG
 TKVEIKGSGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGKGLEWVS~~
 VISGDGSYTYADSVKGRFTISSDNSKNTLYLQMN~~SLRAEDTAVYYCARNFIKYVFANWGQGTLTV~~
 SSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIY
 DKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGSGSGHH
 HHHH* (SEQ ID NO:2265)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSY~~YISWVRQAPGK~~
 GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMN~~SLRAEDTAVYYCALRARPPIRLHPRG~~
 SVMDYWGQGTLTVTSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
 WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYTTPPTFGQG
 TKVEIKGSGSGSGSGSGGEVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTL~~SWVRQAPGK~~
 GLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMN~~SLRAEDTAVYYCARNFIKYVFANWG~~
 QGTLTVTSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQ
 APVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG
 SSGSGHHHHHHH* (SEQ ID NO:2266)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTSY~~YISWVRQAPGK~~
 GLEWVAEISPYSGSTYYADSVKGRFTISADTSKNTAYLQMN~~SLRAEDTAVYYCALRARPPIRLHPRG~~
 SVMDYWGQGTLTVTSSGSAASGSSGGSSSGADIQMTQSPSSLSASVGDRVITITCRASQDVSTAVA
 WYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYTTPPTFGQG
 TKVEIKGSGSGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
 WYVDGVEVHNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQP
 REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL
 TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGSGSGEVQLVESGGGLVQPGGSLRLSCA
 ASGFTFSHYTL~~SWVRQAPGKGLEWVSVISGDGSYTYADSVKGRFTISSDNSKNTLYLQMN~~SLRAE
 DTAVYYCARNFIKYVFANWGQGTLTVTSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARIS
 CSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ
 SYANTLSLVFGGGTKLTVL* (SEQ ID NO:2267)

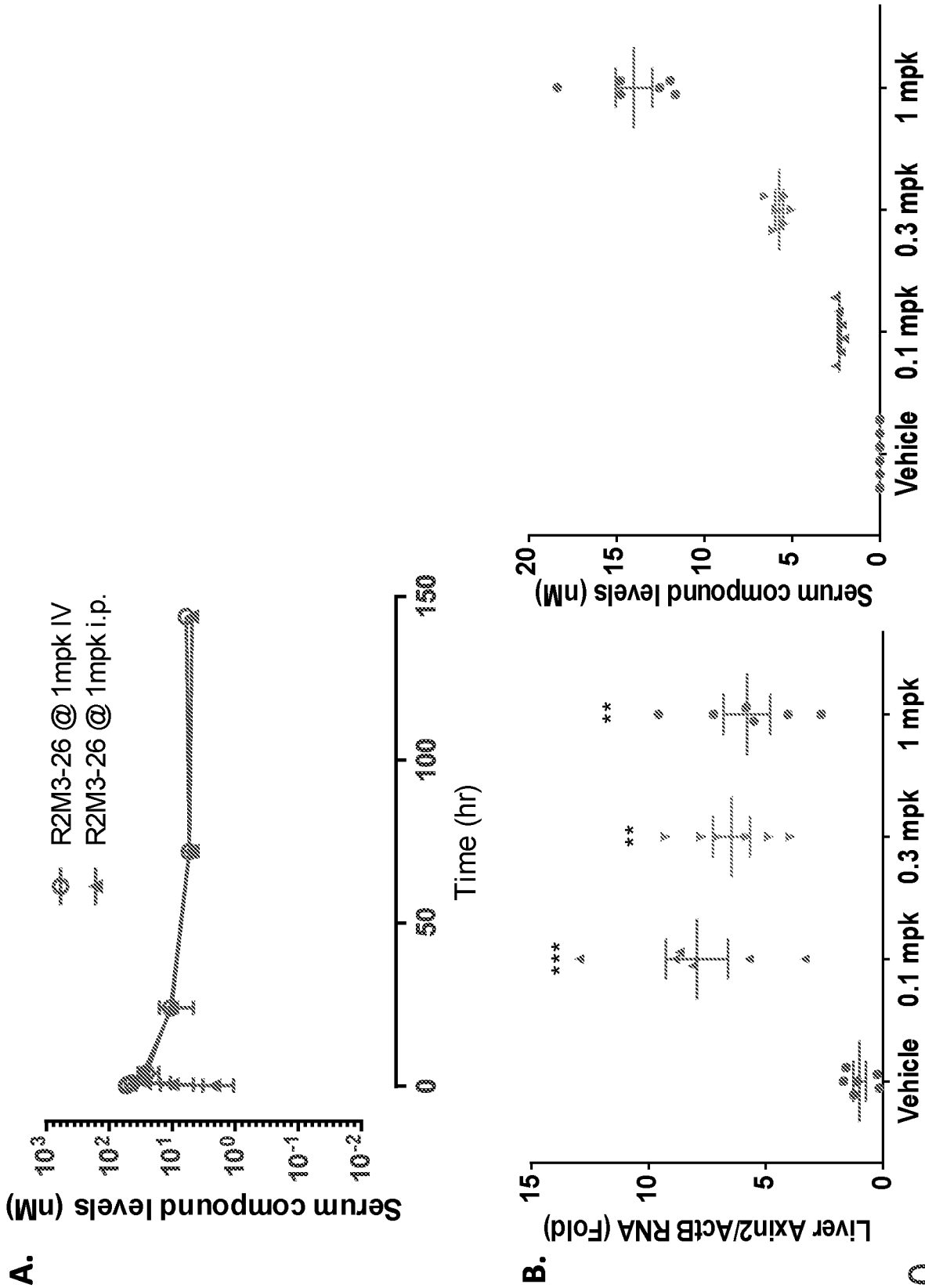


FIG. 20

A.

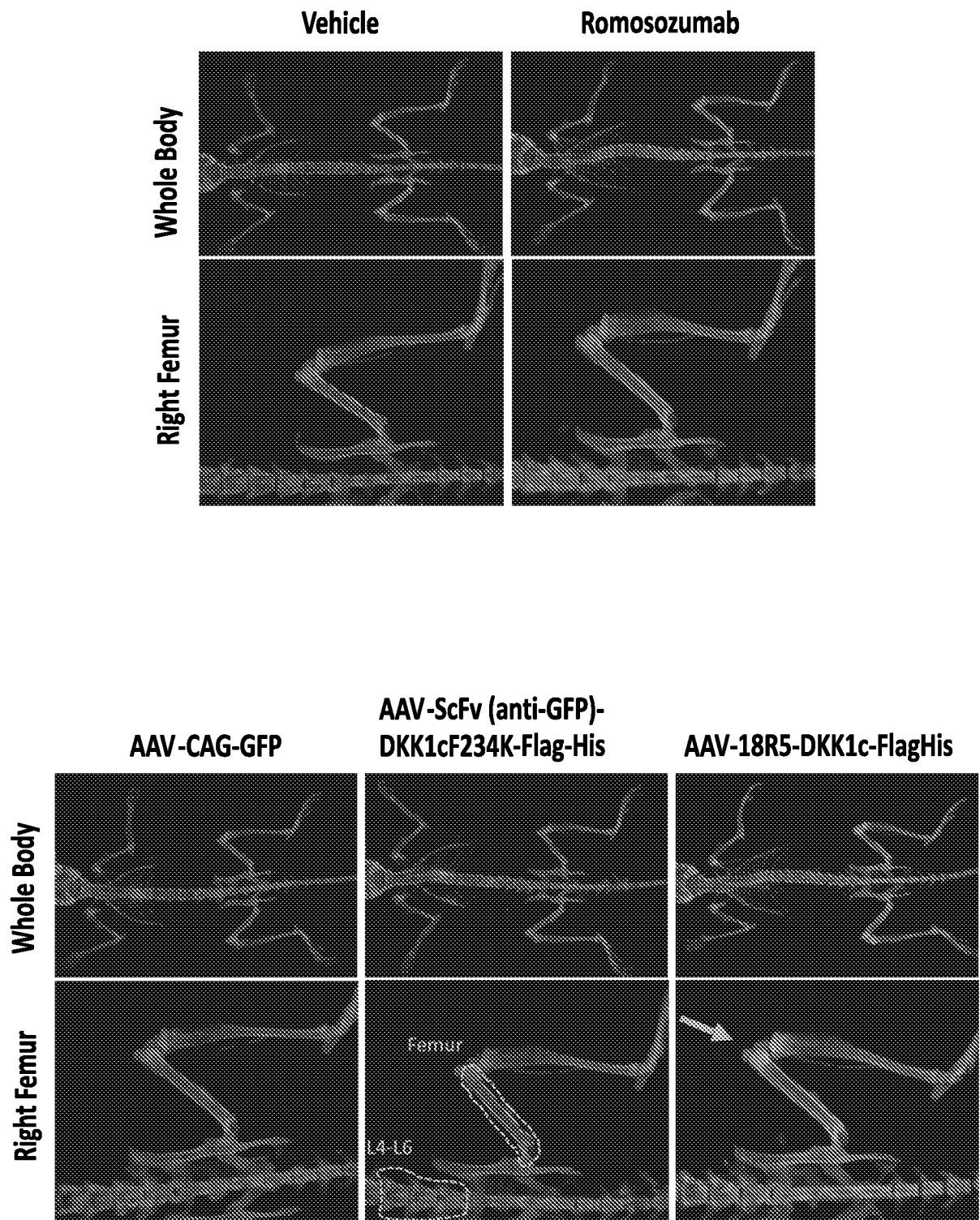


FIG. 21A

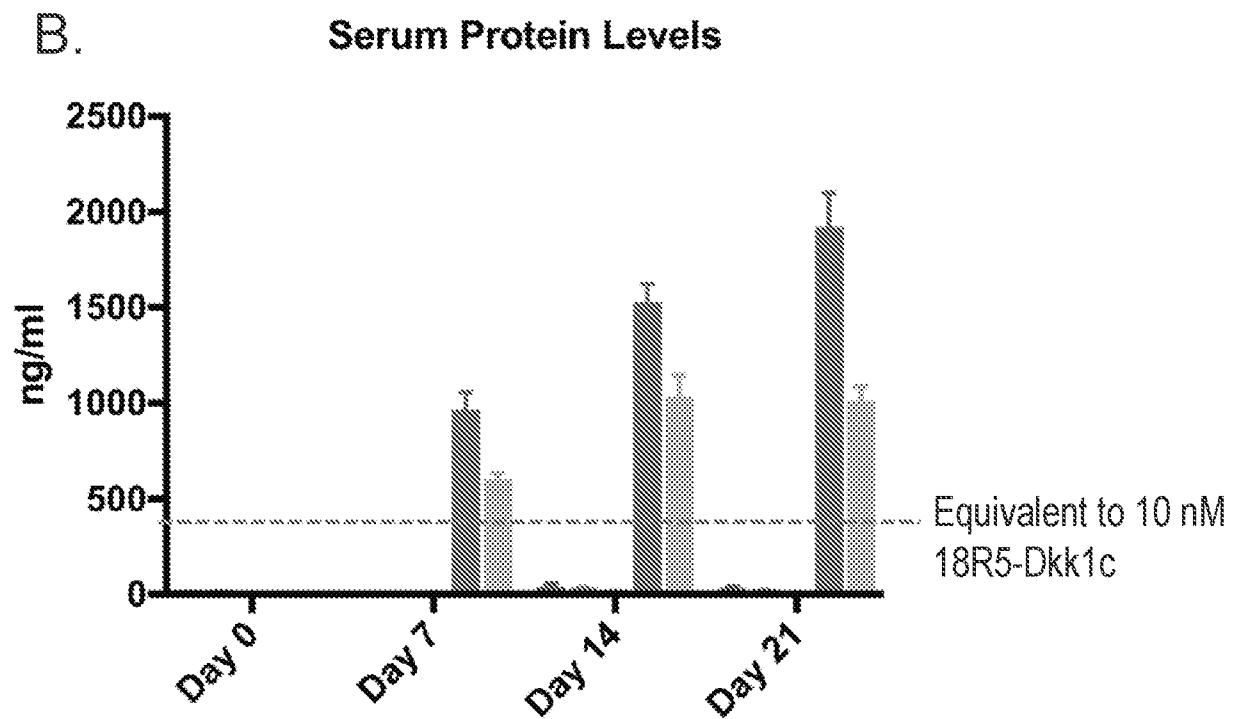


FIG. 21B

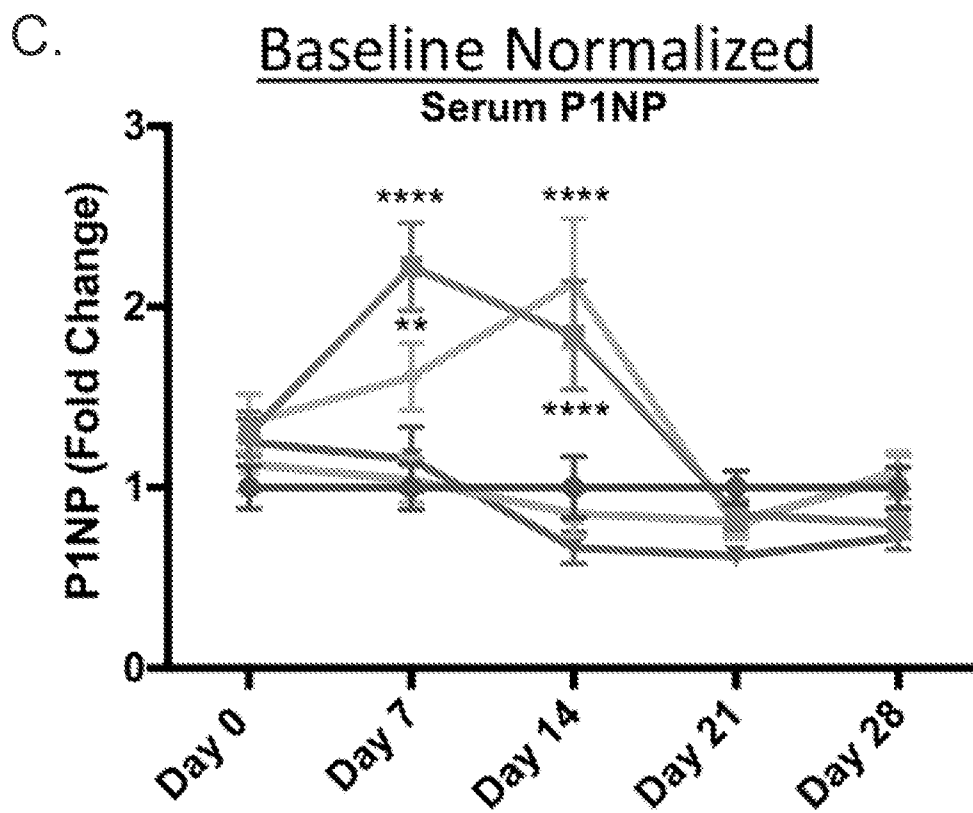


FIG. 21C

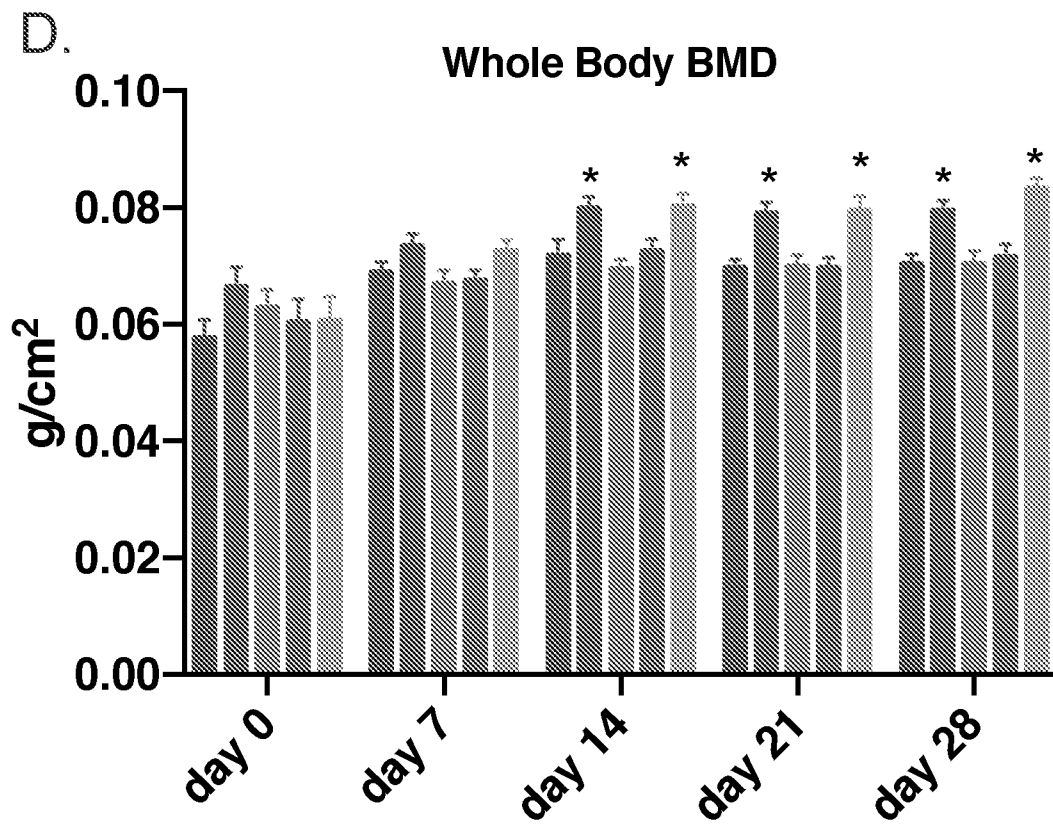
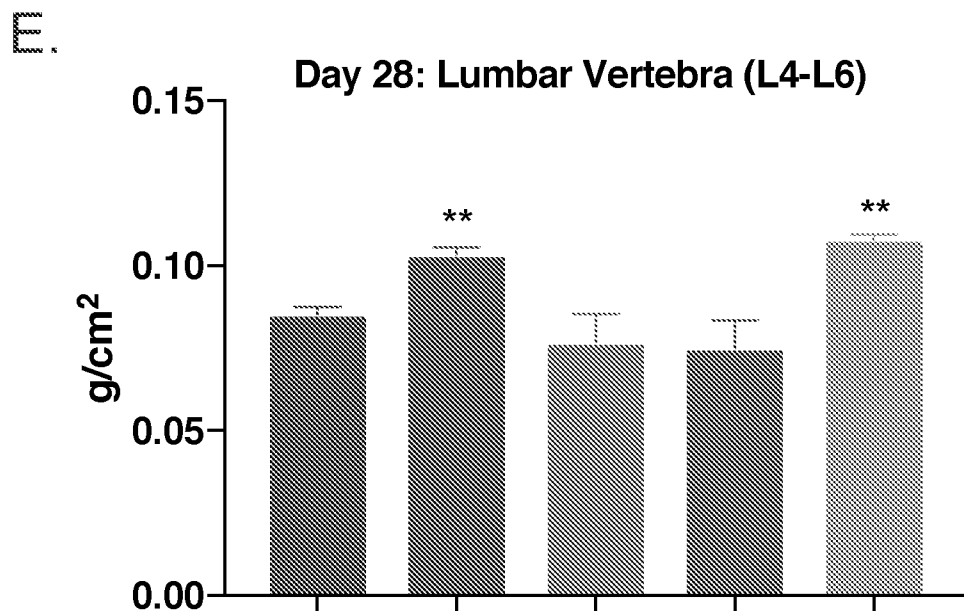


FIG. 21D

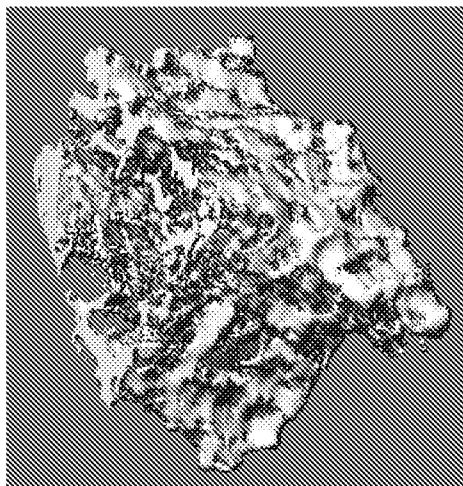


- Vehicle
- Romosozumab
- AAV-CAG-GFP
- AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His
- AAV-18R5-DKK1c-FlagHis

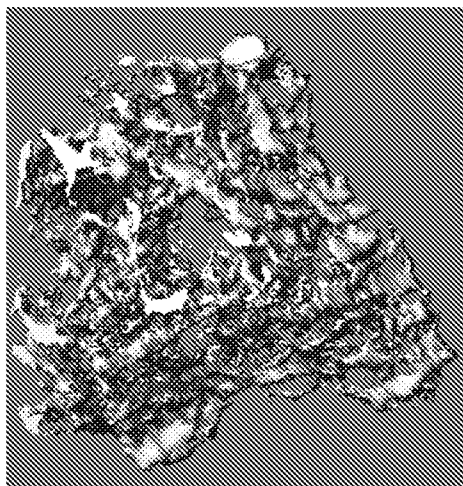
** P value < 0.05
**** P value < 0.000.1

FIG. 21E

Romosozumab

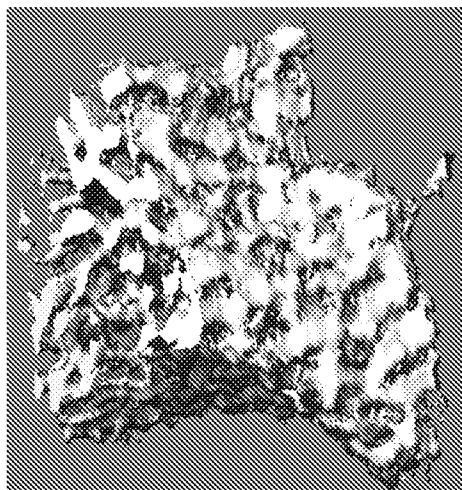


Vehicle

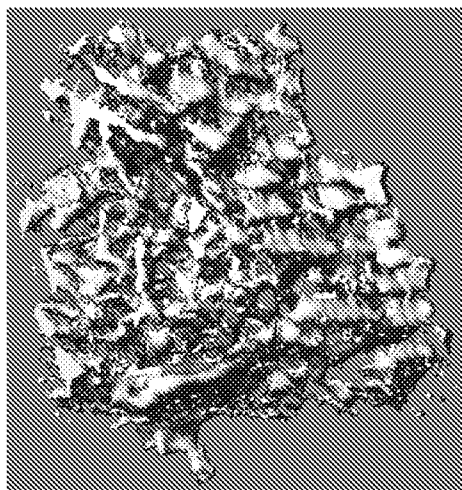


Day 28 tibia

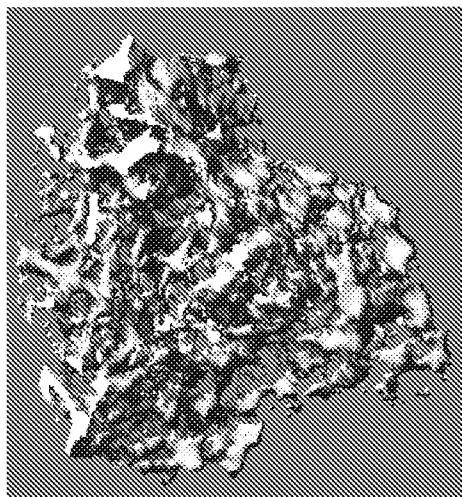
AAV-18R5-DKK1c-FlagHis



**AAV-ScFv (anti-GFP)-
DKK1cF234K-Flag-His**



AAV-CAG-GFP



Day 28 tibia

FIG. 22A

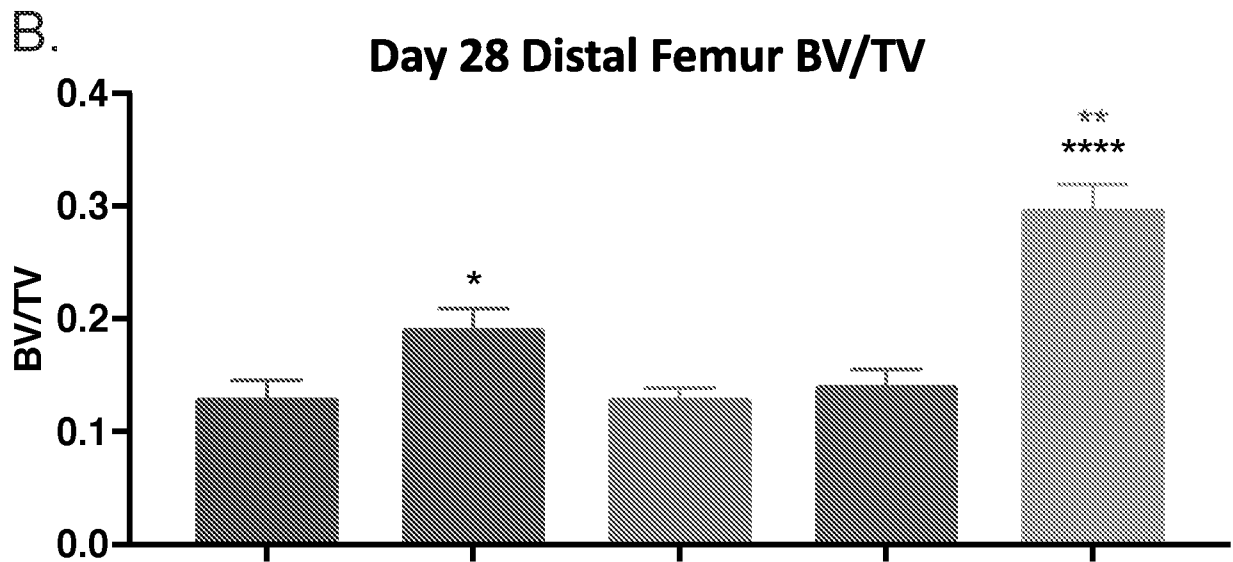
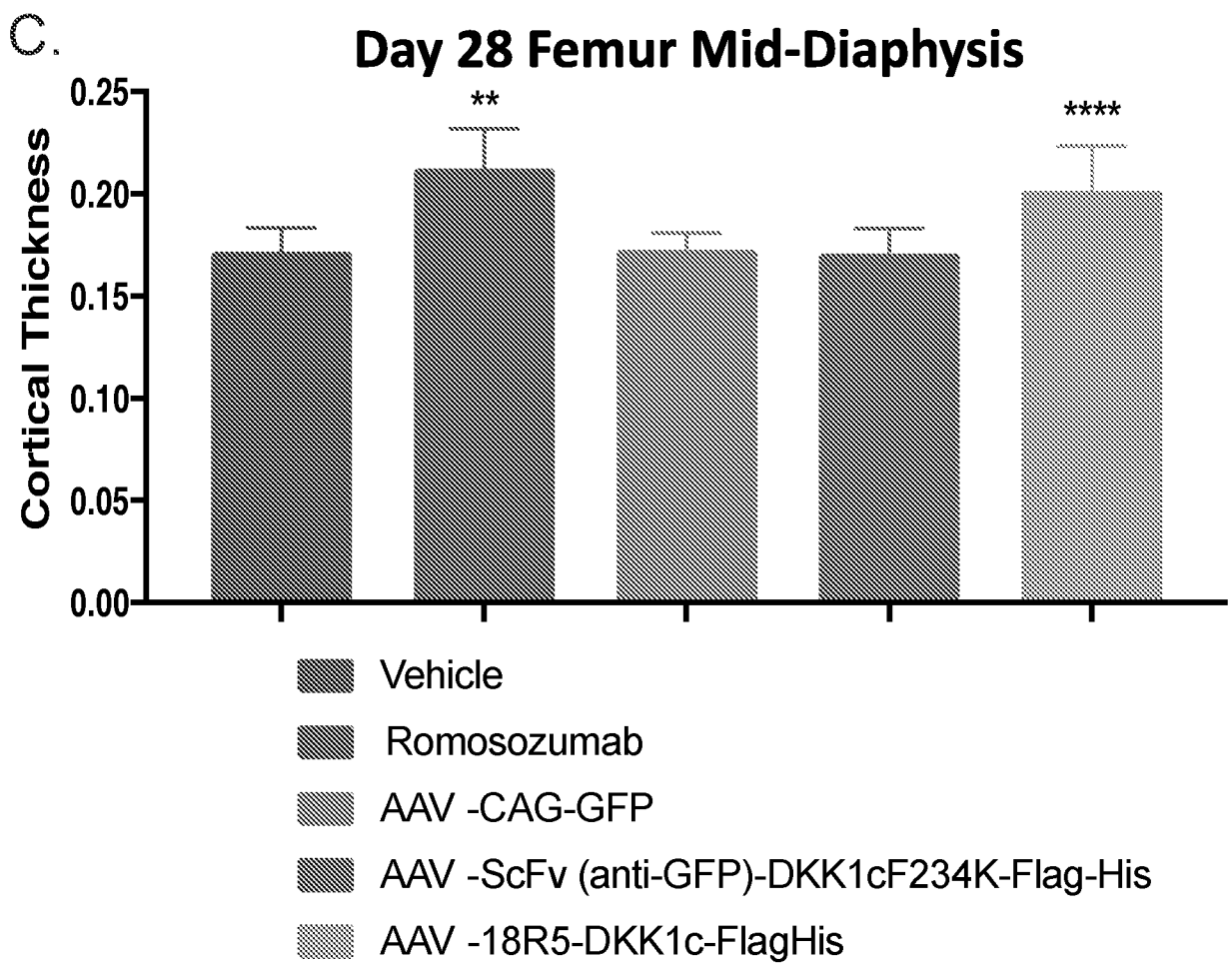


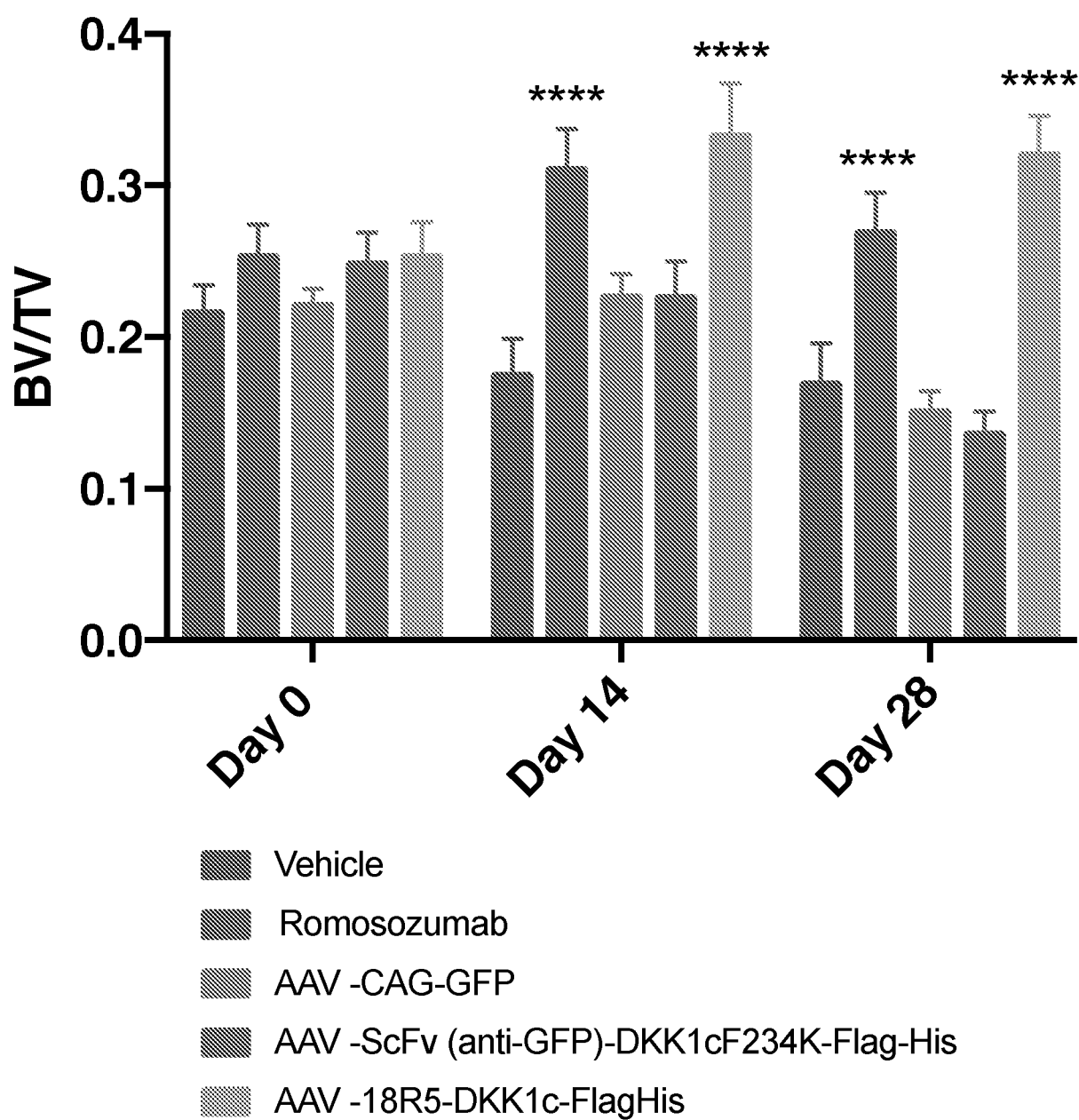
FIG. 22B



**** P value <0.0001

FIG. 22C

D.



**** P value <0.0001

FIG. 22D

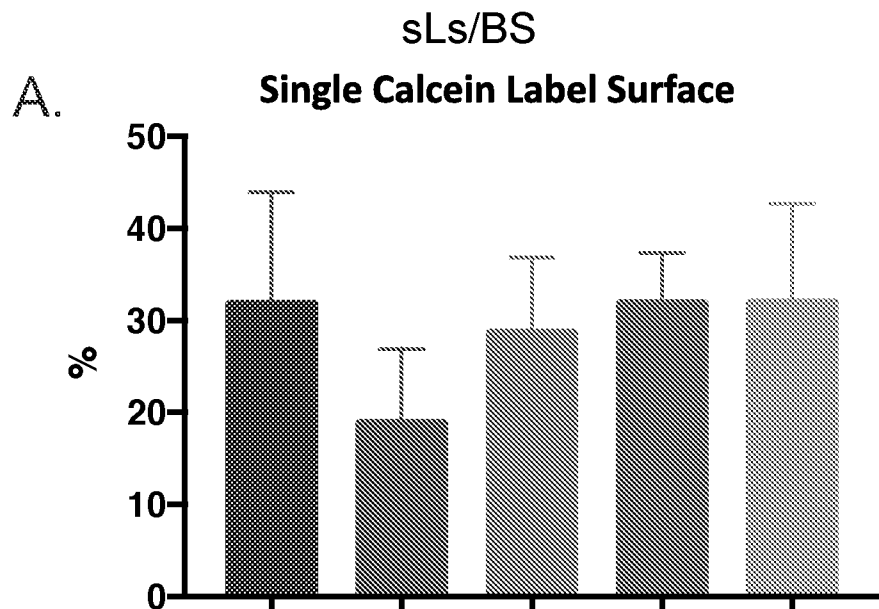


FIG. 23A

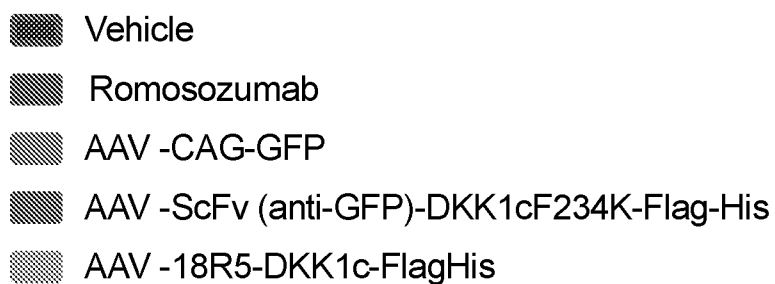
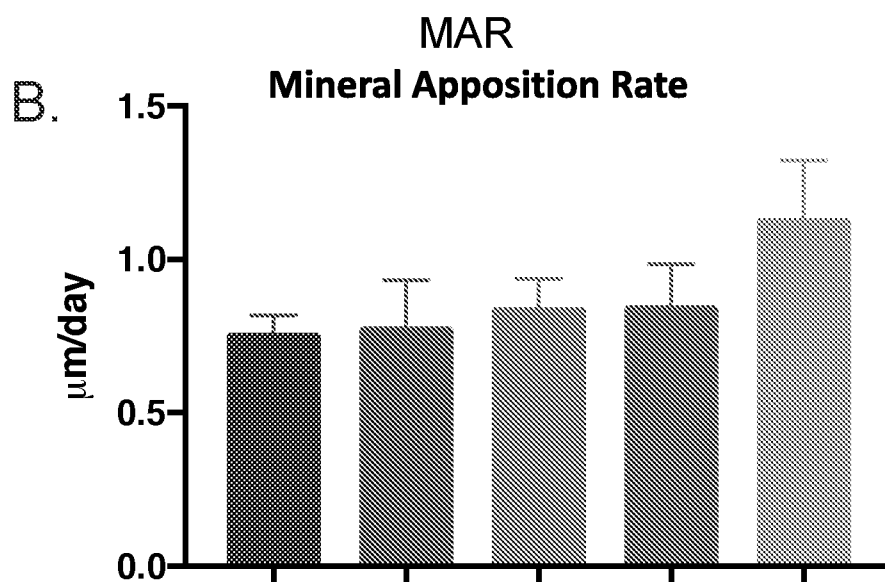


FIG. 23B

FIG. 24A-C

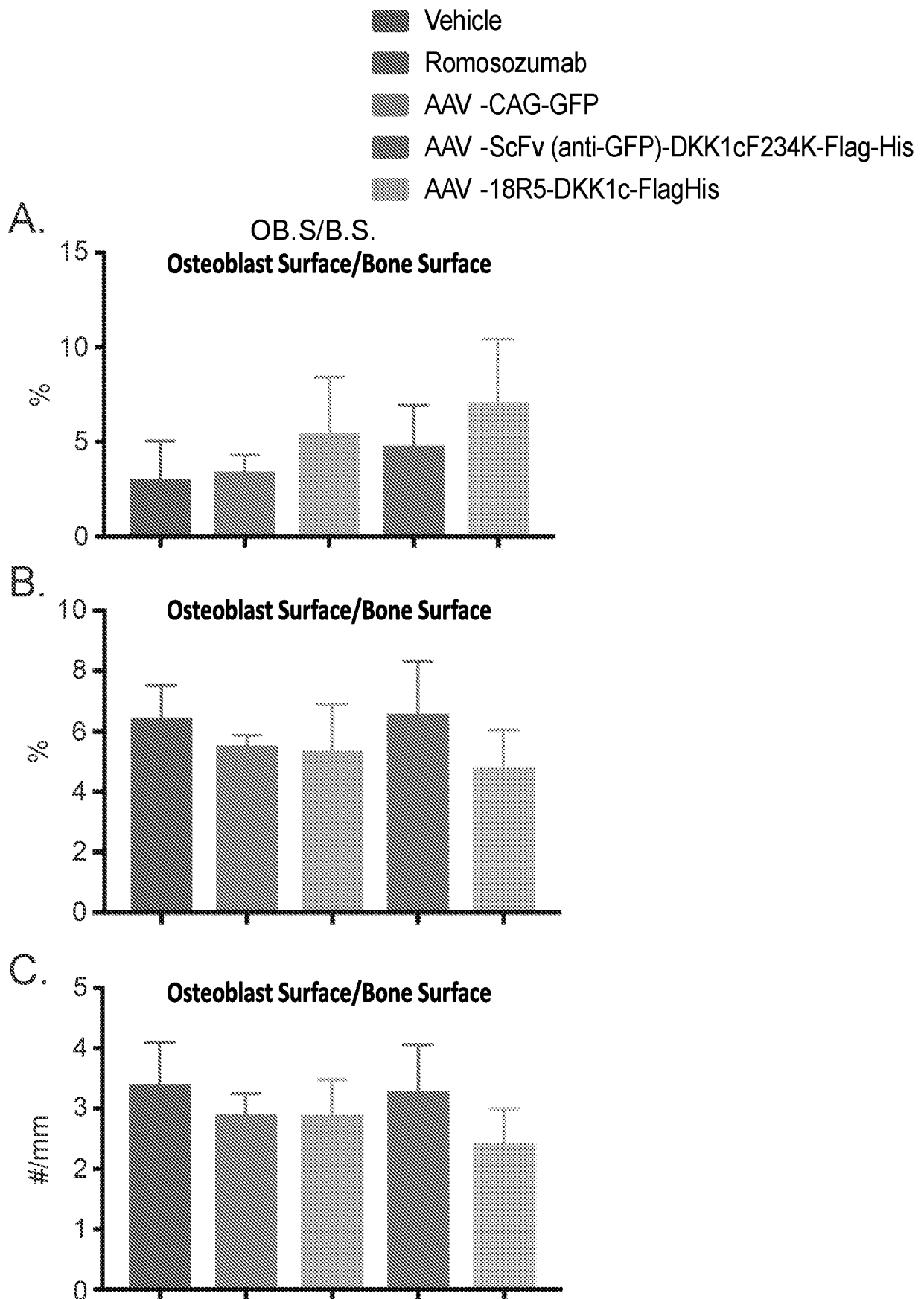


FIG. 24D

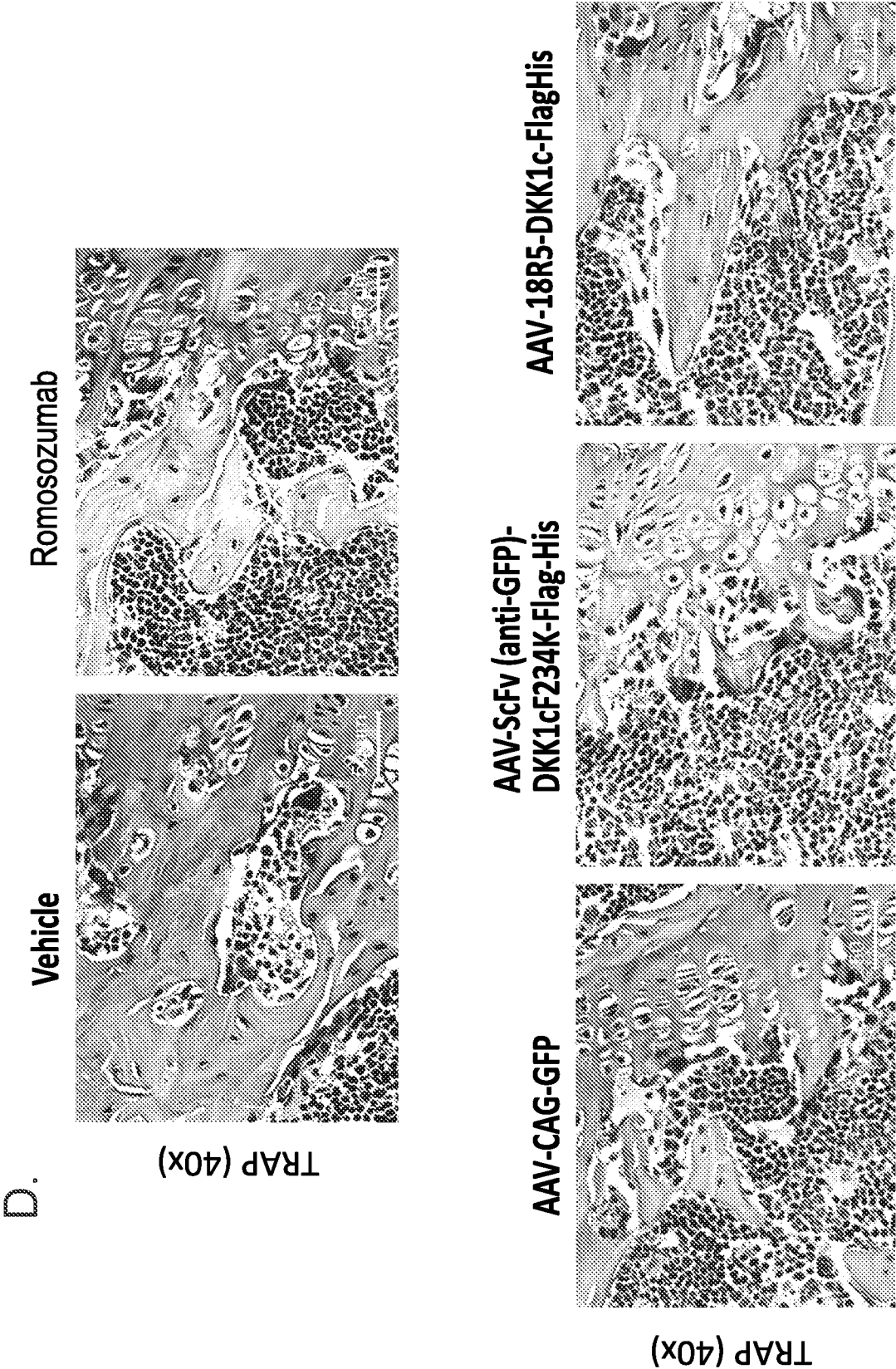


FIG. 25A

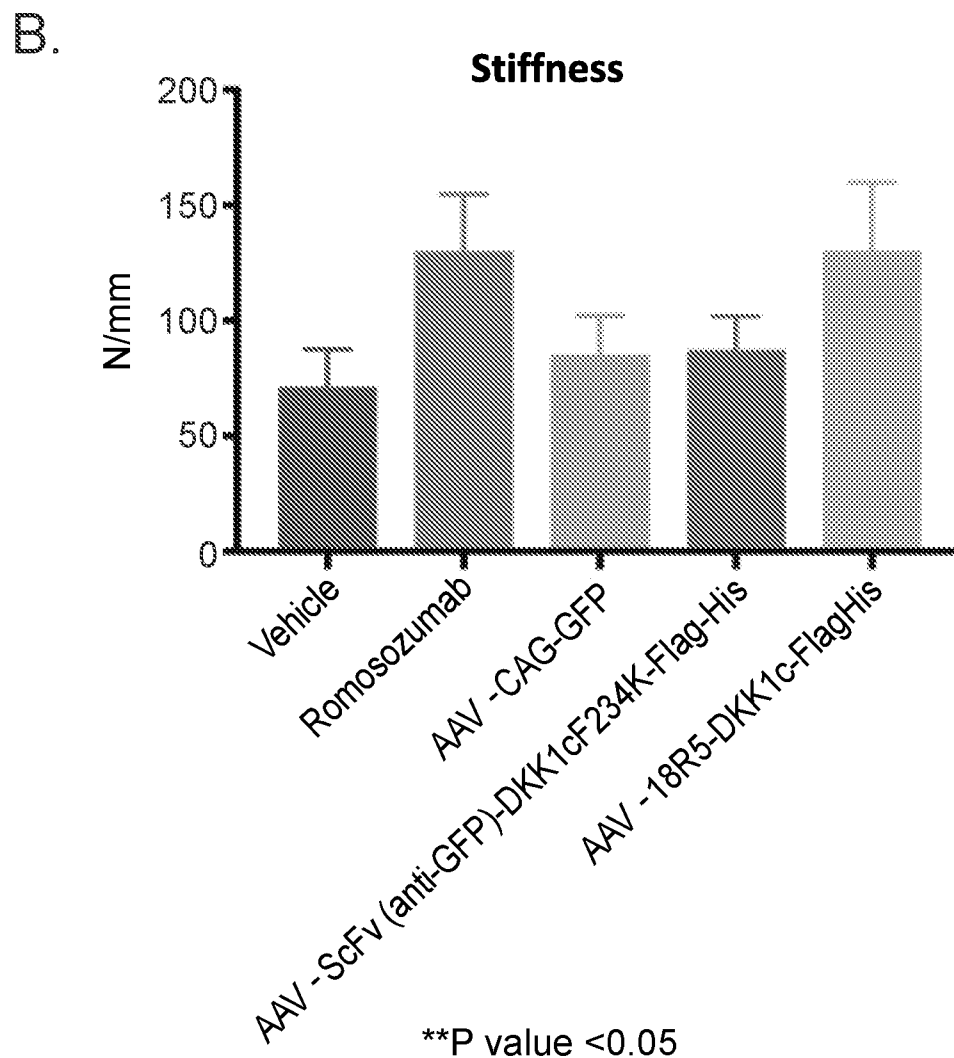
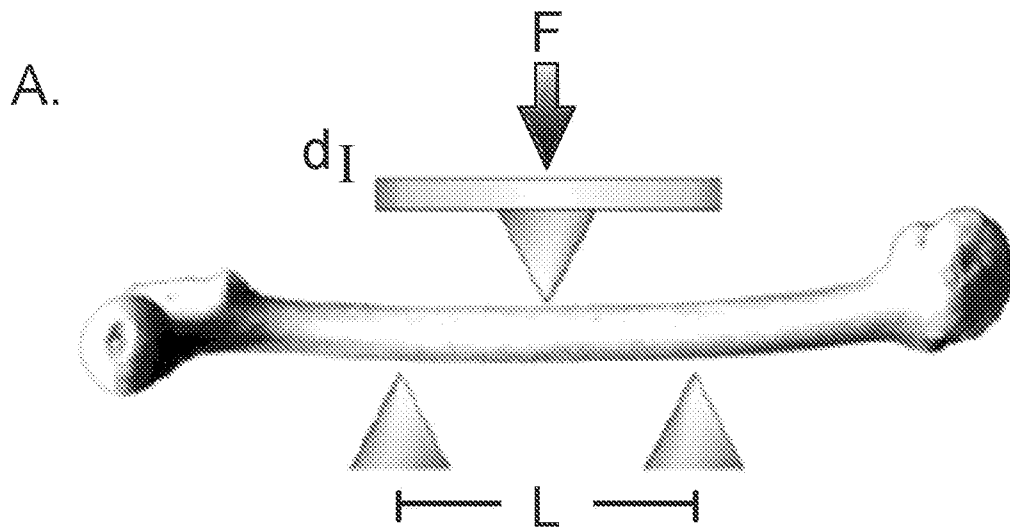
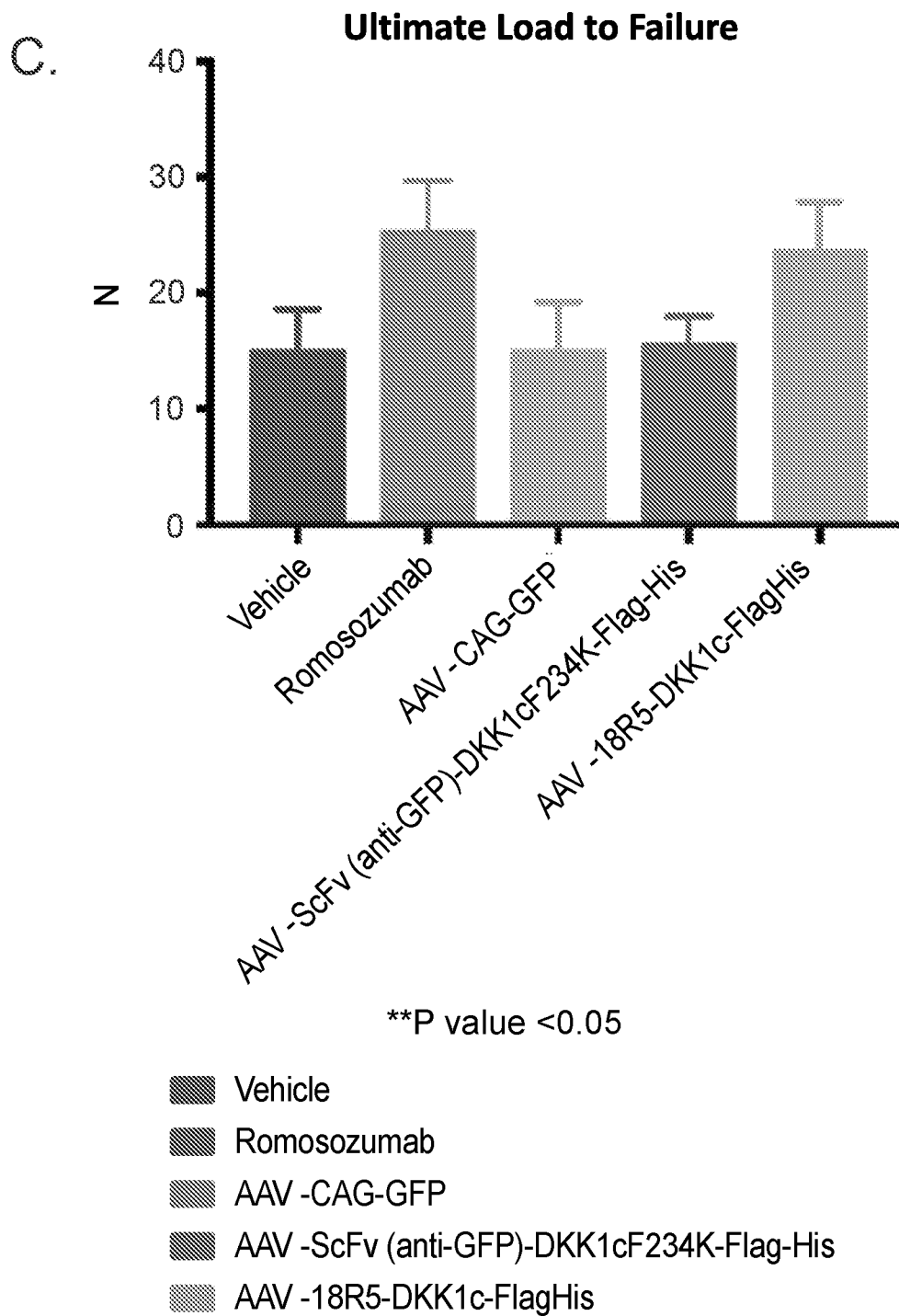
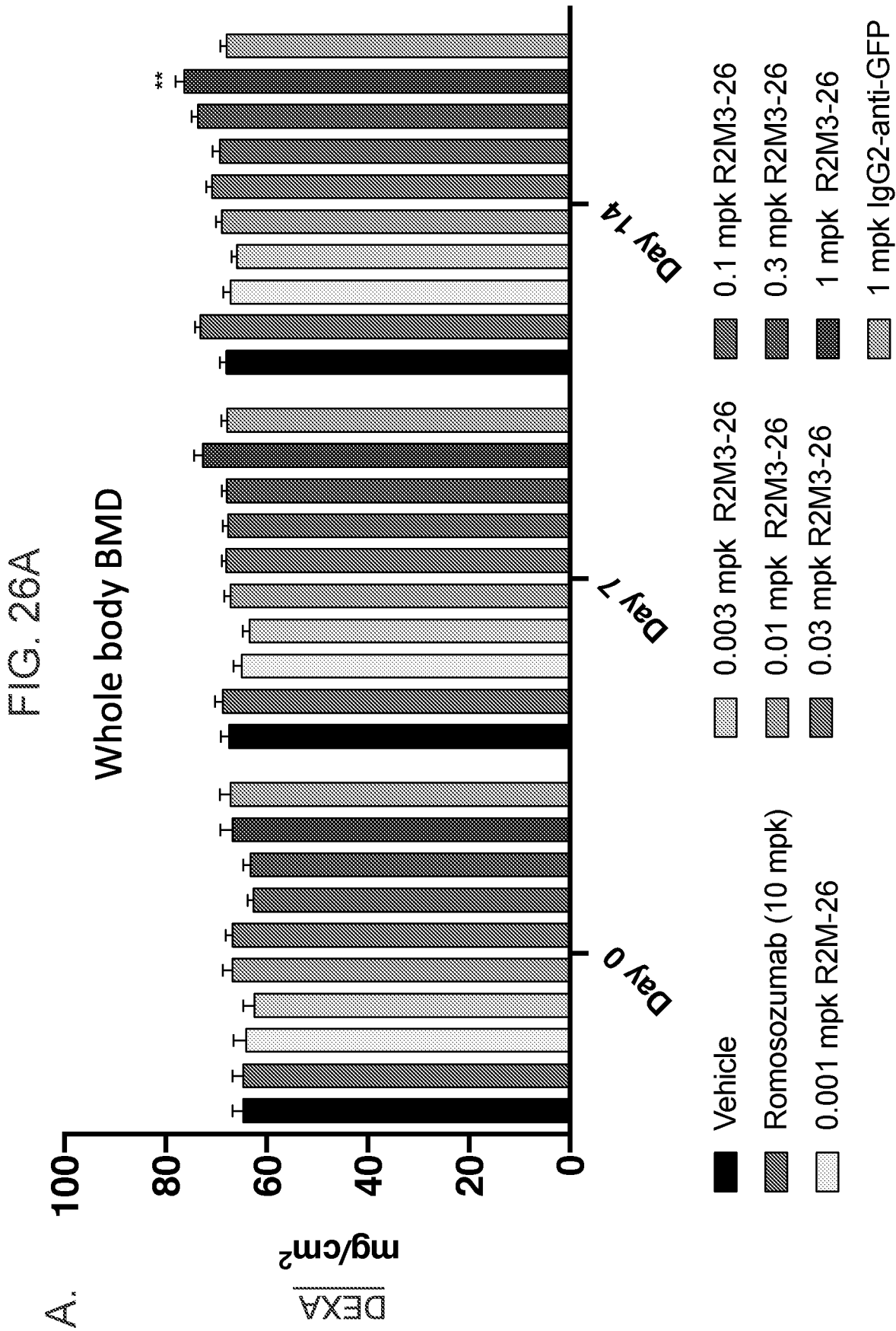


FIG. 25C





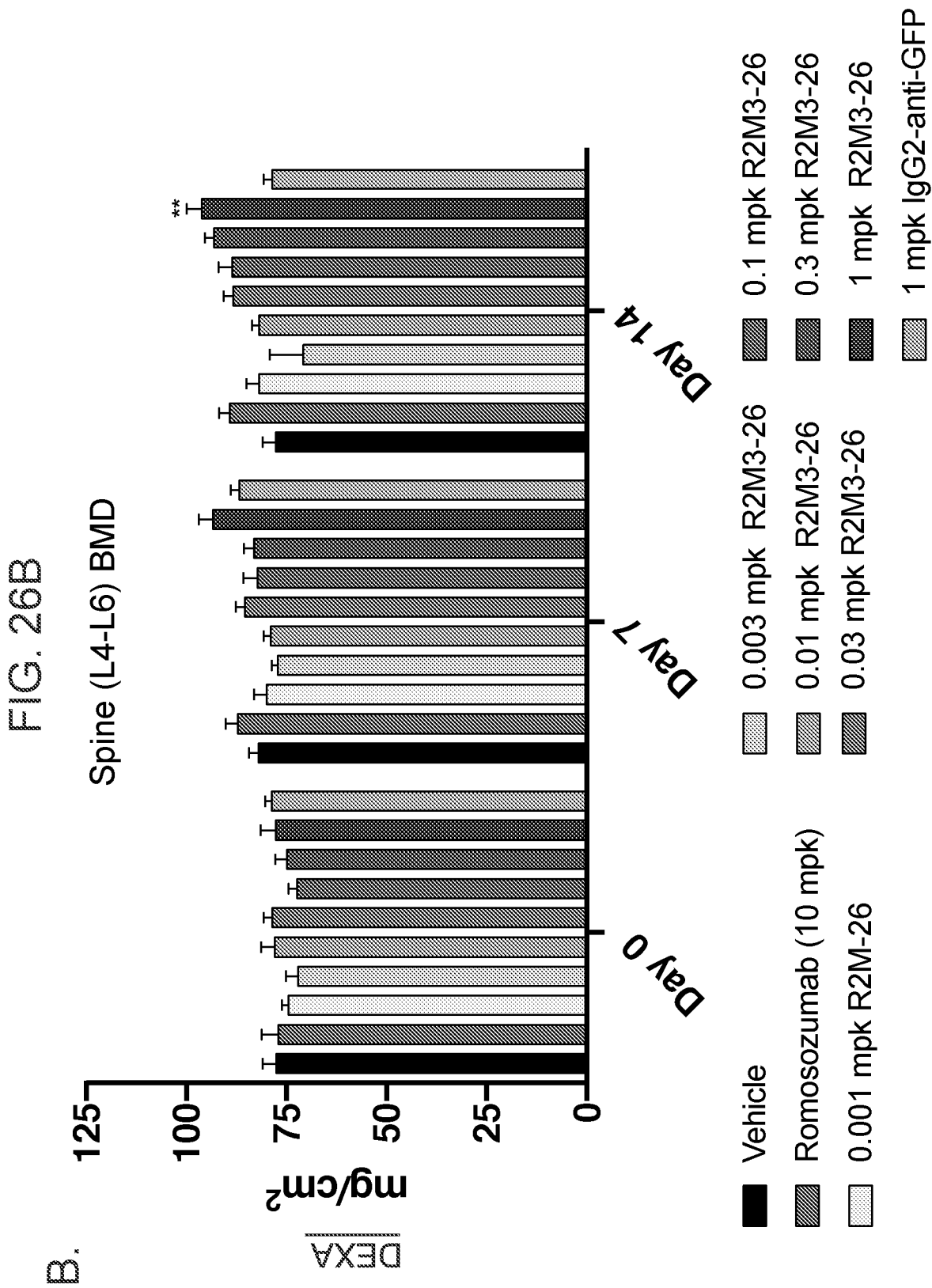


FIG. 26C

Proximal tibia μ CT

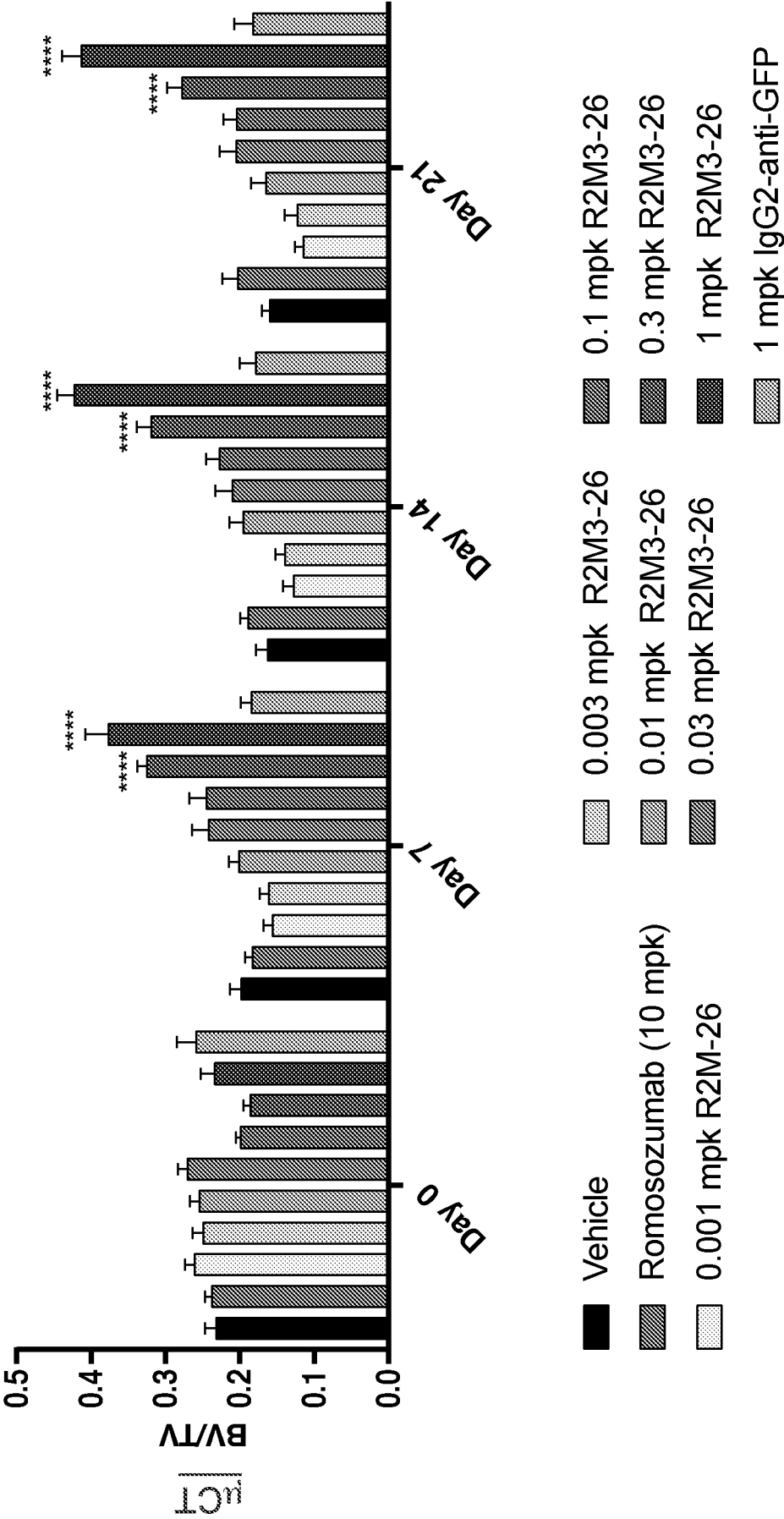
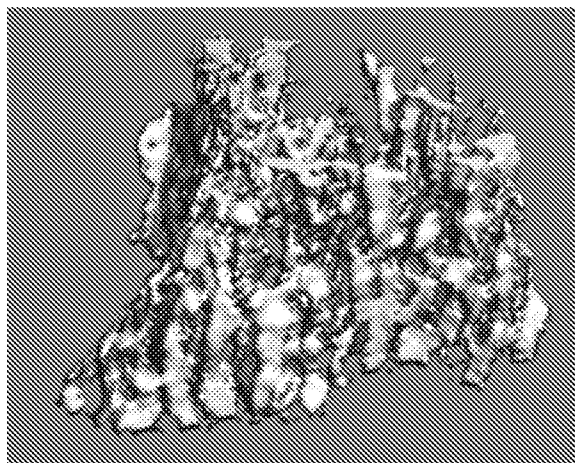


FIG. 26D

D.

Vehicle



1 mpk R2M3-26

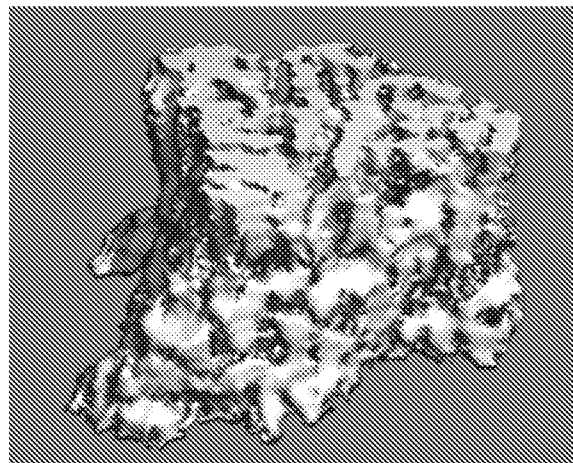
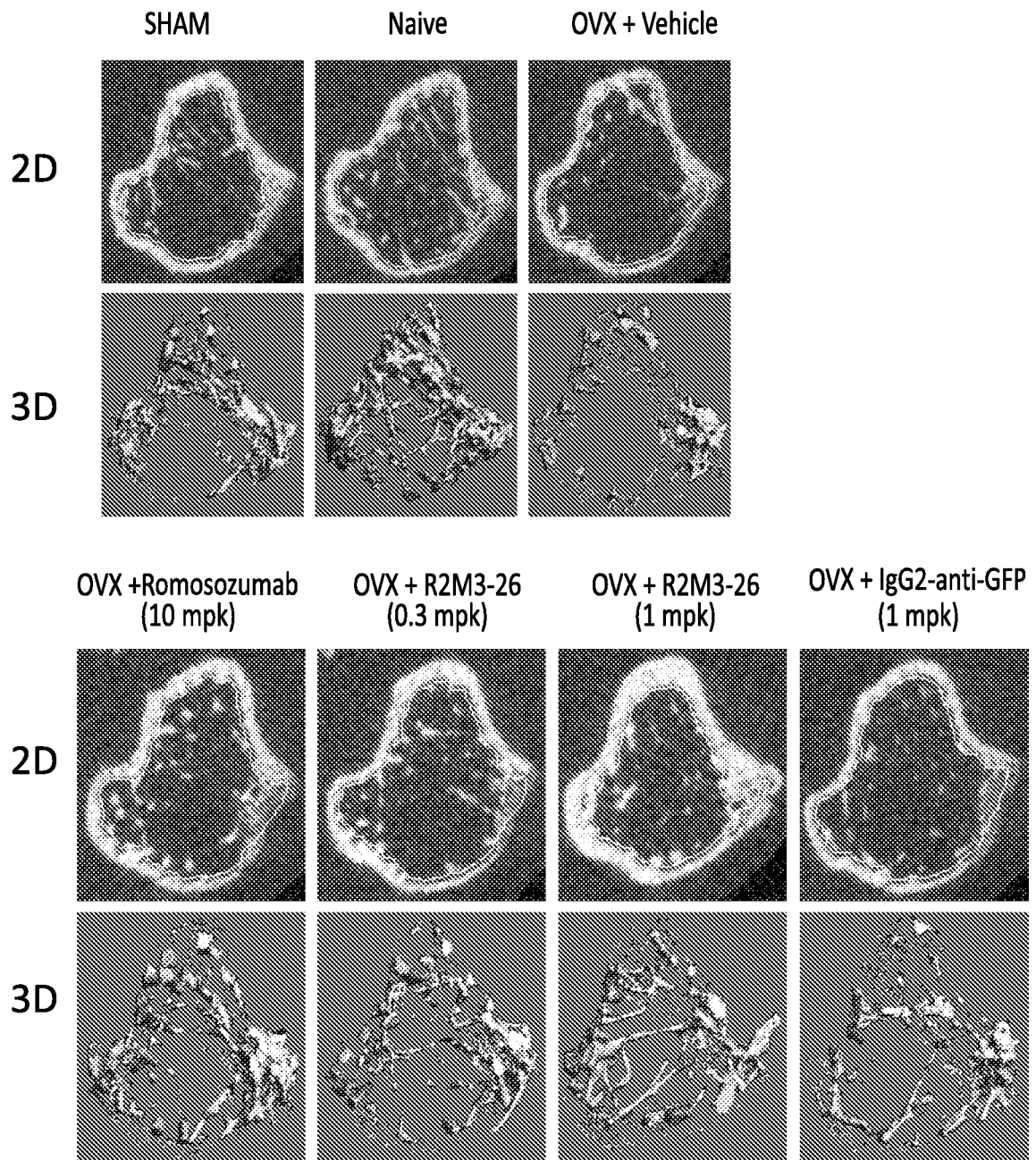


FIG. 27A

A.

Day 21

B.

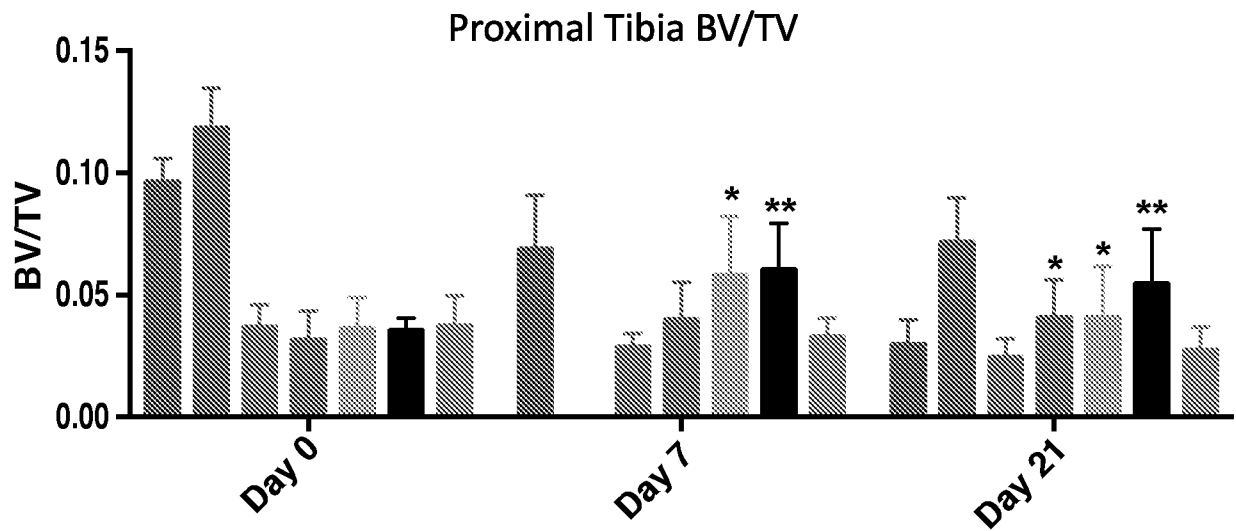
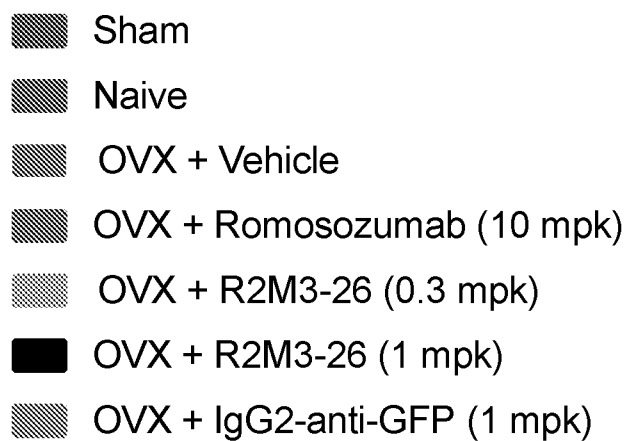
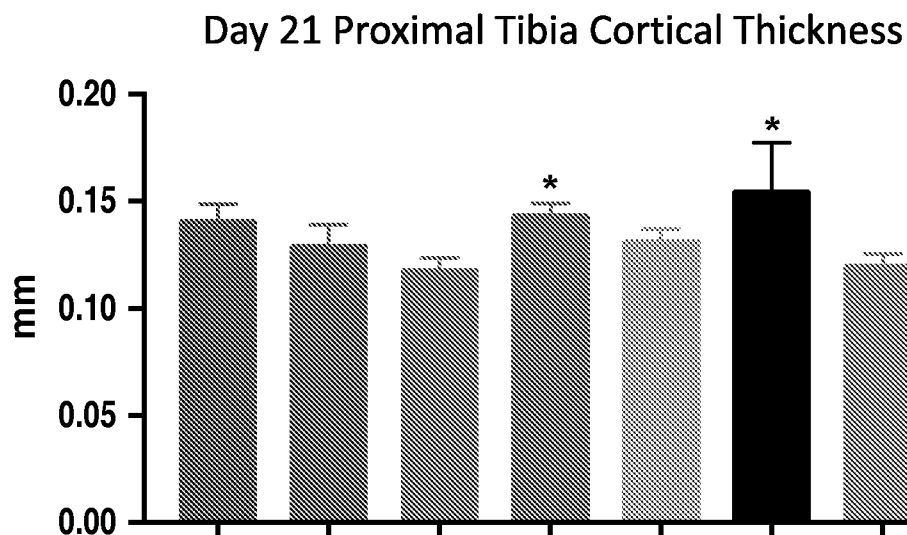


FIG. 27B

C.



*P value <0.05

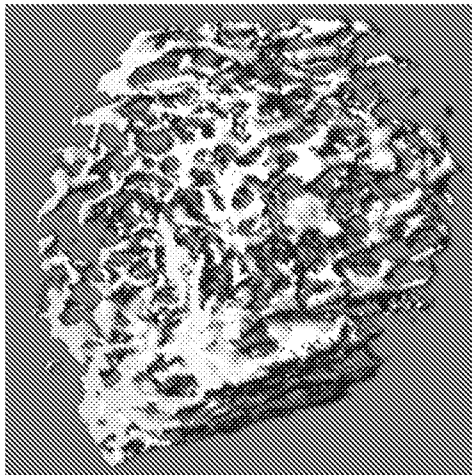
** P value <0.0001 Compared to OVX + Veh

FIG. 27C

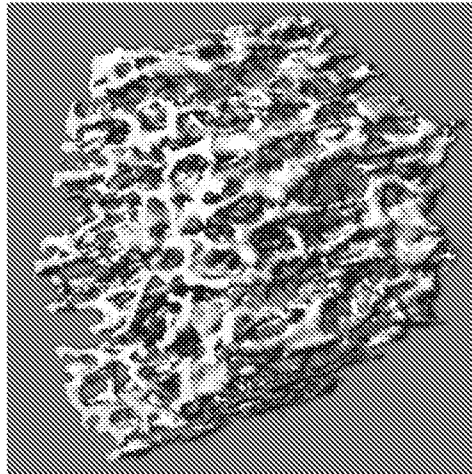
A.

FIG. 28A

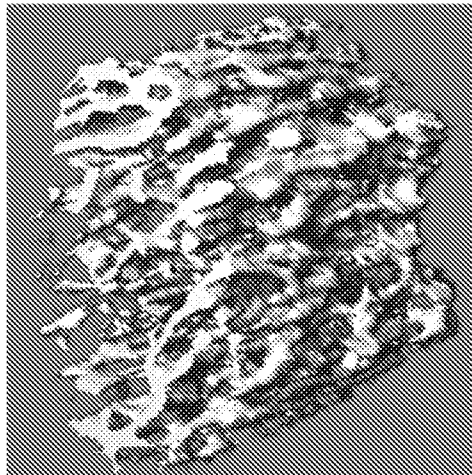
Vehicle



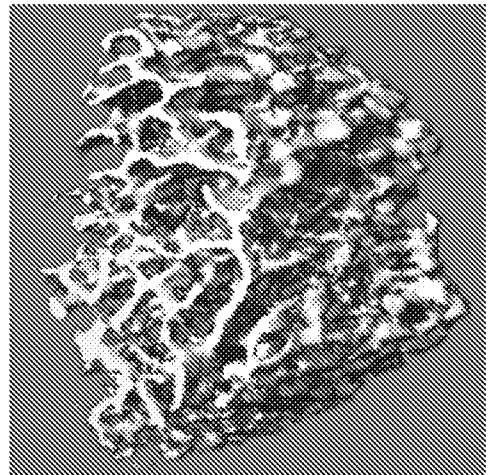
IgG1-anti-GFP (1 mpk)



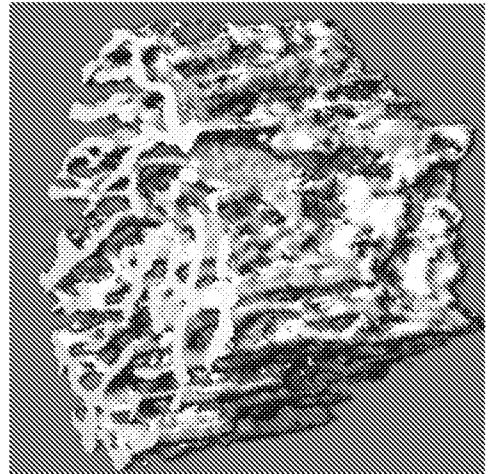
Romozozumab (30 mpk)



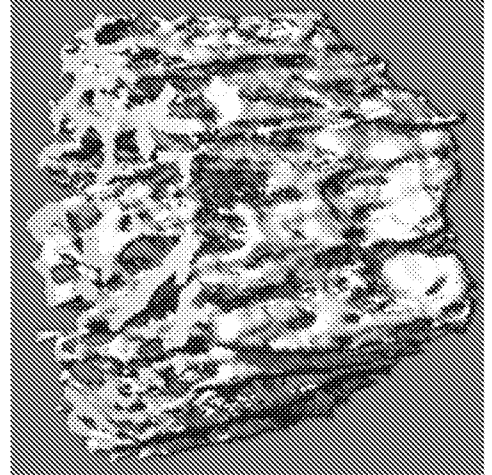
R2M3-26 (0.03 mpk)



R2M3-26 (0.3 mpk)



R2M3-26 (1 mpk)



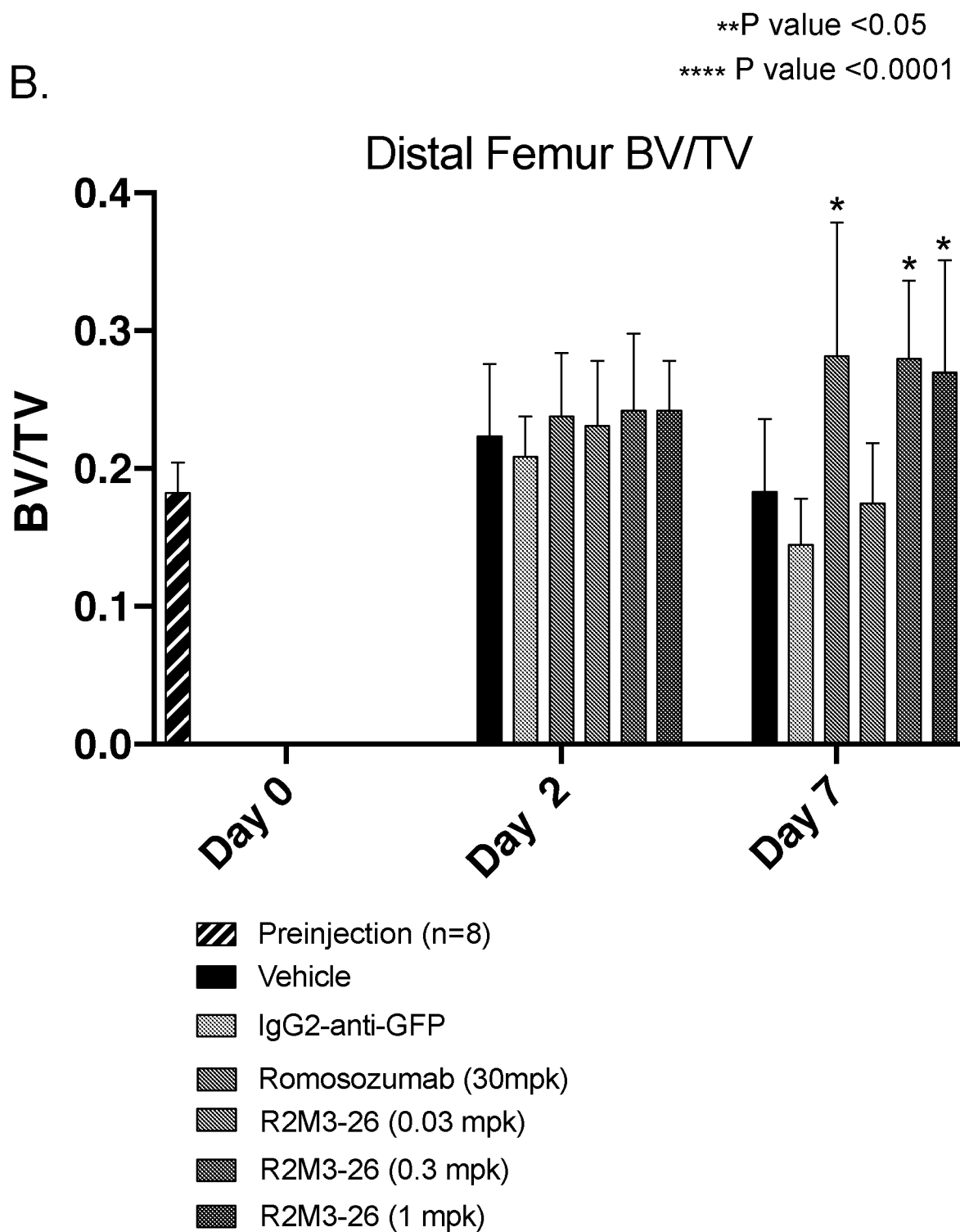


FIG. 28B

C.

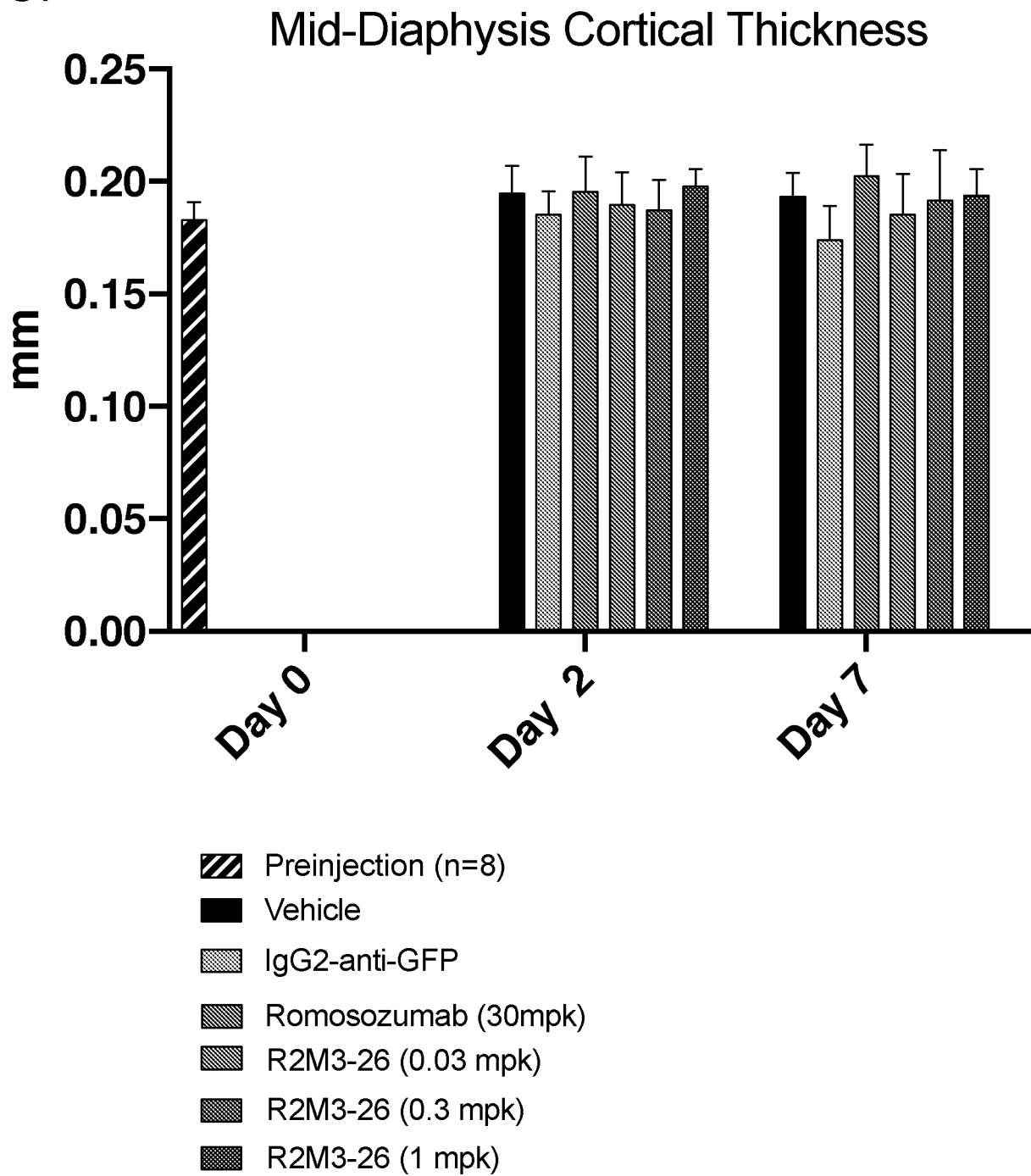


FIG. 28C

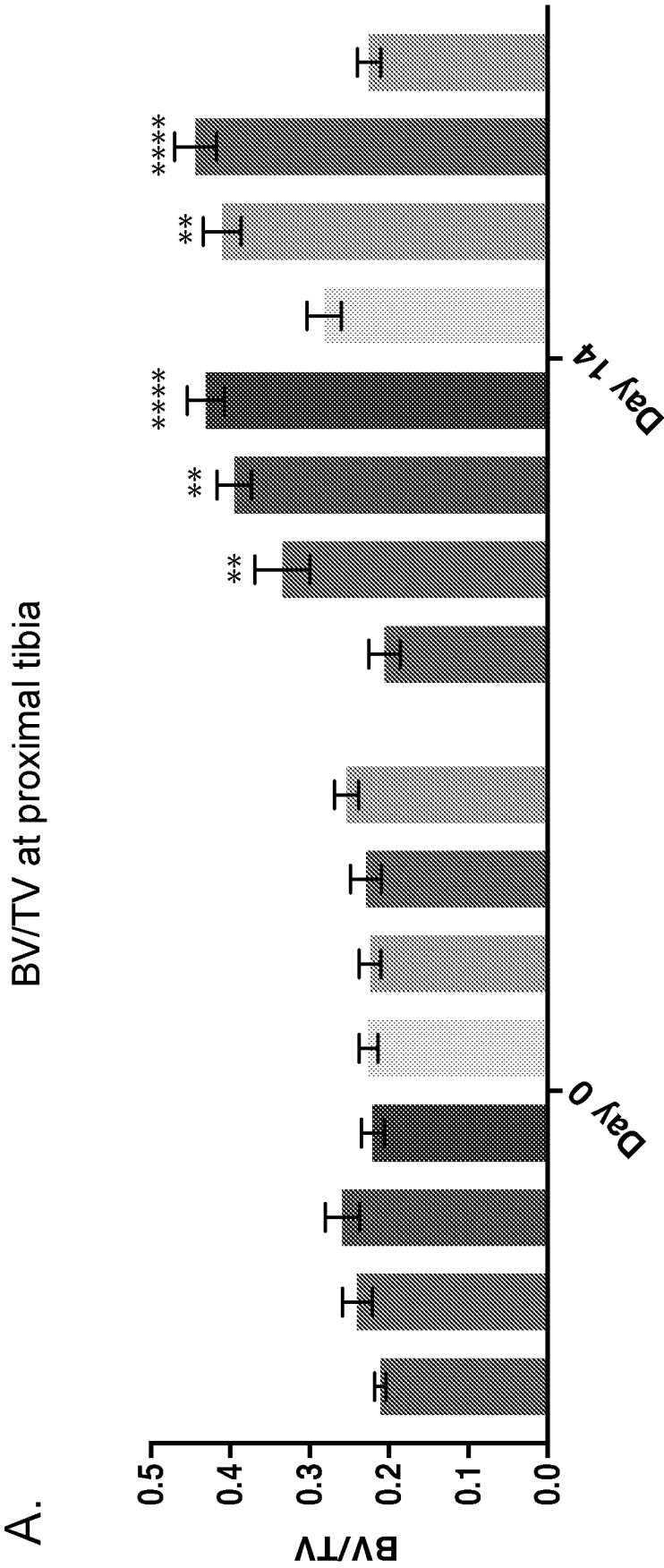


FIG. 29A

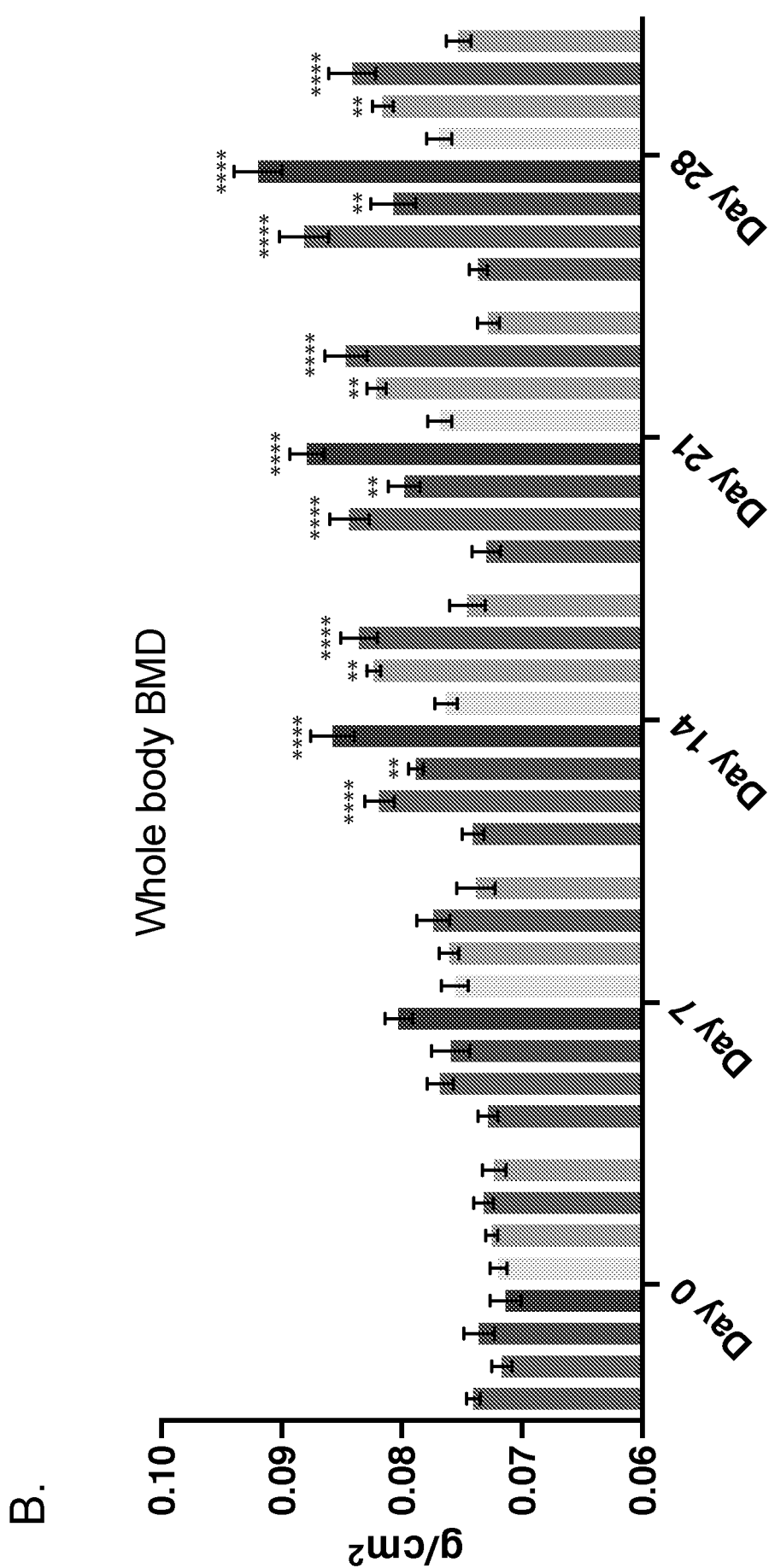


FIG. 29B

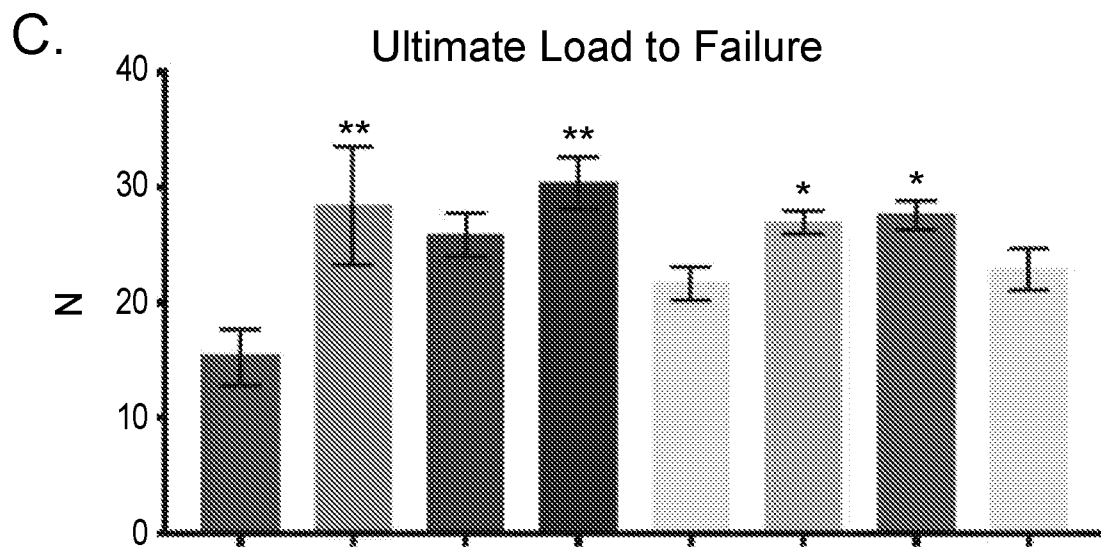


FIG. 29C

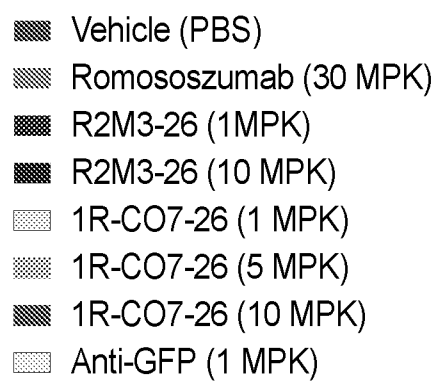
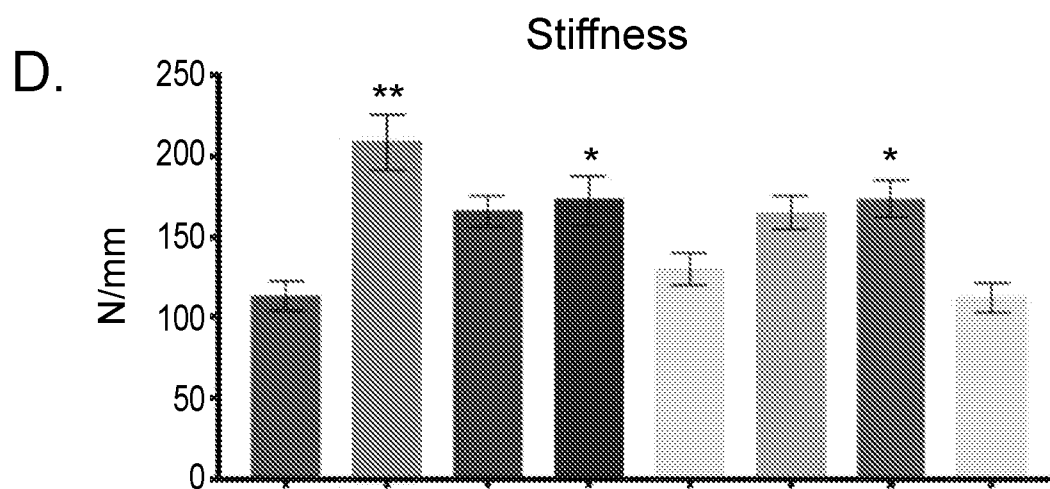


FIG. 29D

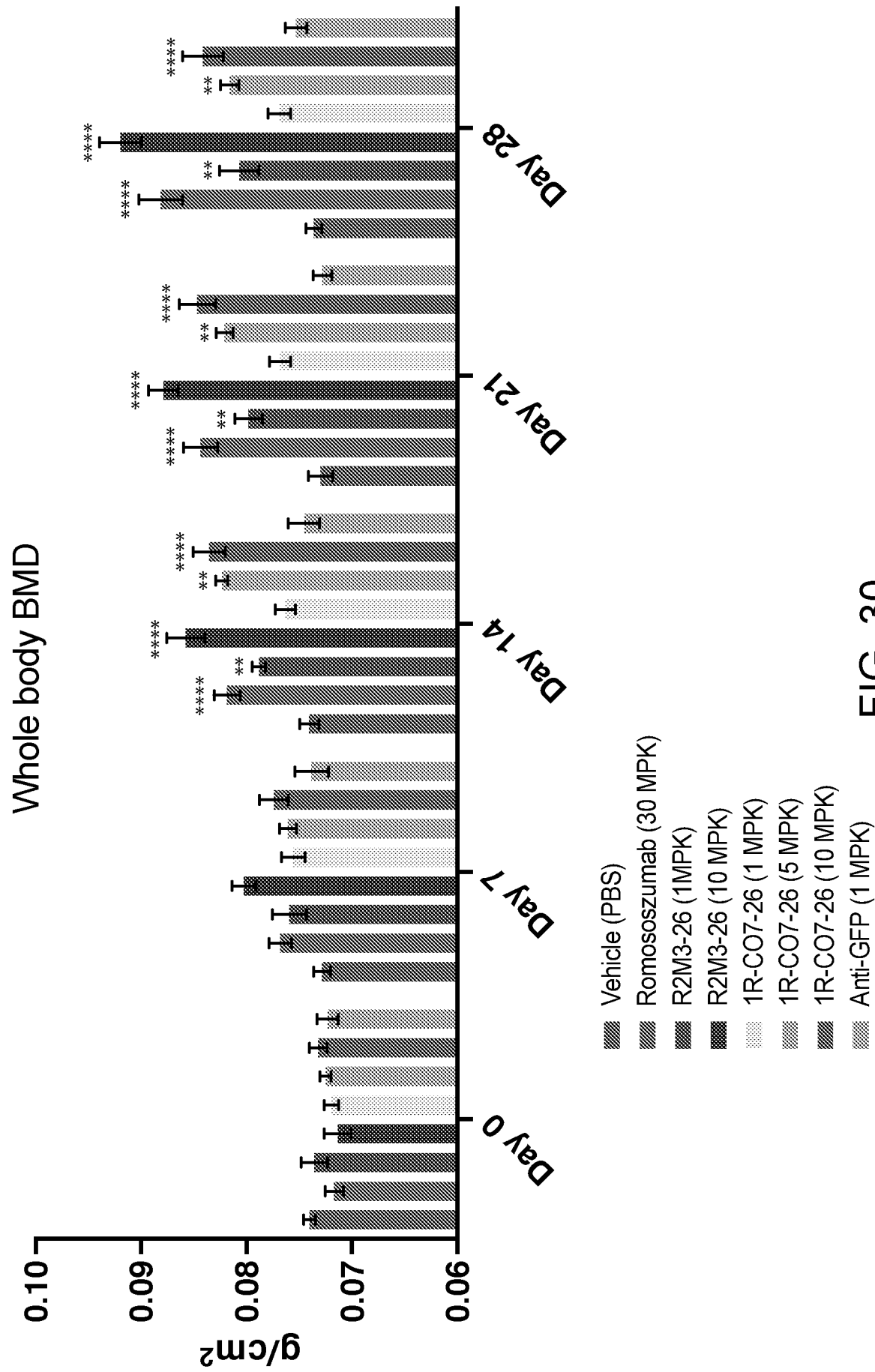


FIG. 30

FIG. 31

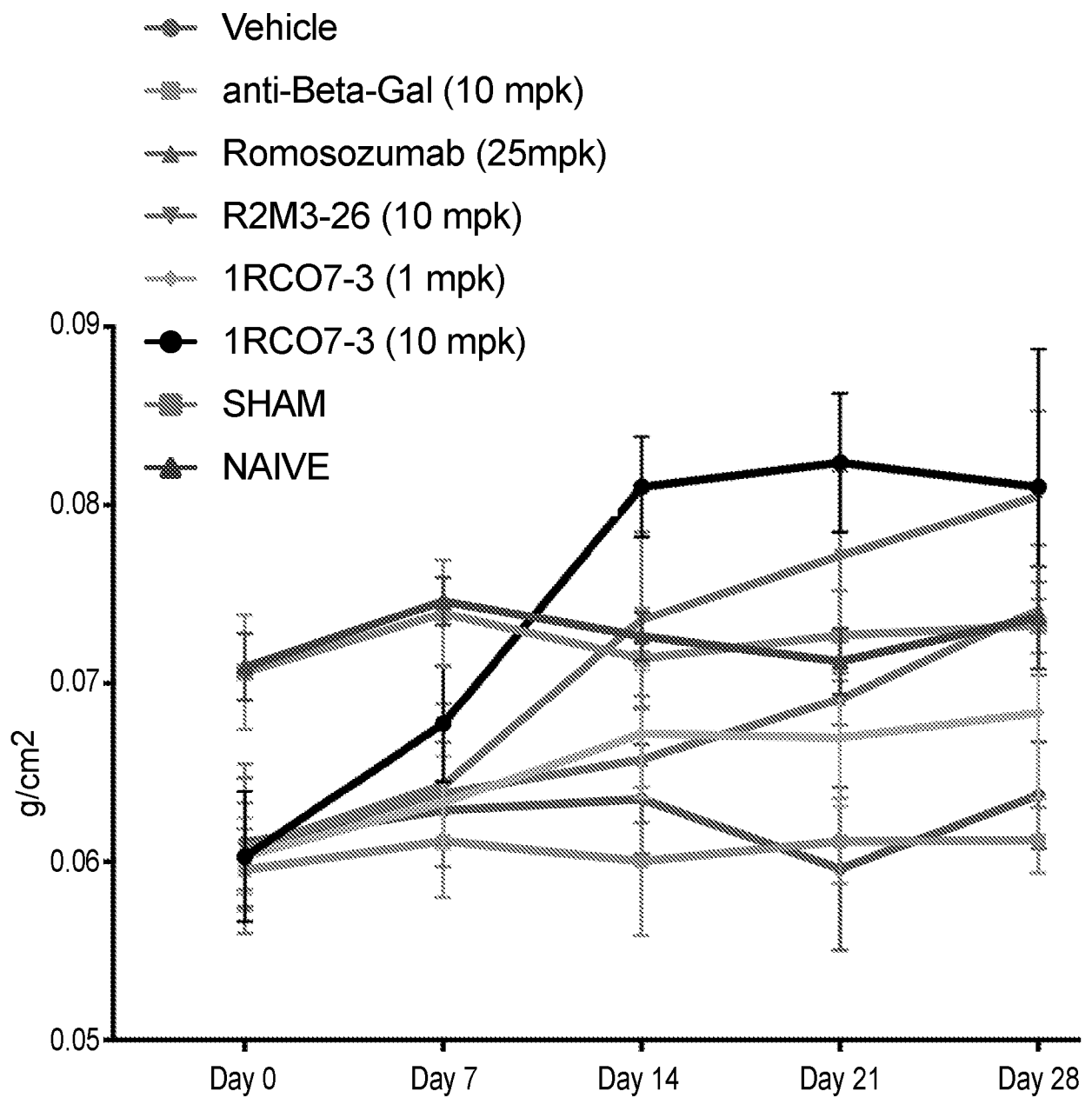


FIG. 32

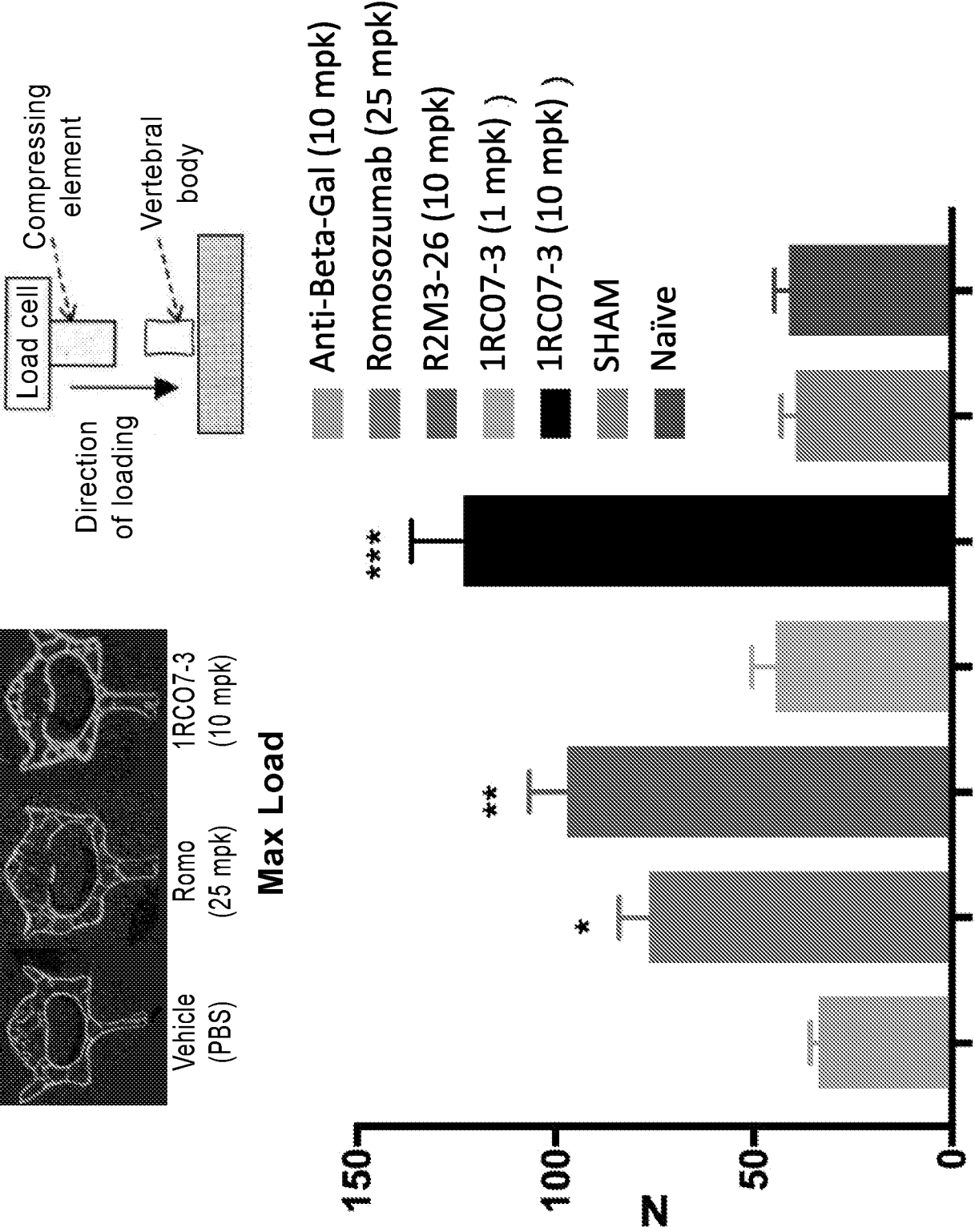


FIG. 33A 1 week of treatment

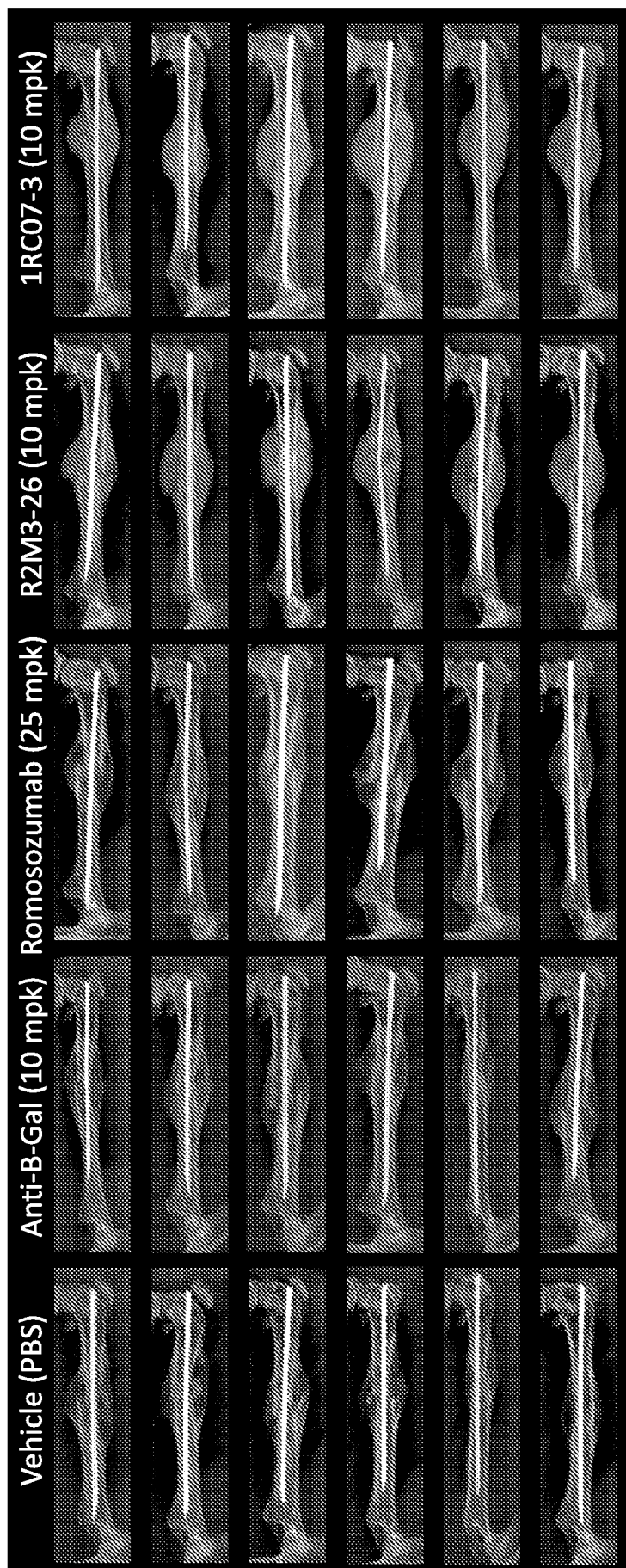


FIG. 33B 6 week of treatment

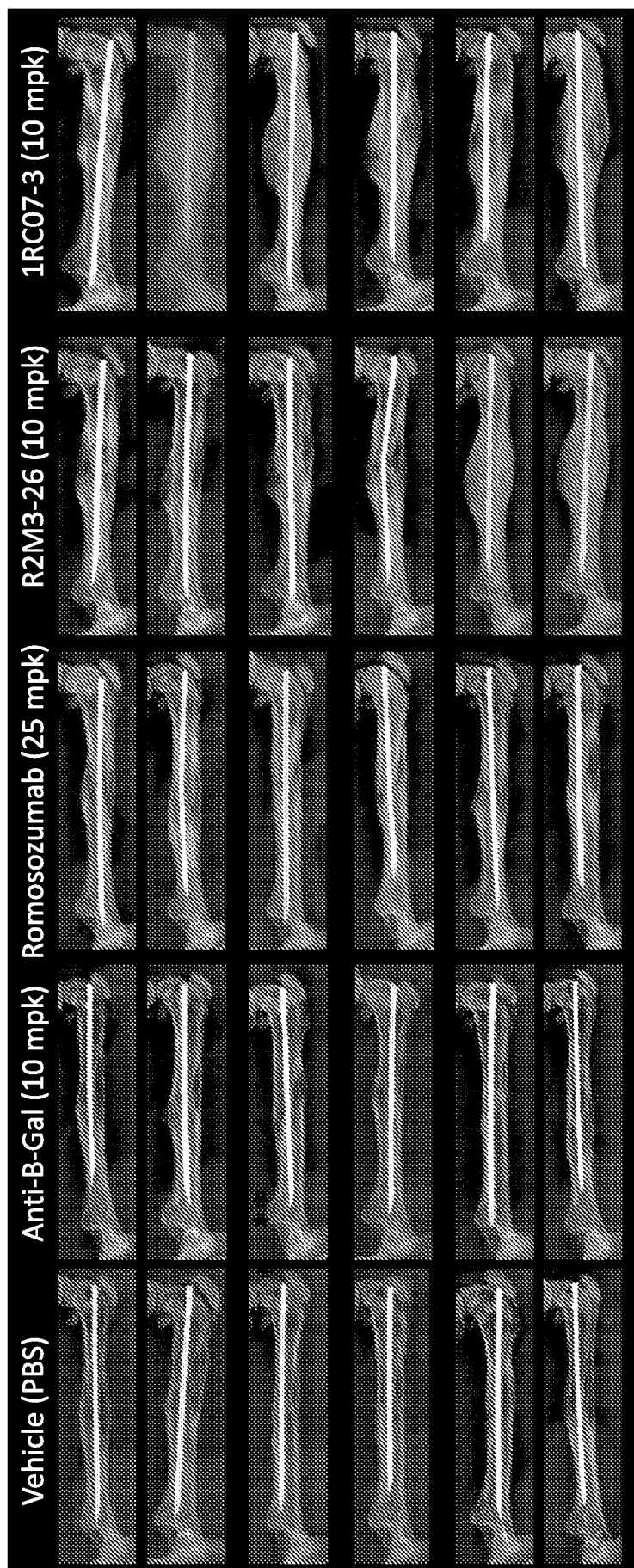


FIG. 33C

Day 42 BMD Contralateral Femur

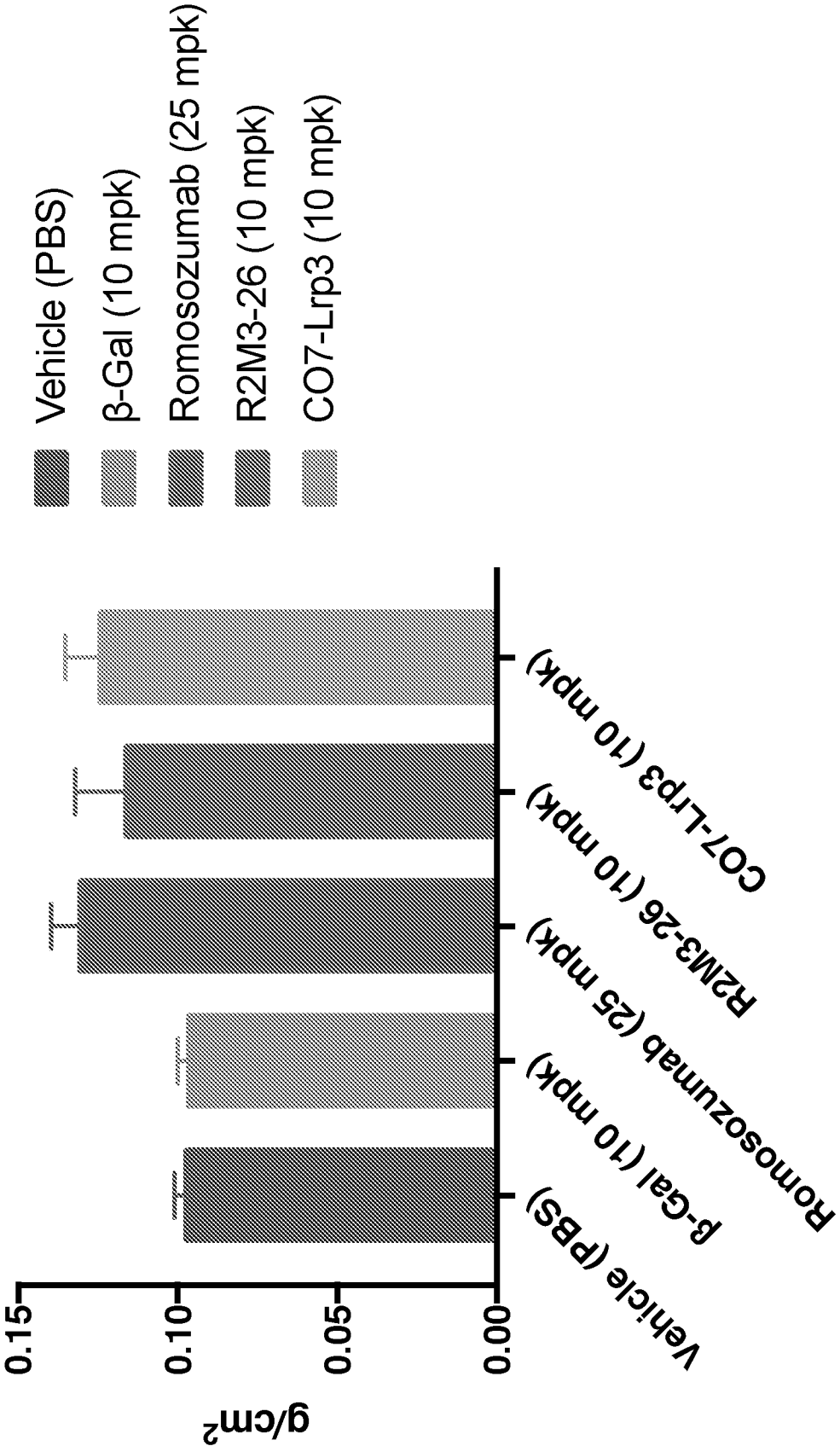
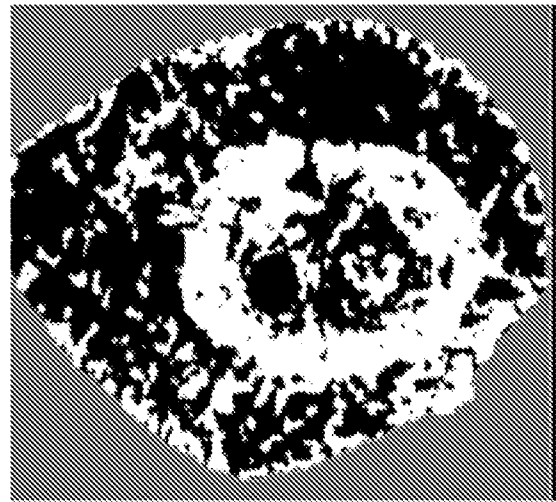
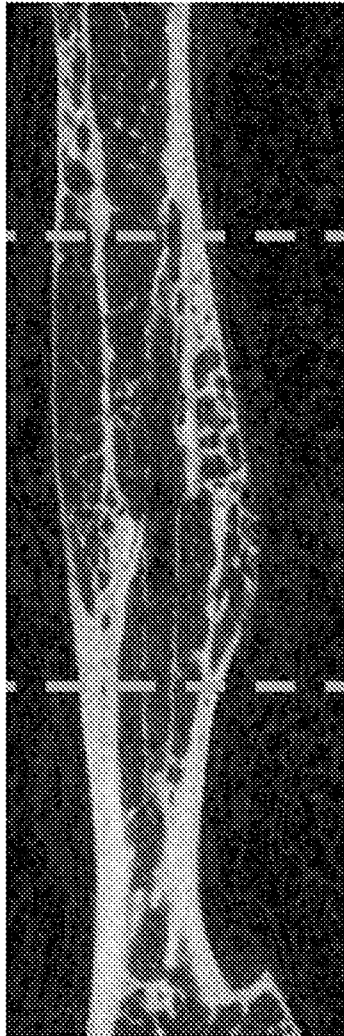
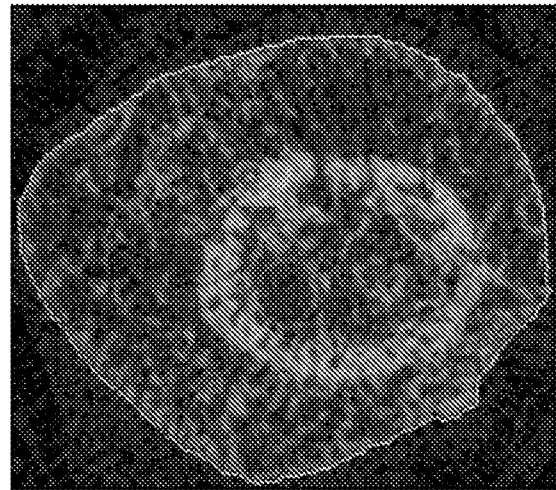


FIG. 33D

400 SLICES, 4.2 MM



Bone area



Tissue area

FIG. 33D (contd.)

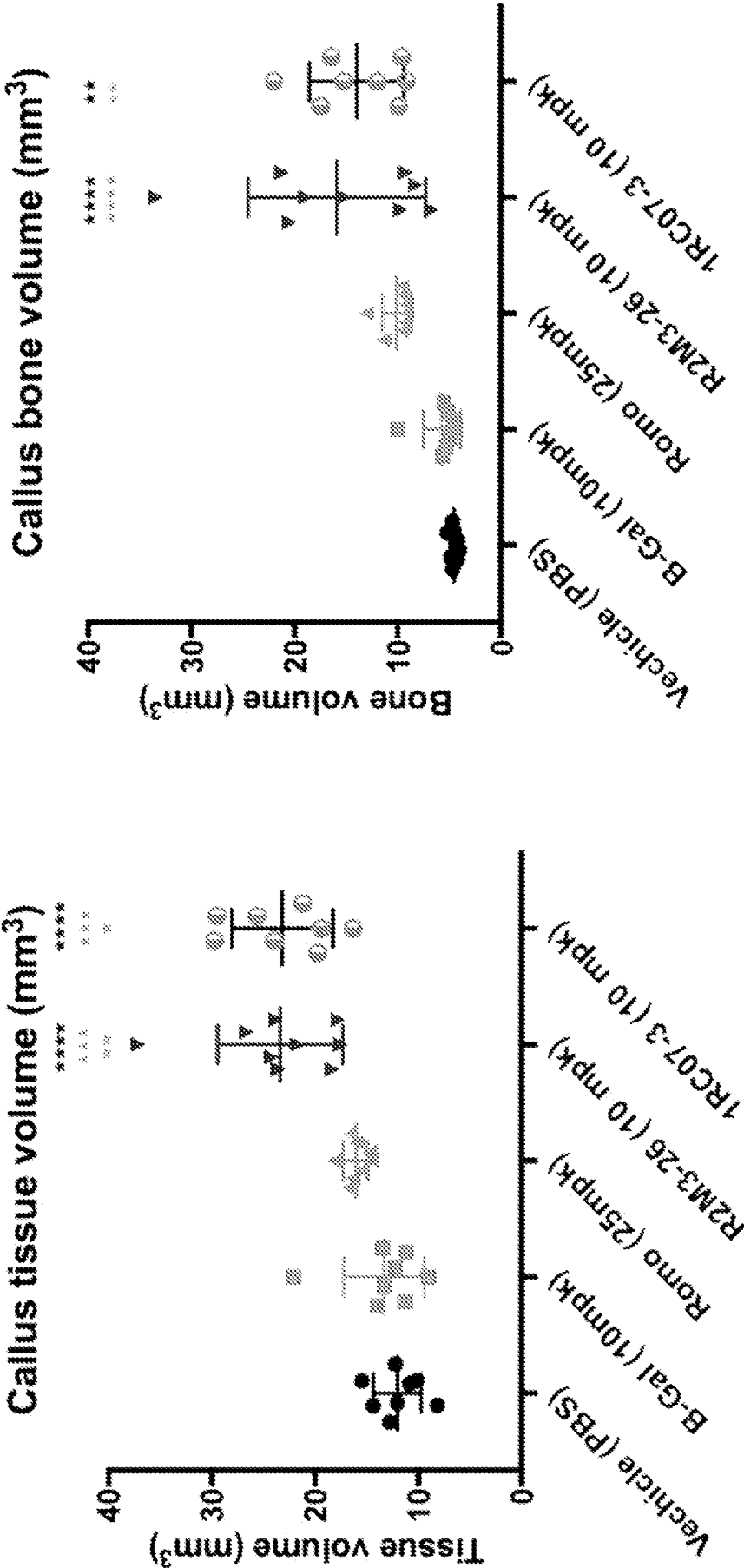


FIG. 33D (contd.)

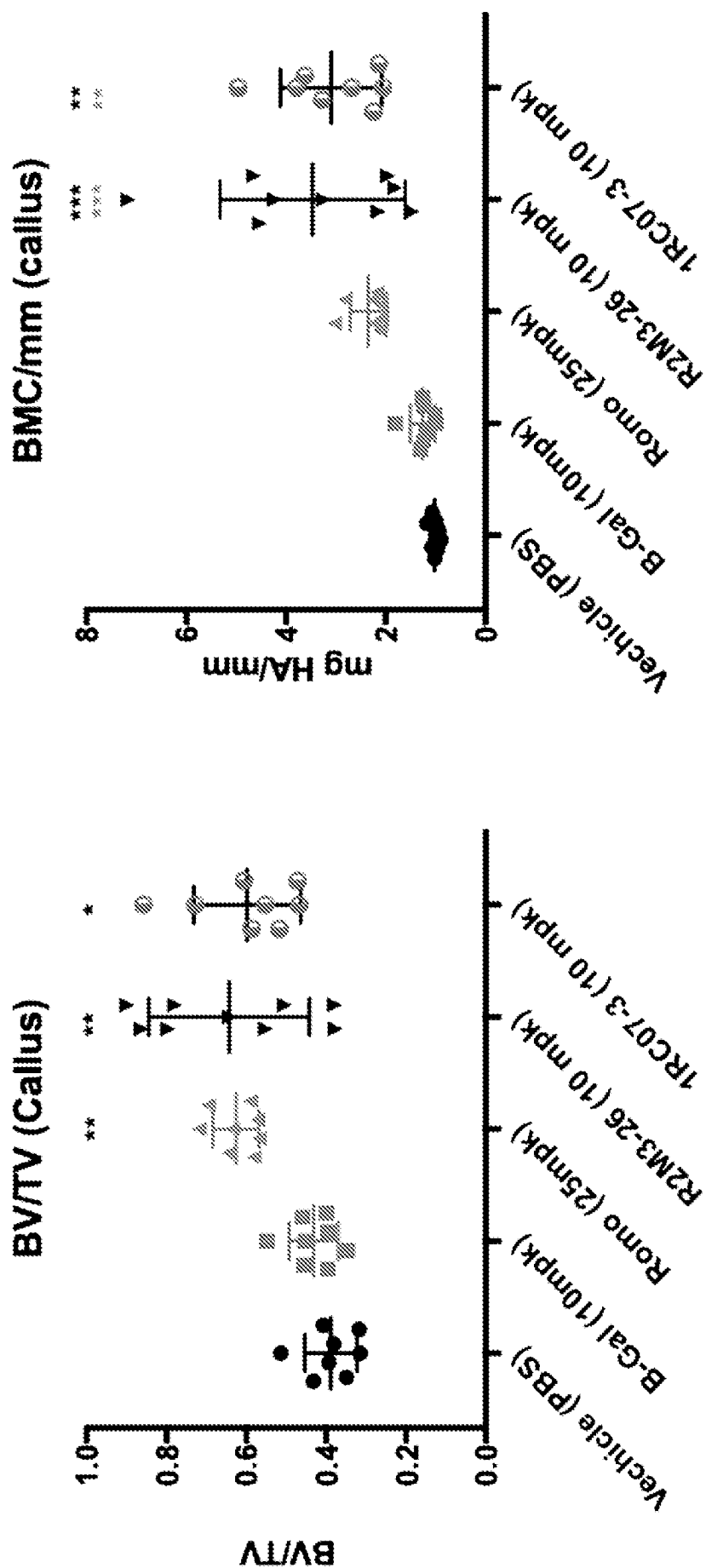


FIG. 33D (contd.)

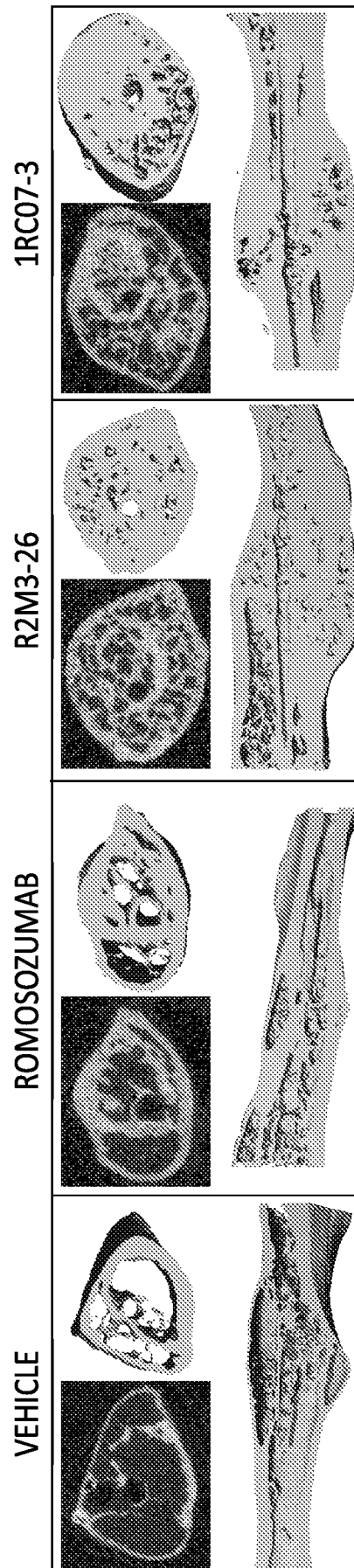


FIG. 34

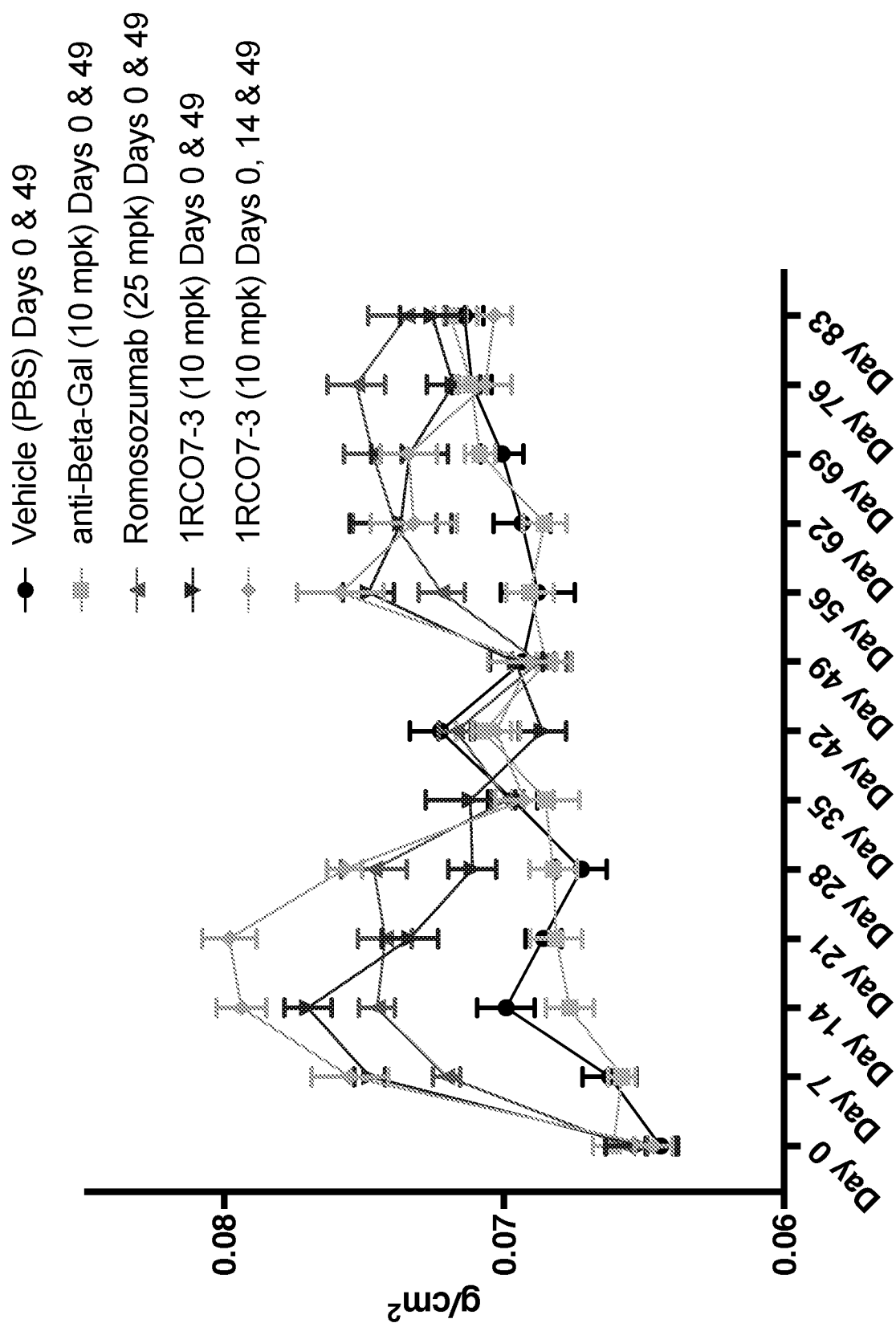


FIG. 35

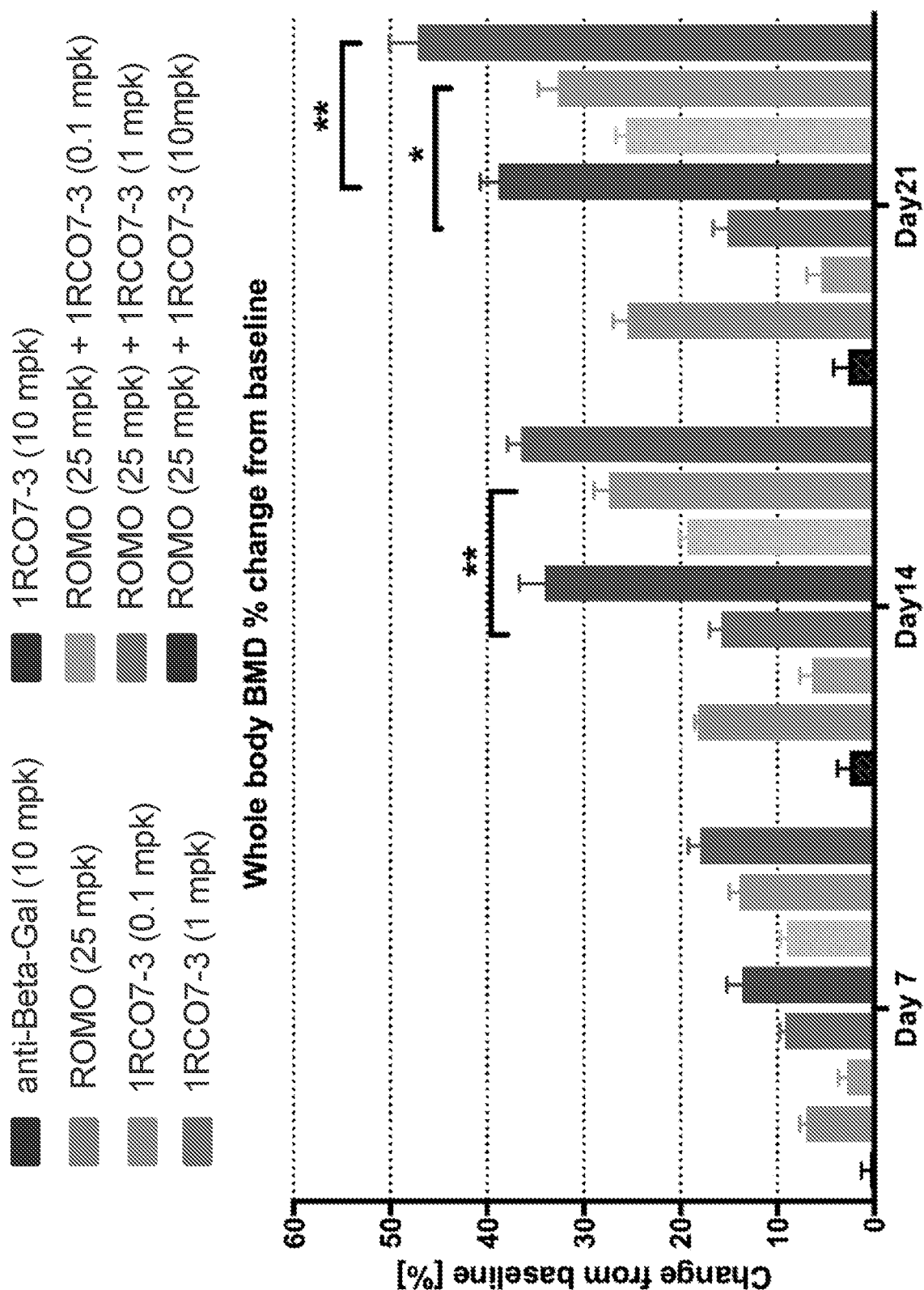
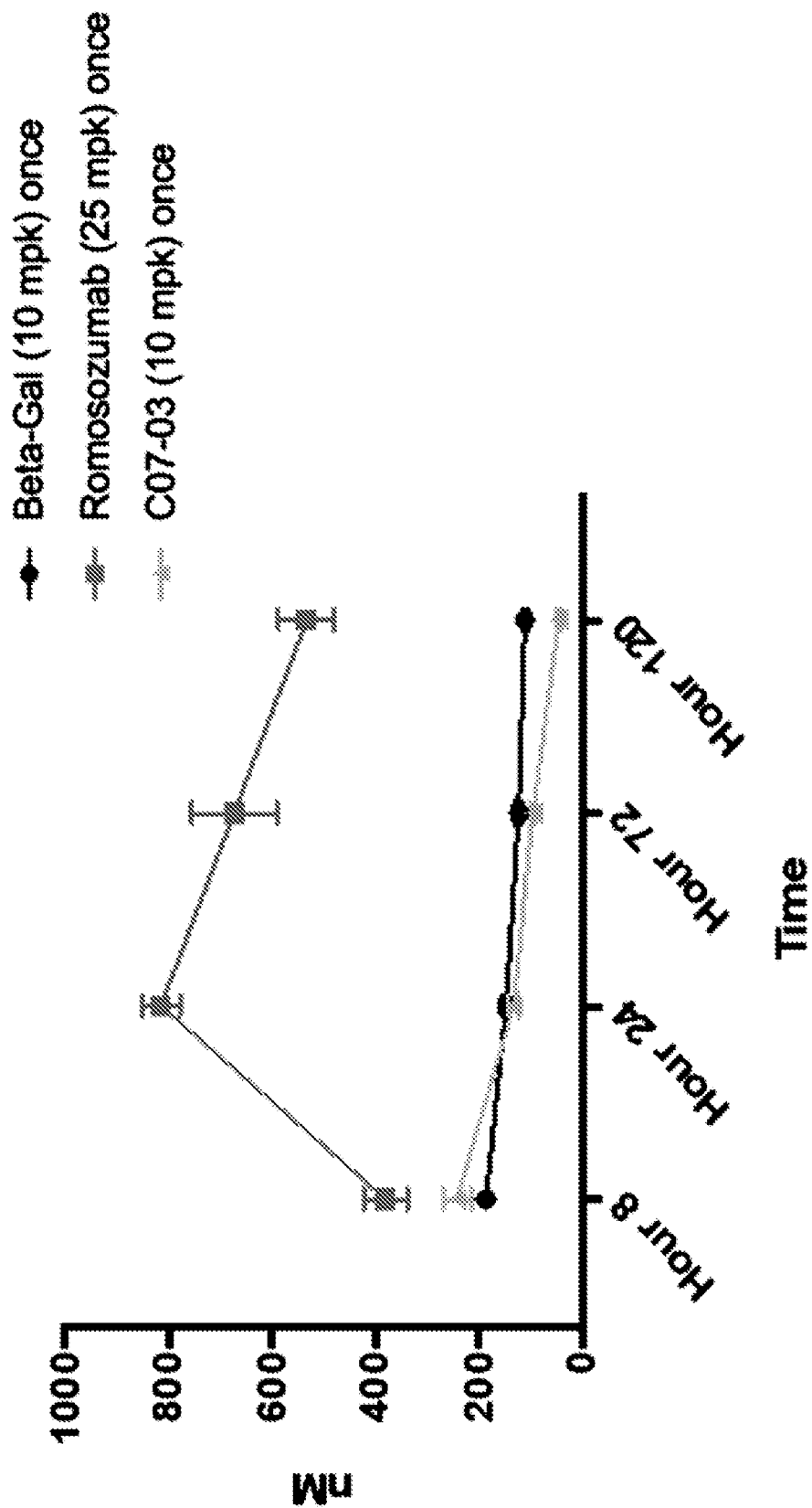


FIG. 36
Protein Serum Exposure



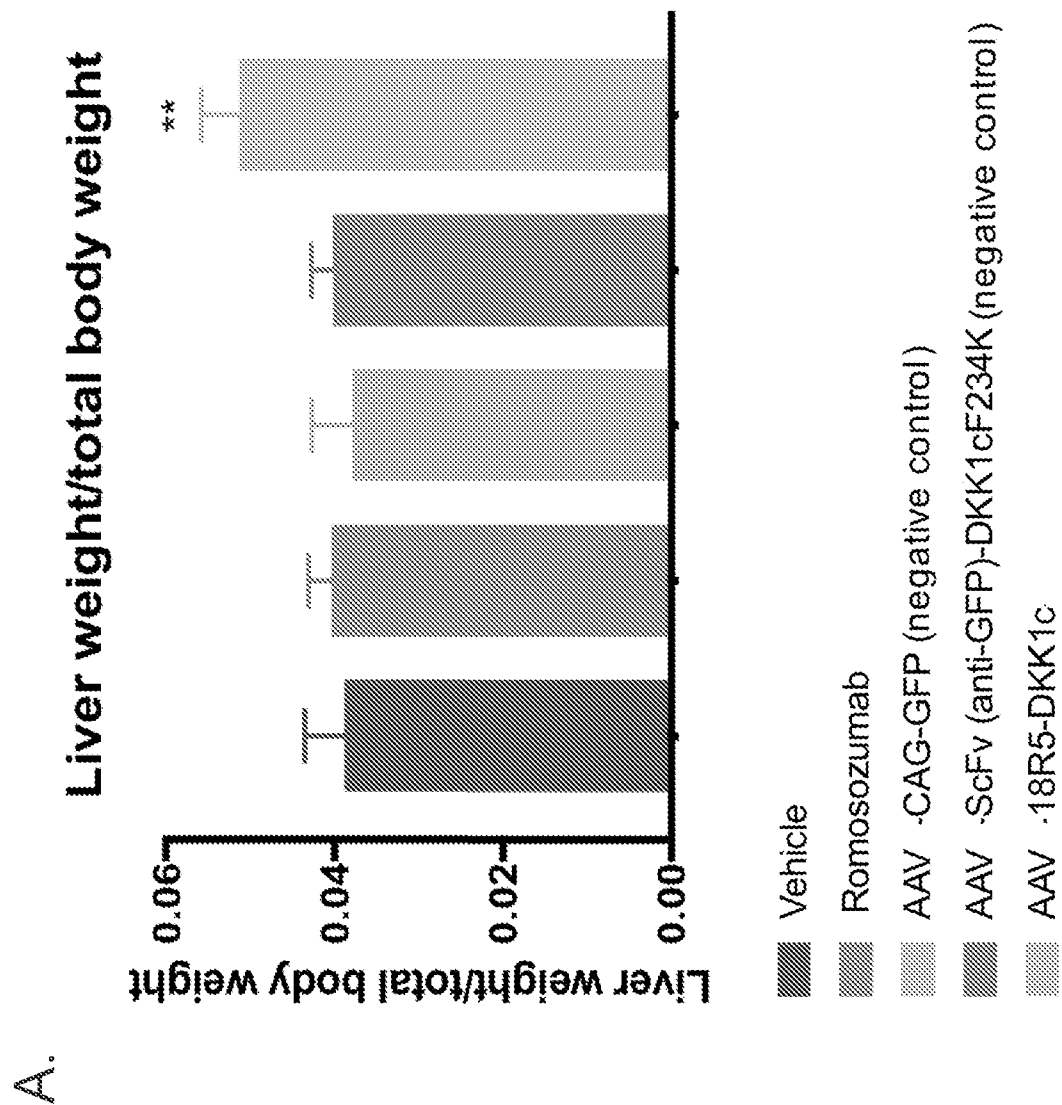


FIG. 37

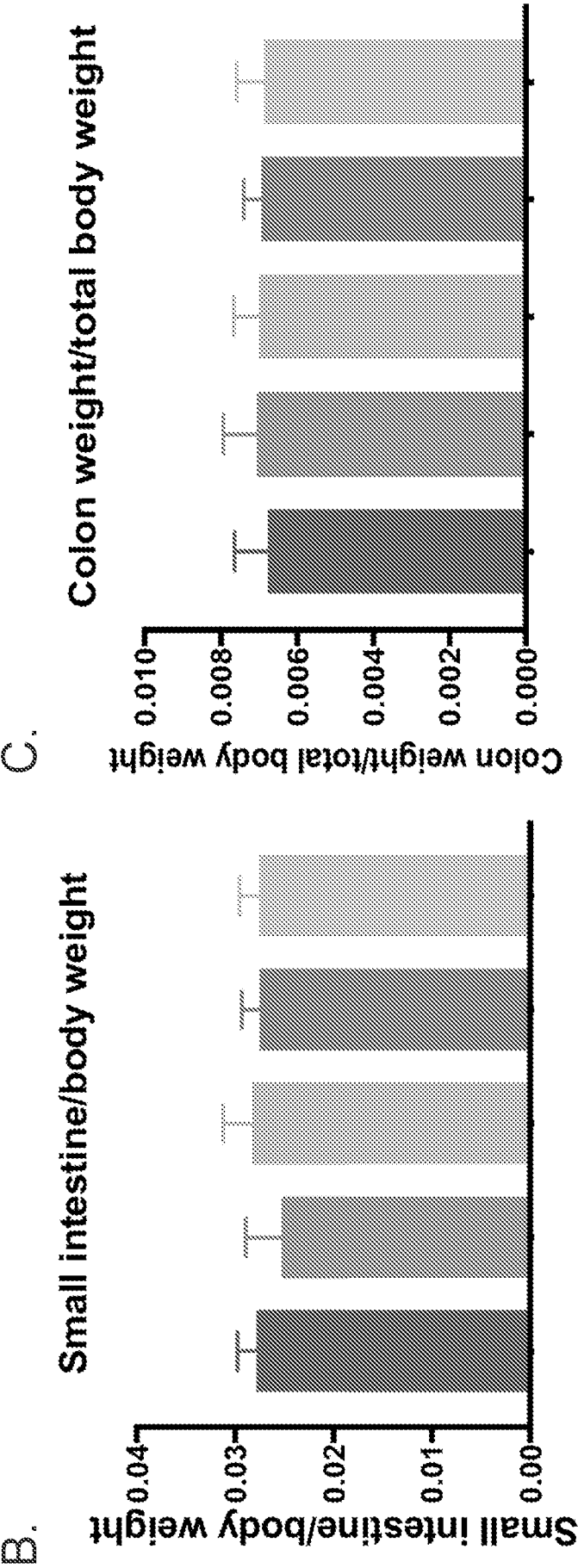
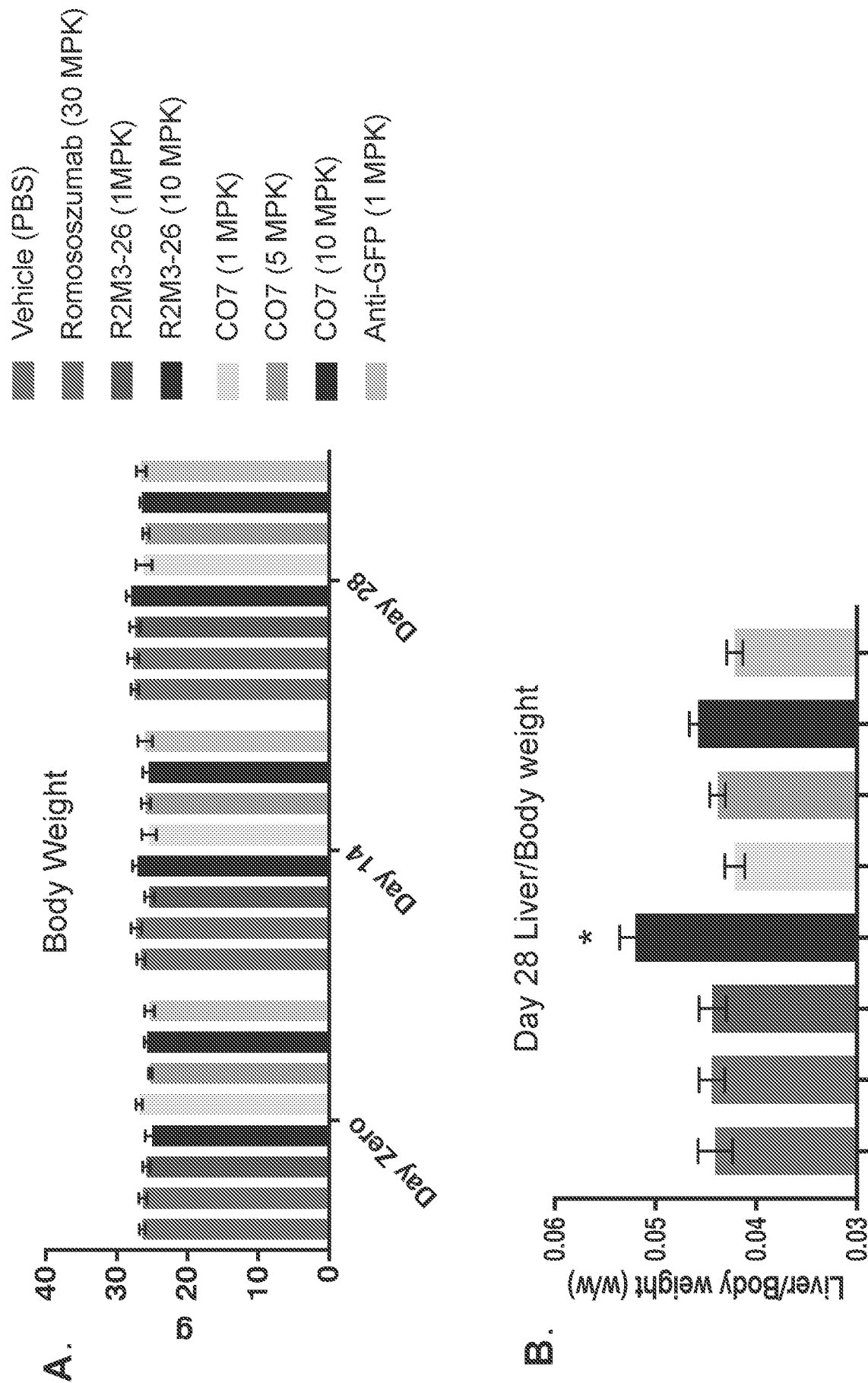


FIG. 37 (contd.)

FIG. 38



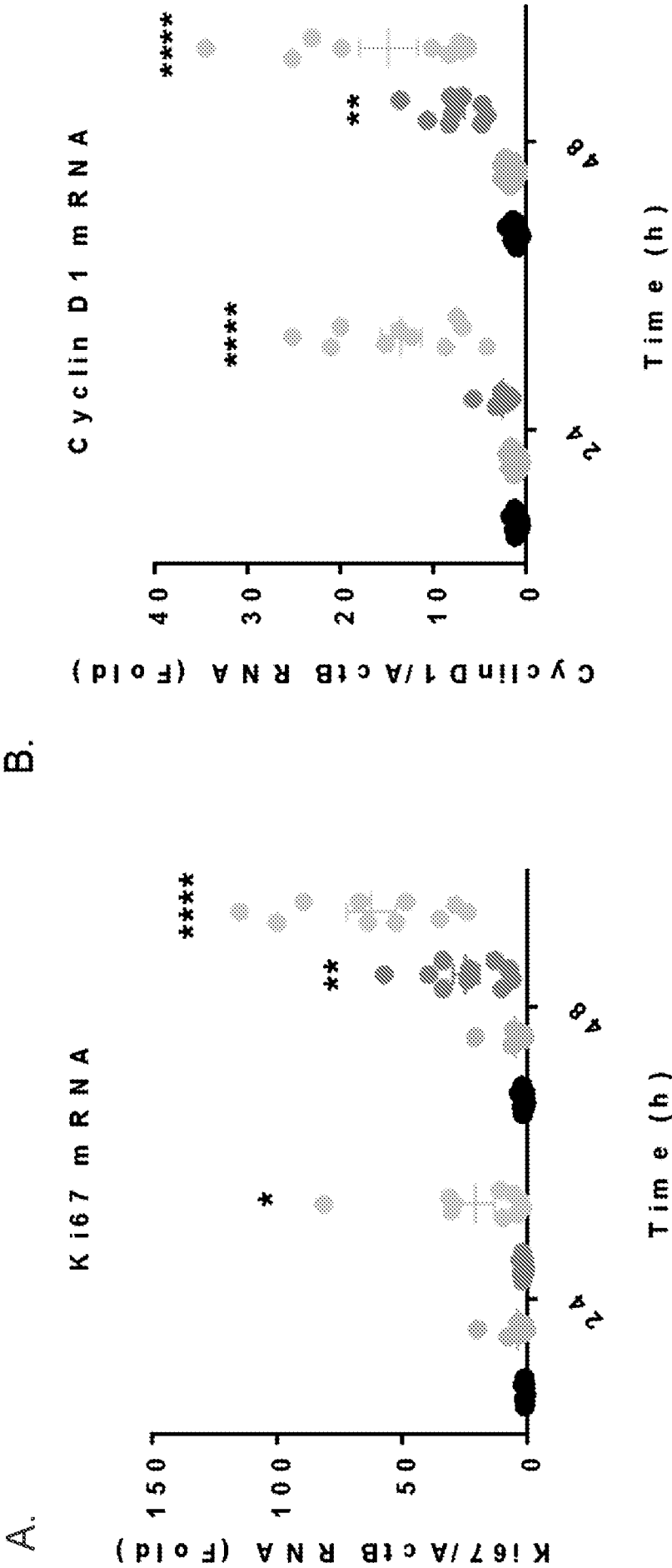


FIG. 39

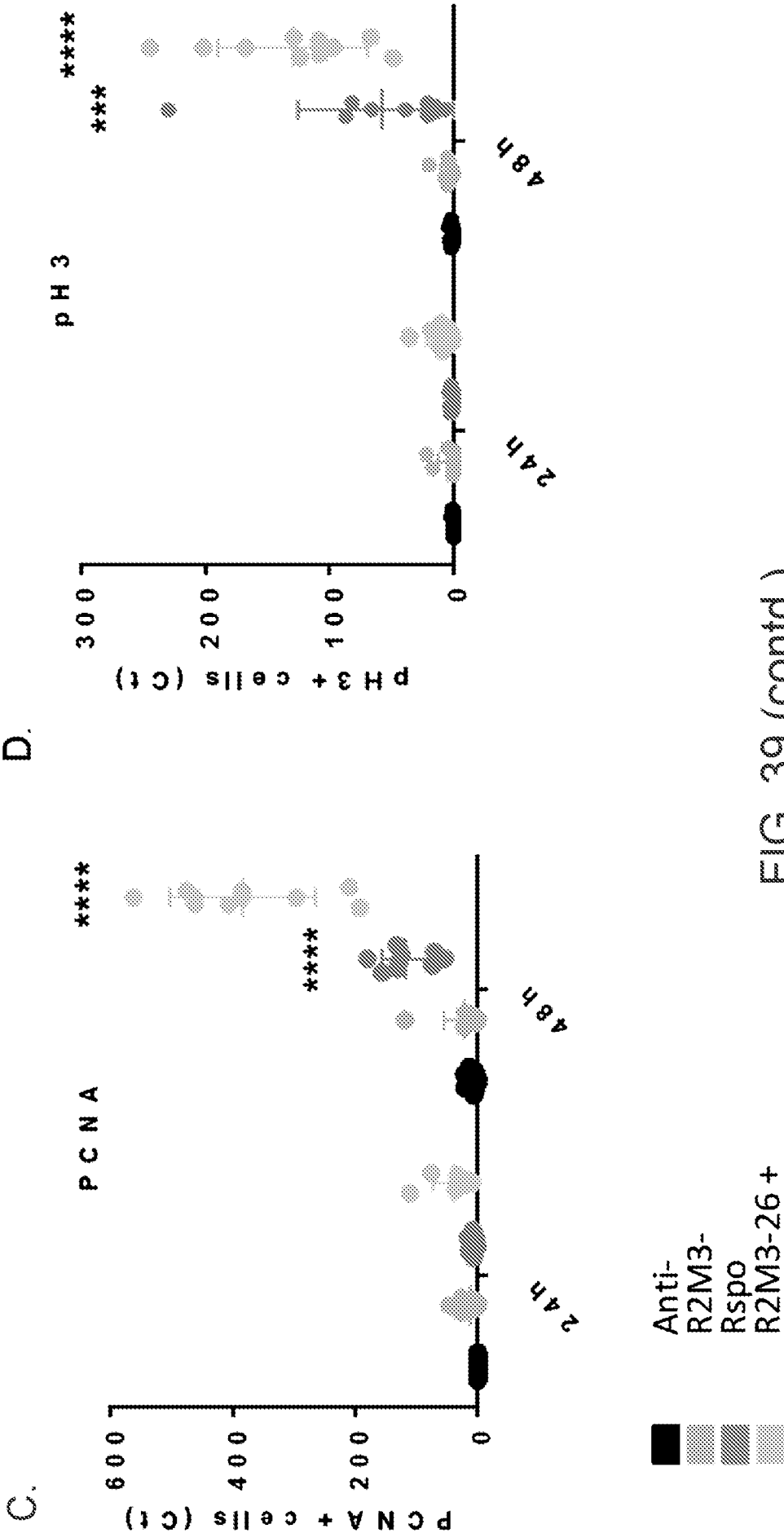
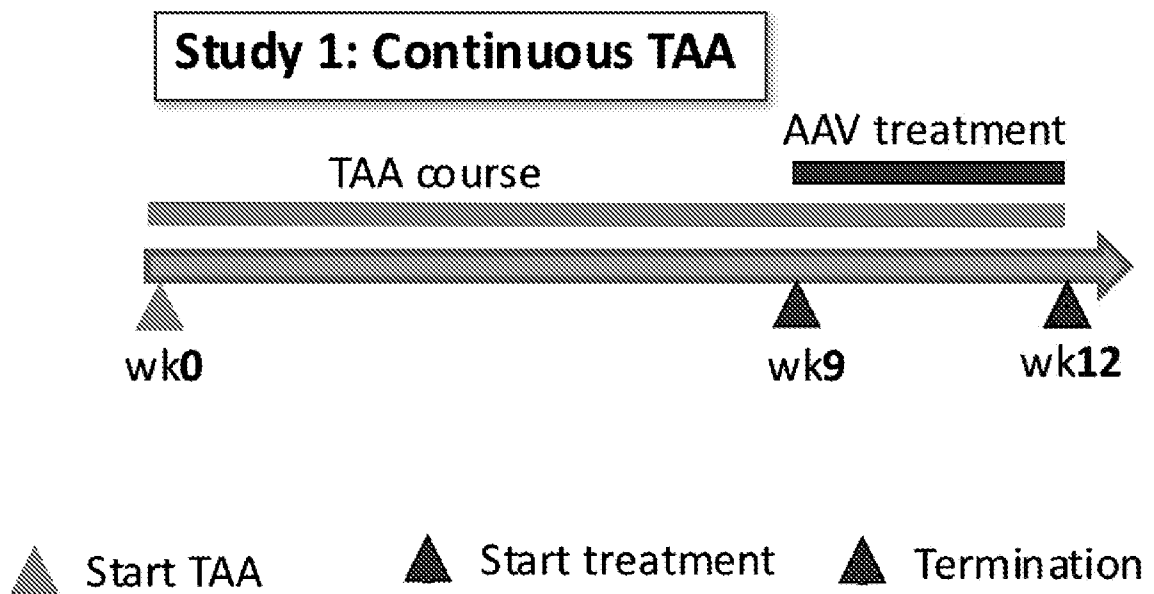


FIG. 39 (contd.)

FIG. 40A

A.



B.

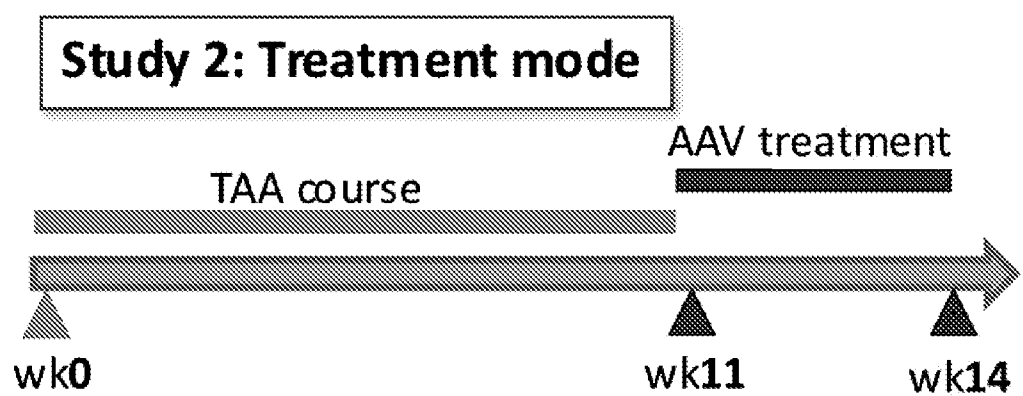


FIG. 40B

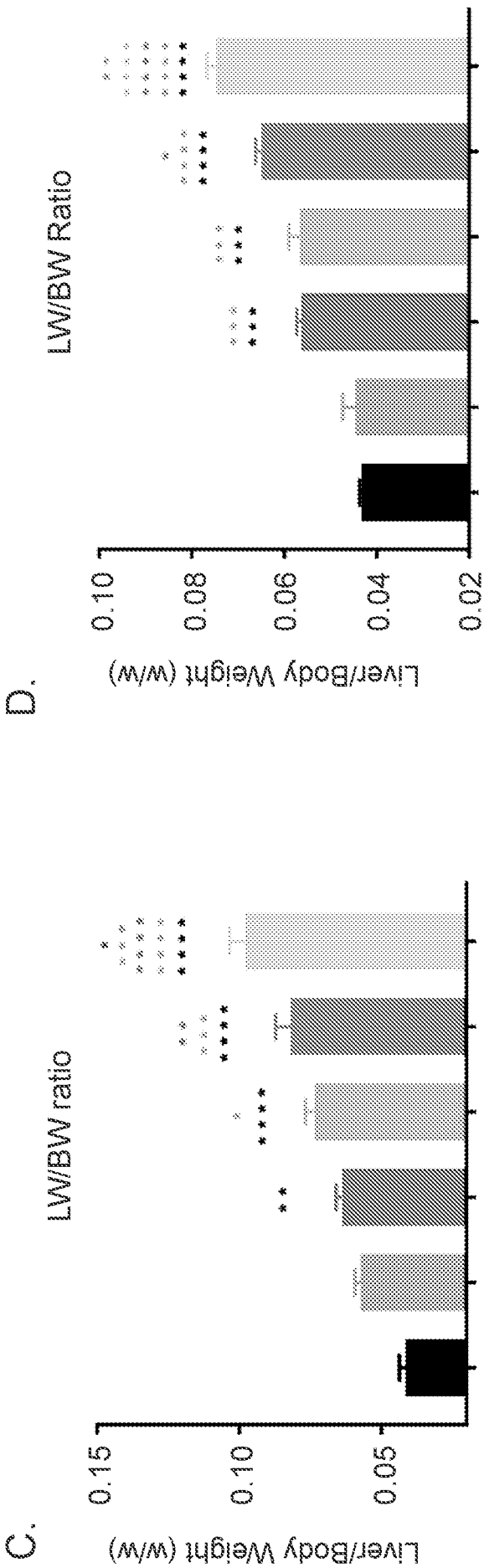


FIG. 40 (contd.)

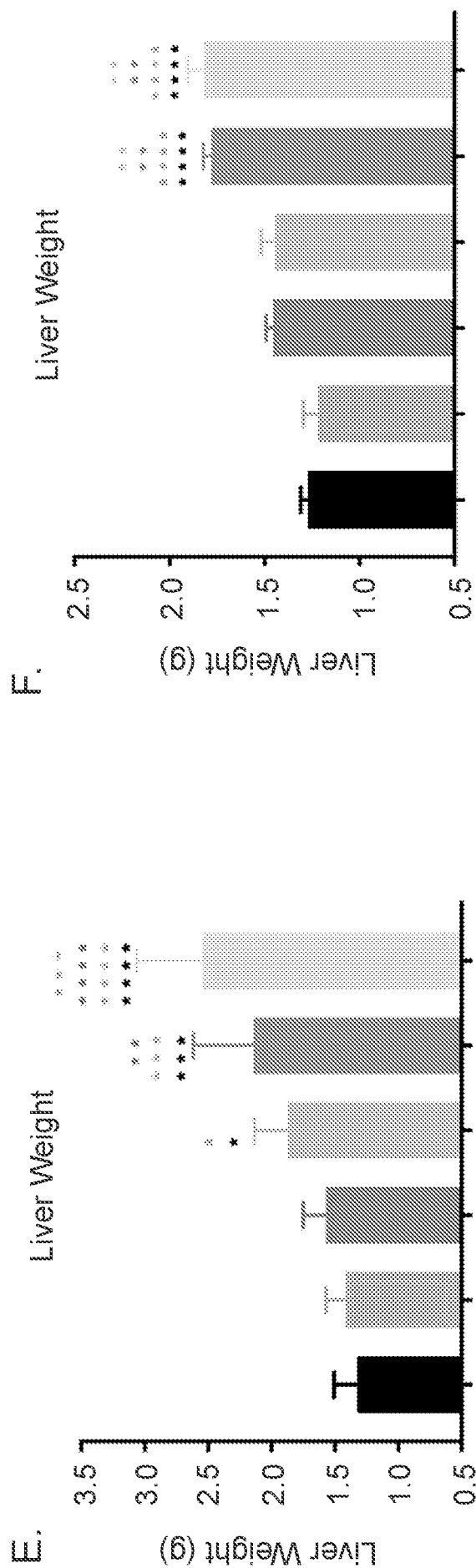
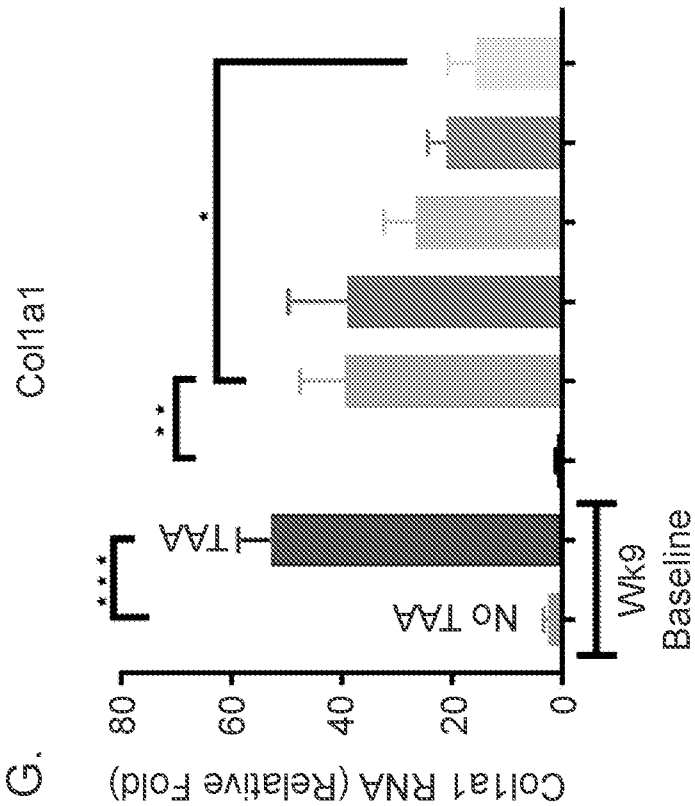
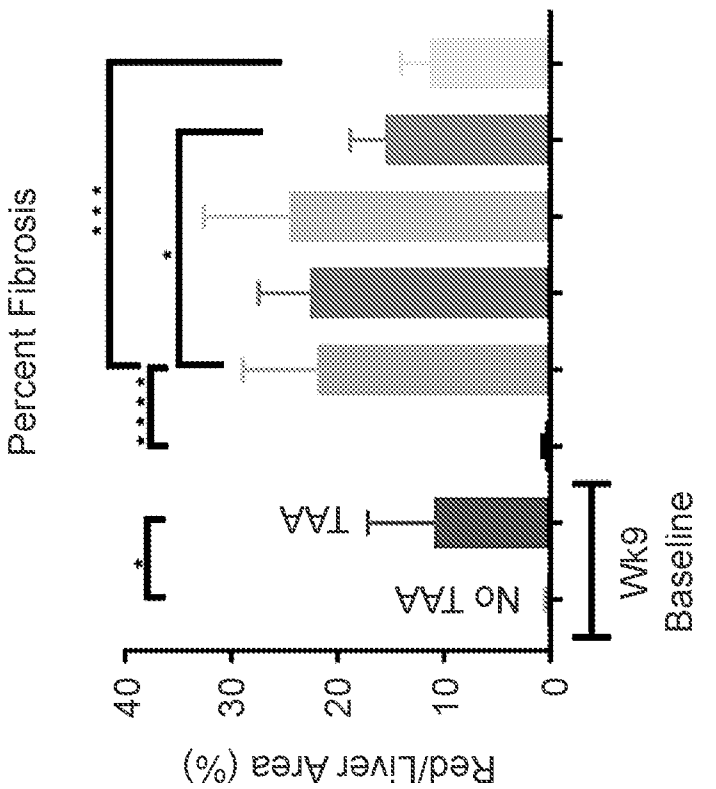


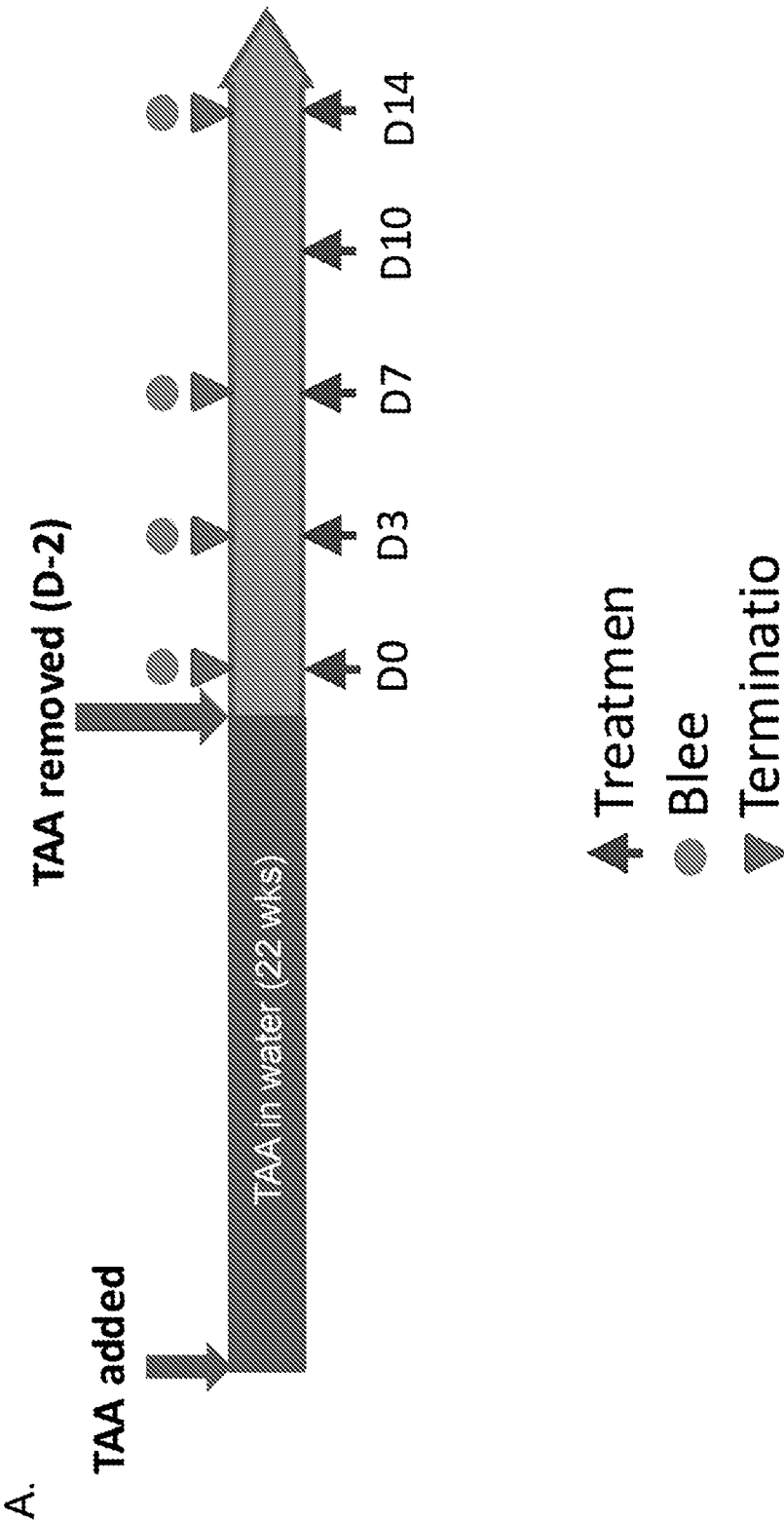
FIG. 40 (contd.)



- No TAA
- eGFP
- 18R5Dkk1FH
- 18R5Dkk1FH
- Rspo2
- 18R5Dkk1FH 3e10 + Rspo2 1e11

FIG. 40 (contd.)

FIG. 41A



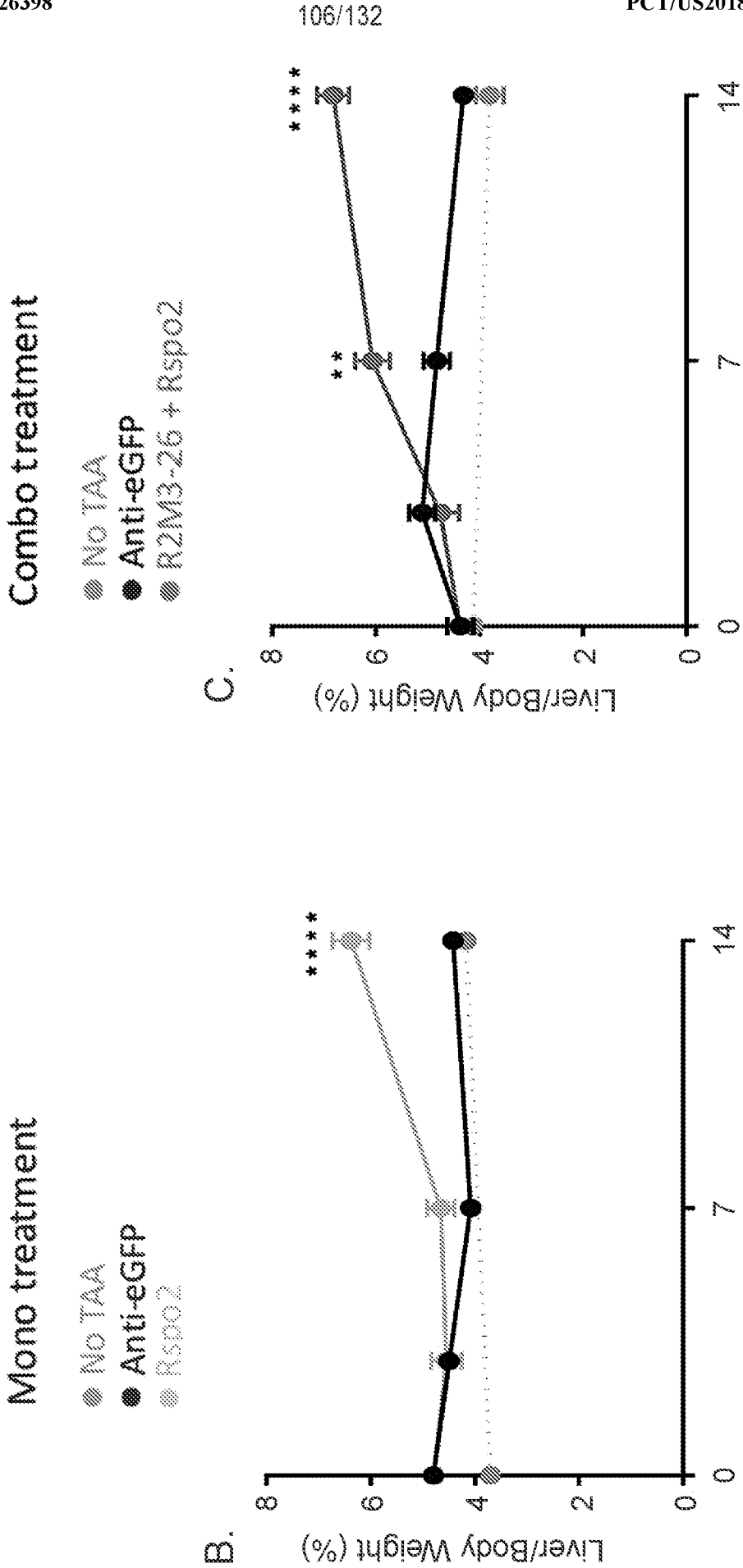


FIG. 41 (contd.)

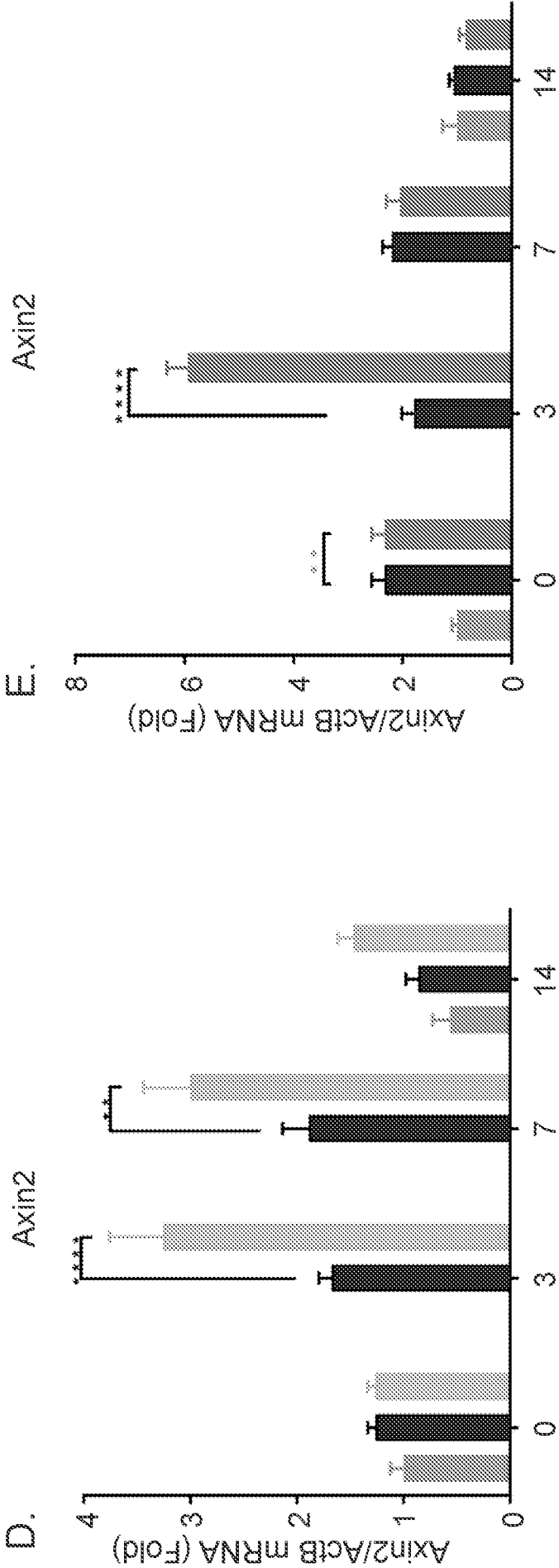


FIG. 41 (contd.)

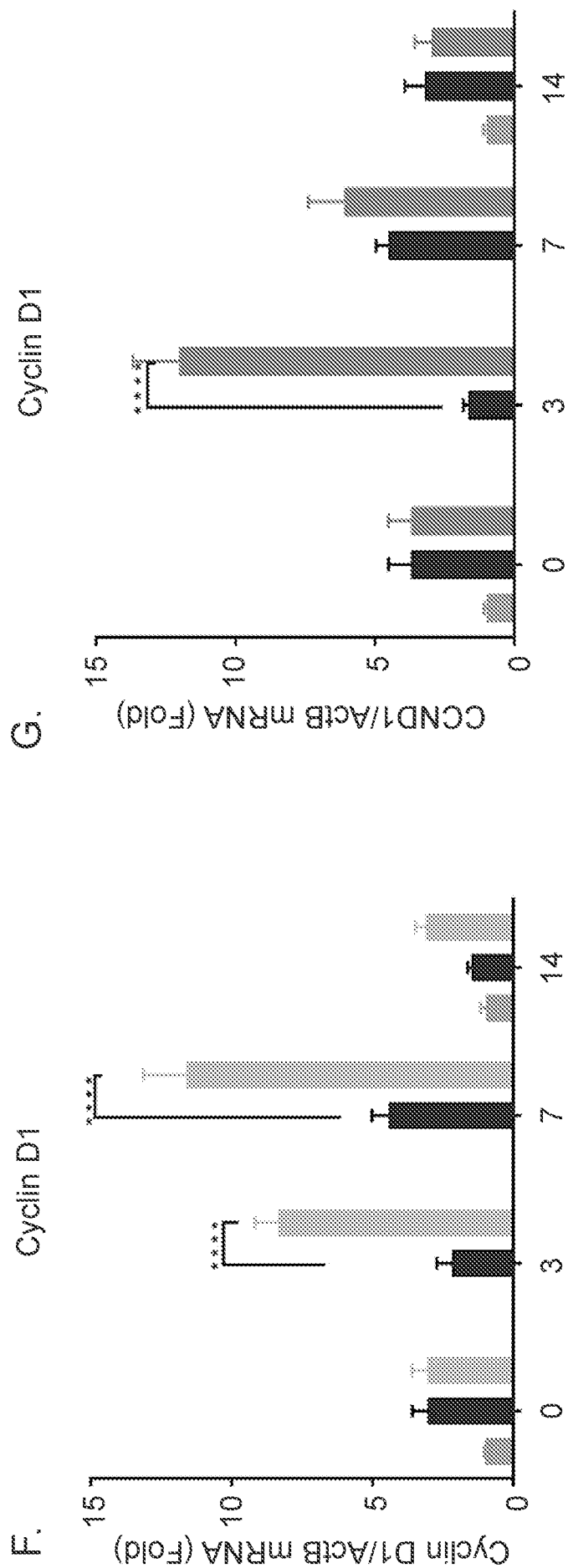


FIG. 41 (contd.)

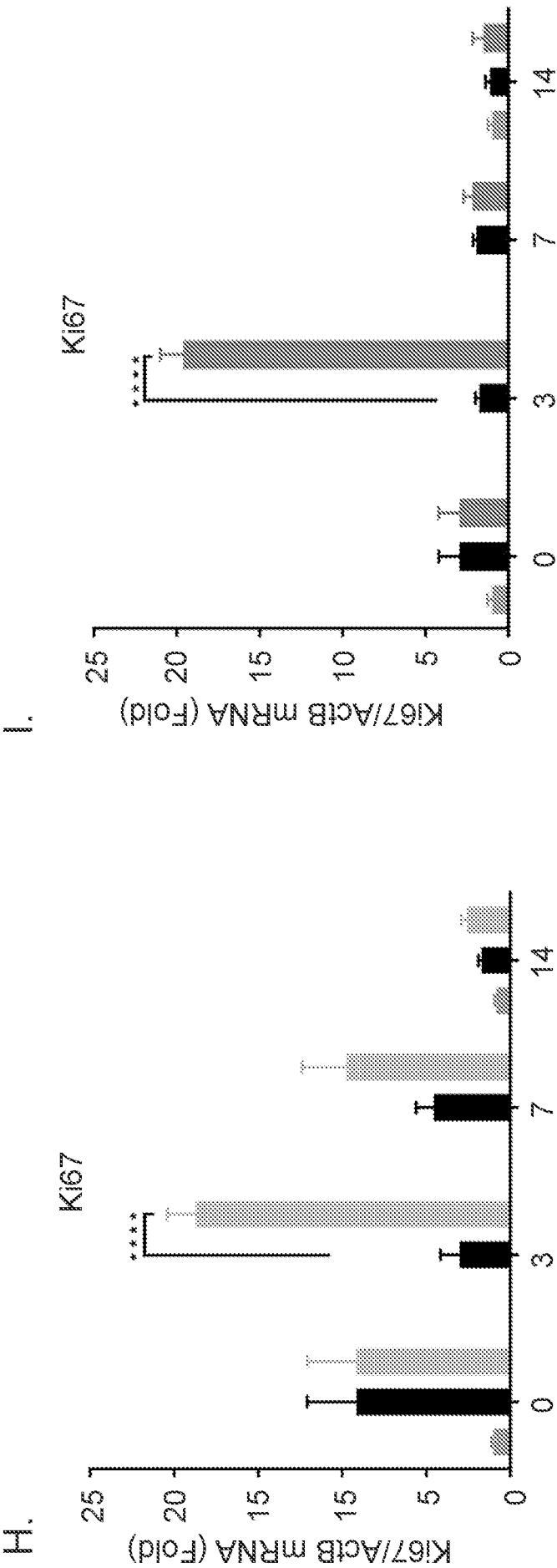


FIG. 41 (contd.)

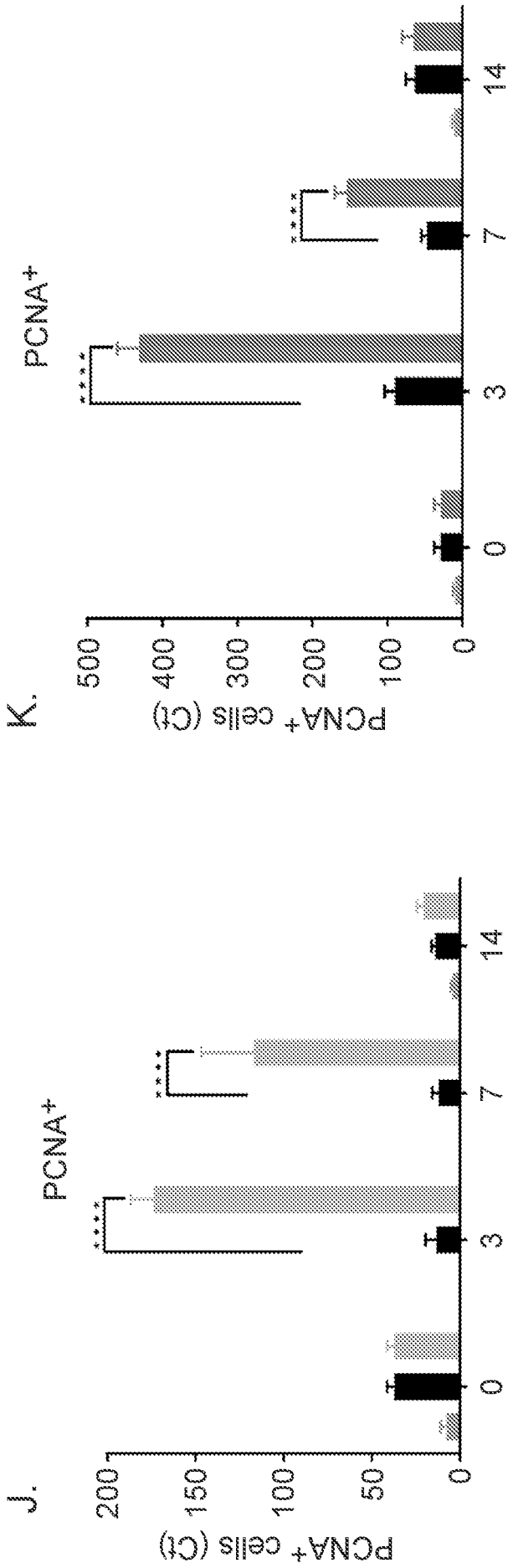


FIG. 41 (contd.)

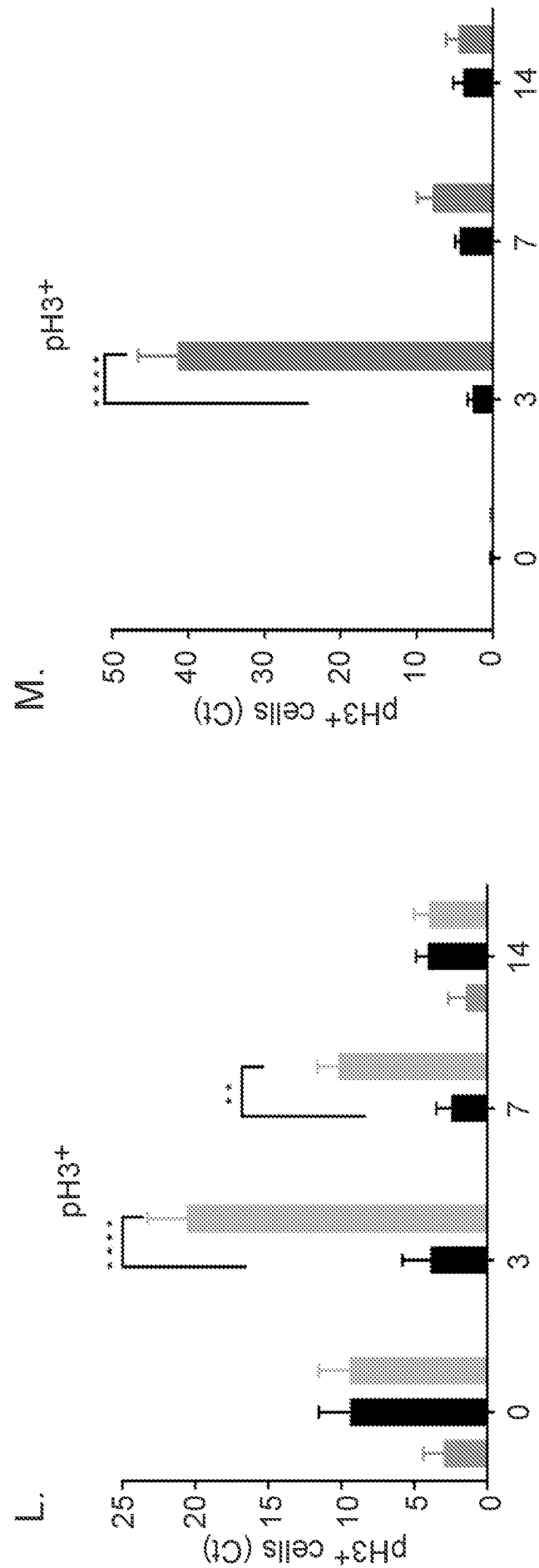


FIG. 41 (contd.)

FIG. 41N

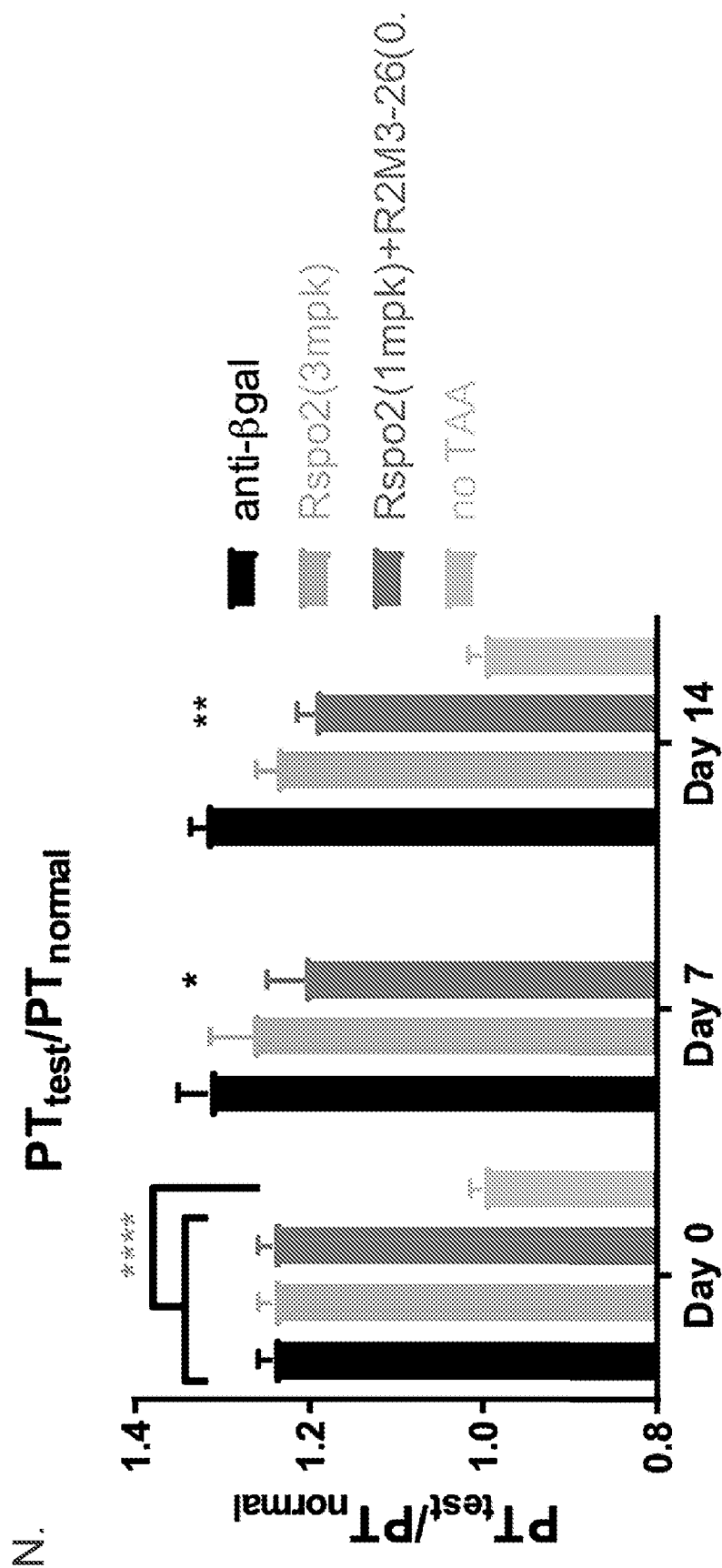


FIG. 42

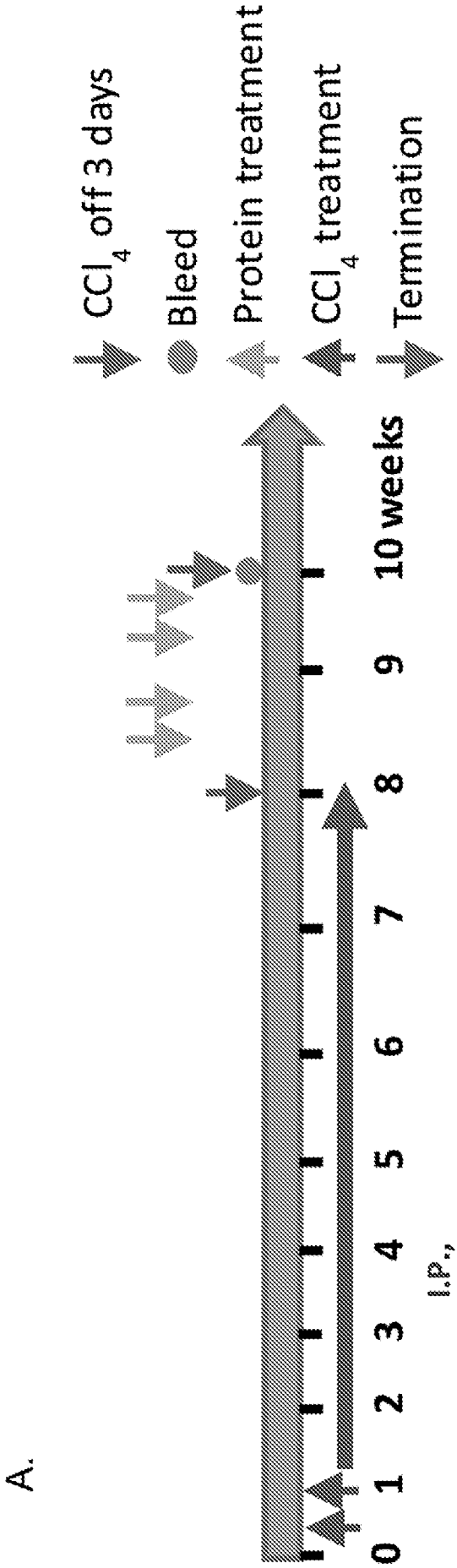


FIG. 42 (contd.)

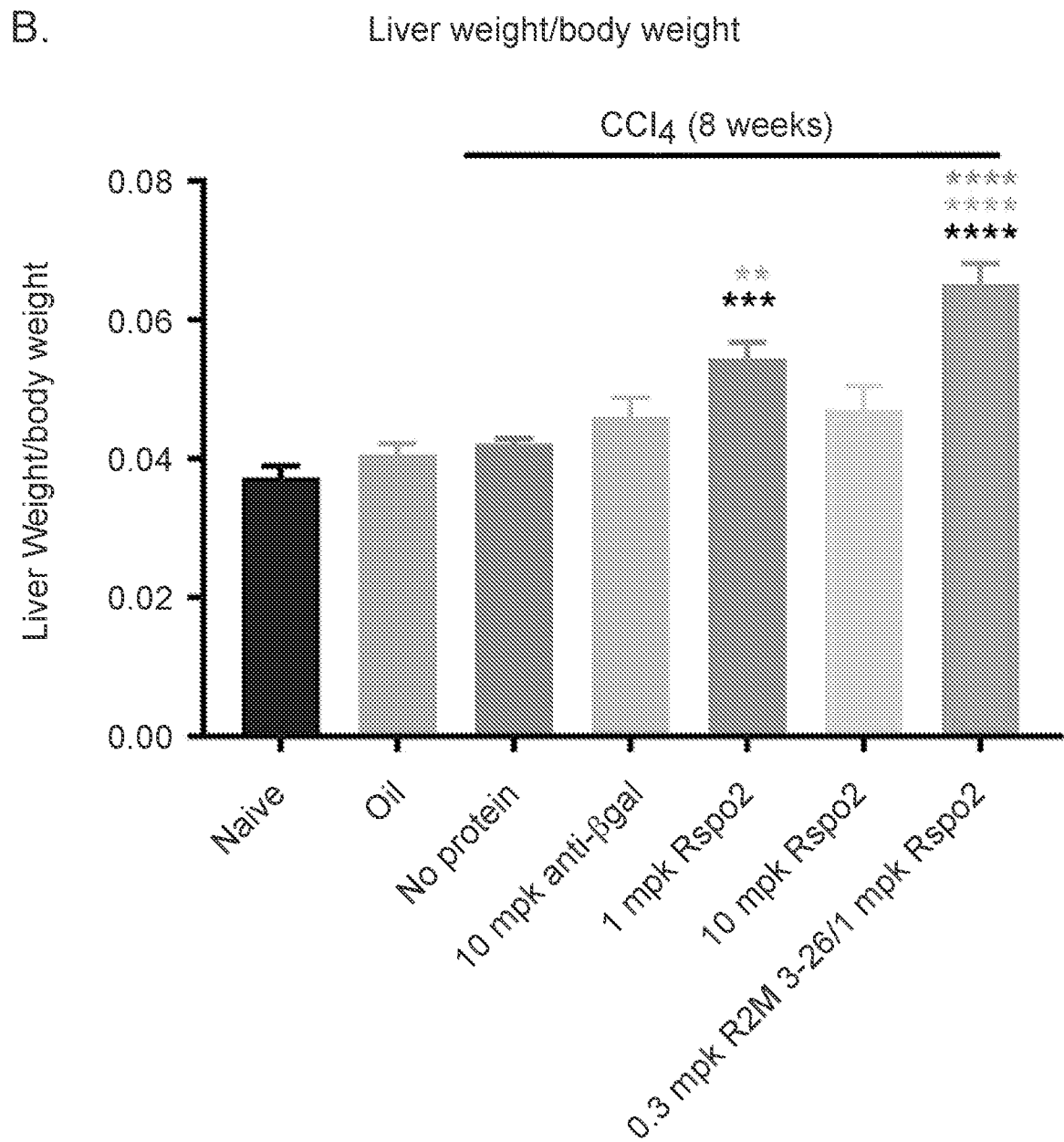


FIG. 42 (contd.)

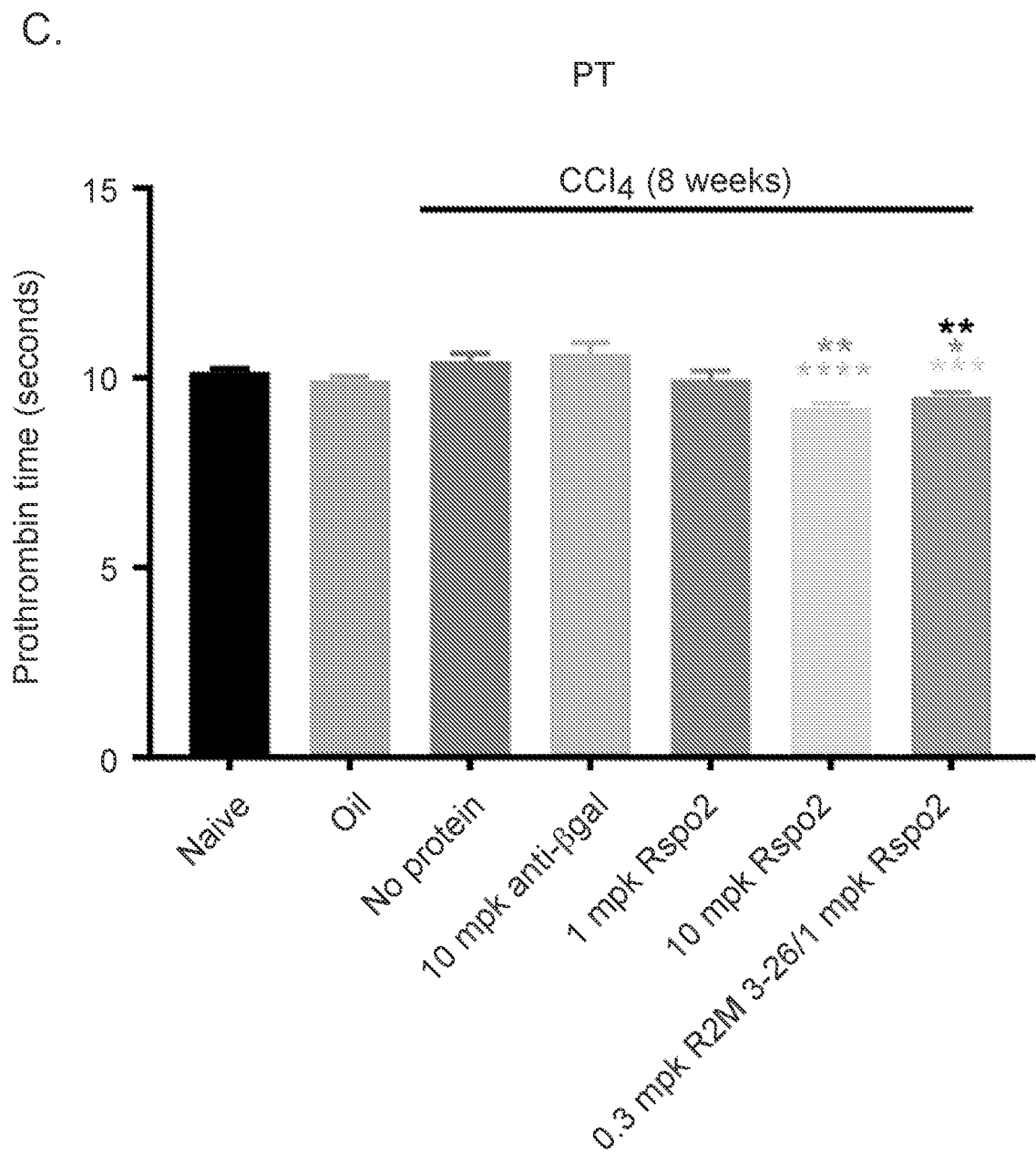


FIG. 42 (contd.)

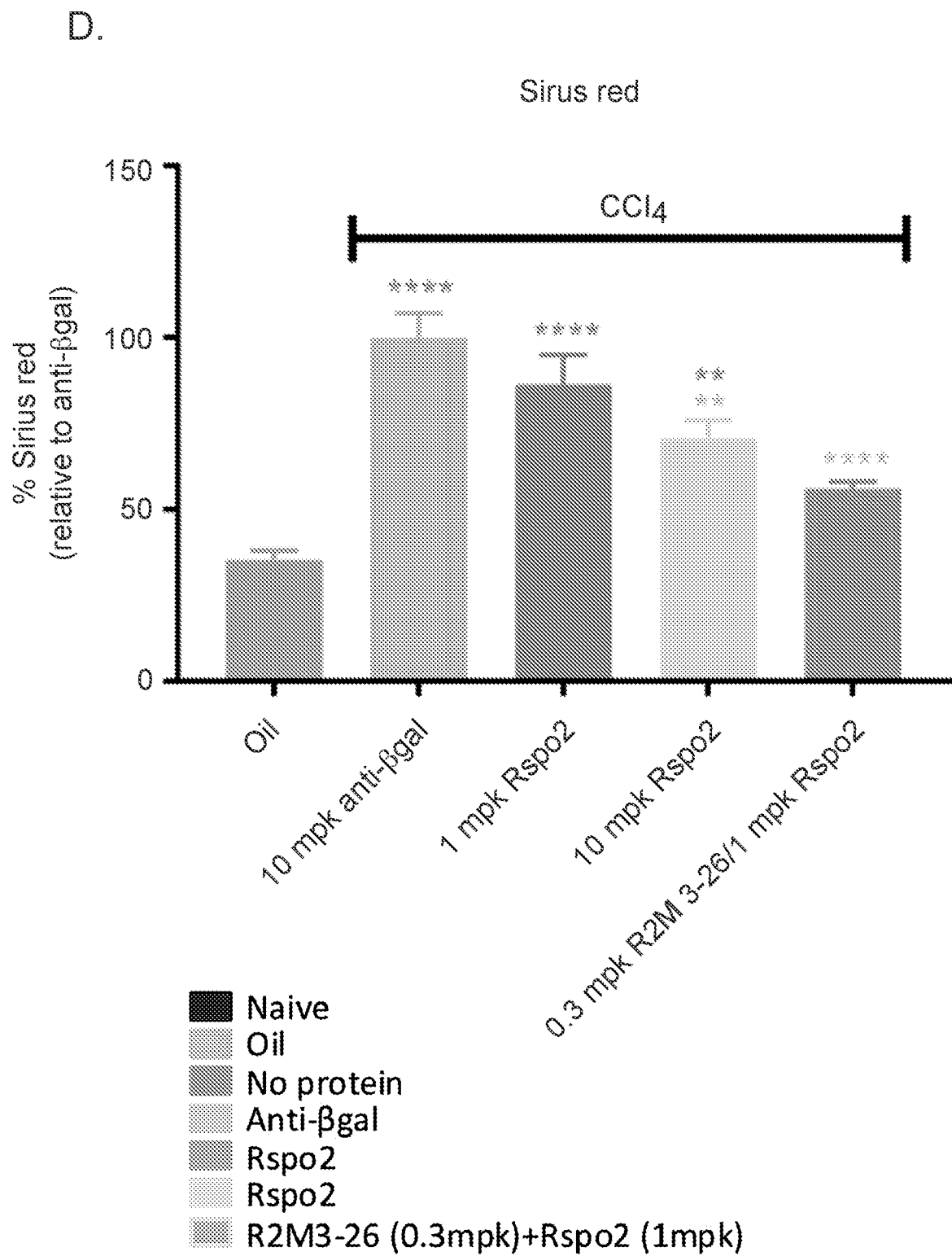


FIG. 43

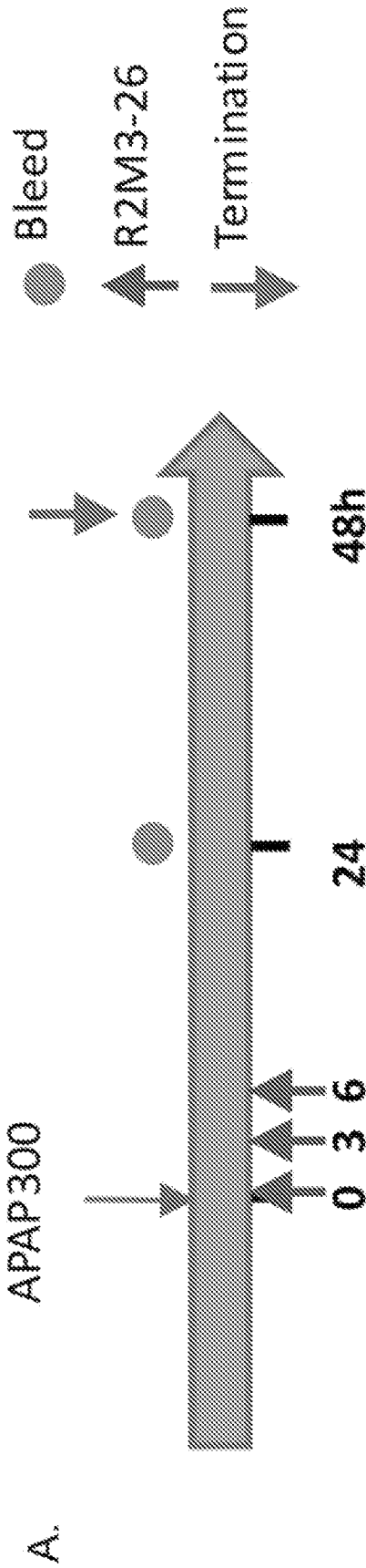
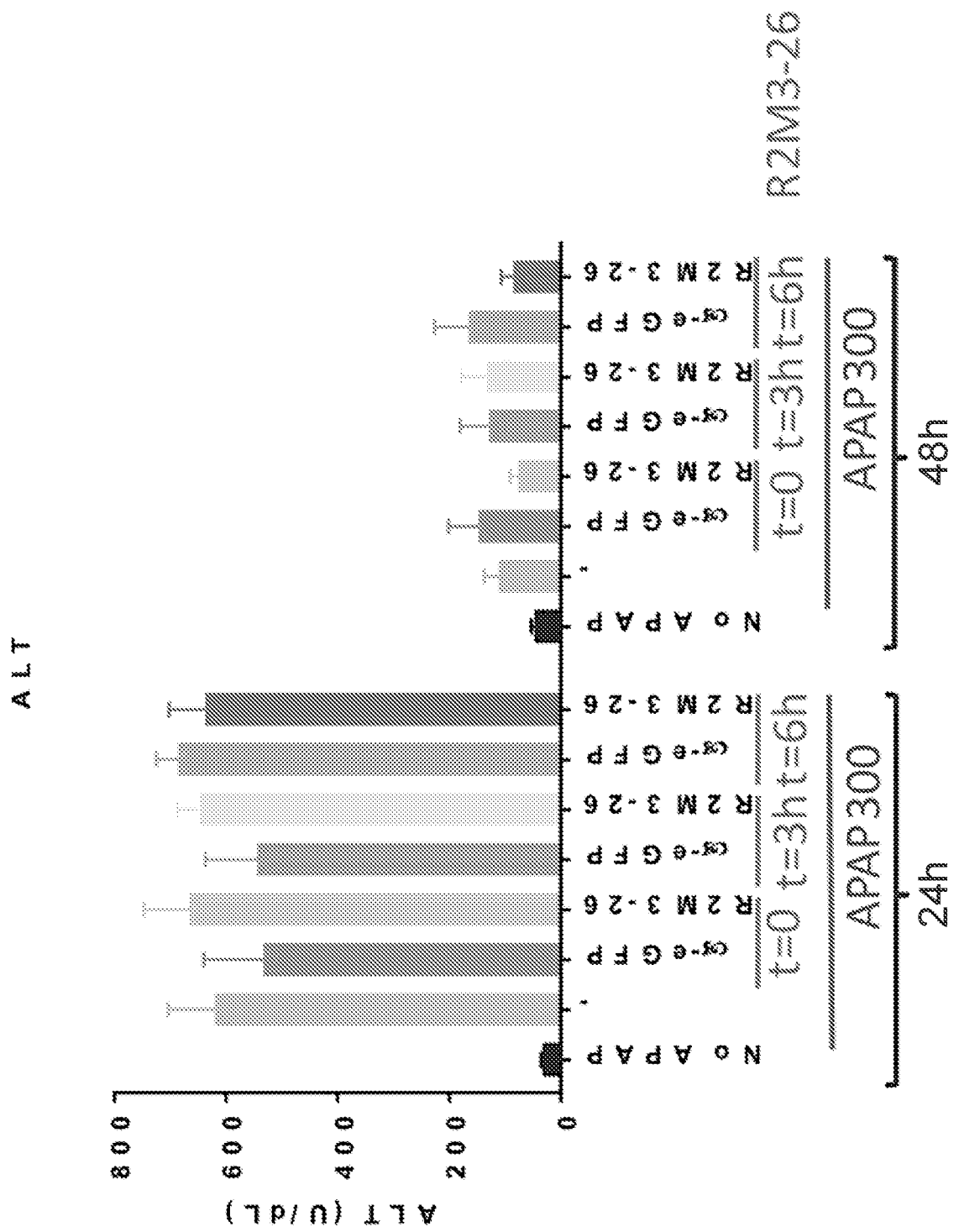
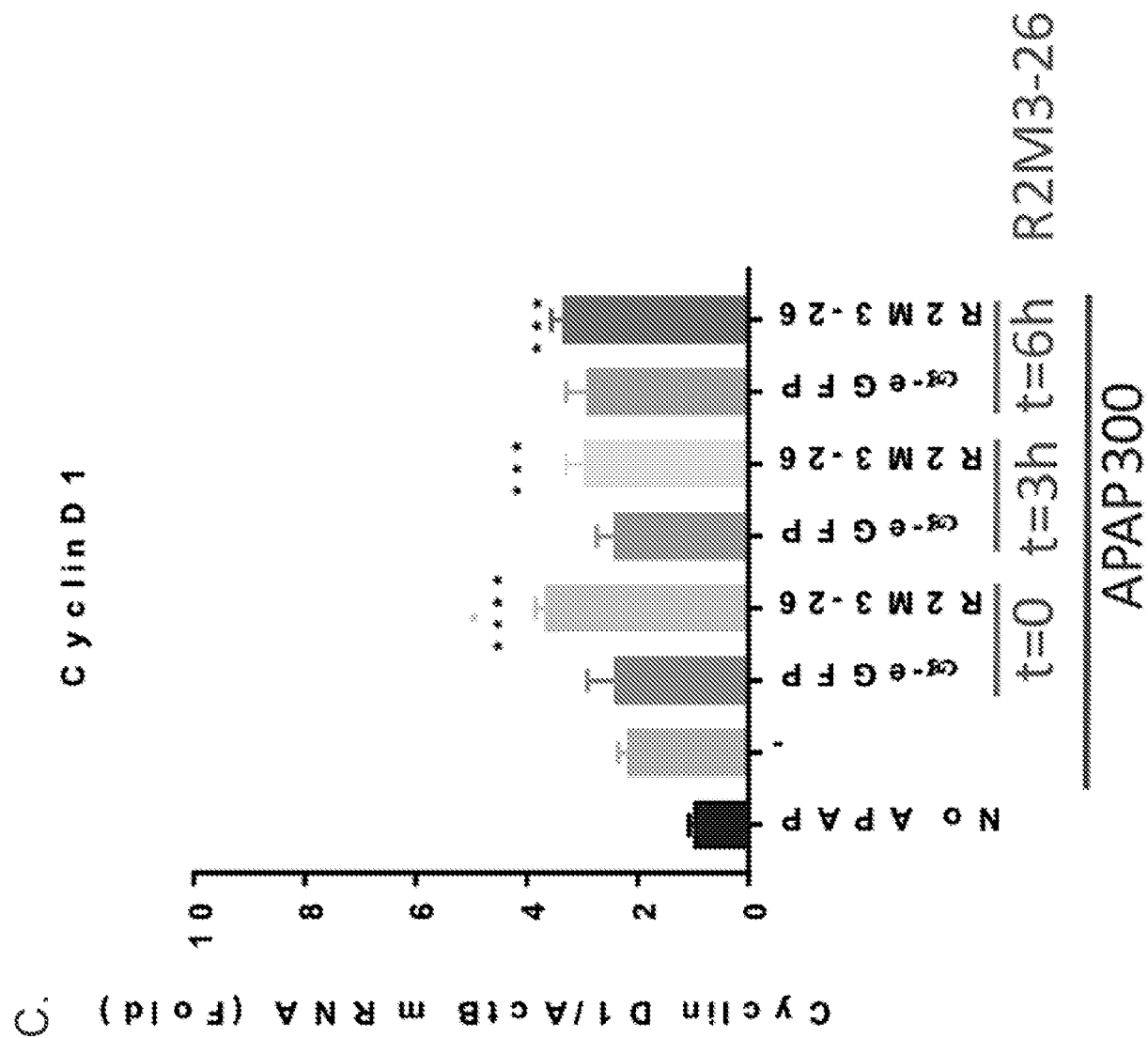


FIG. 43 (contd.)^K



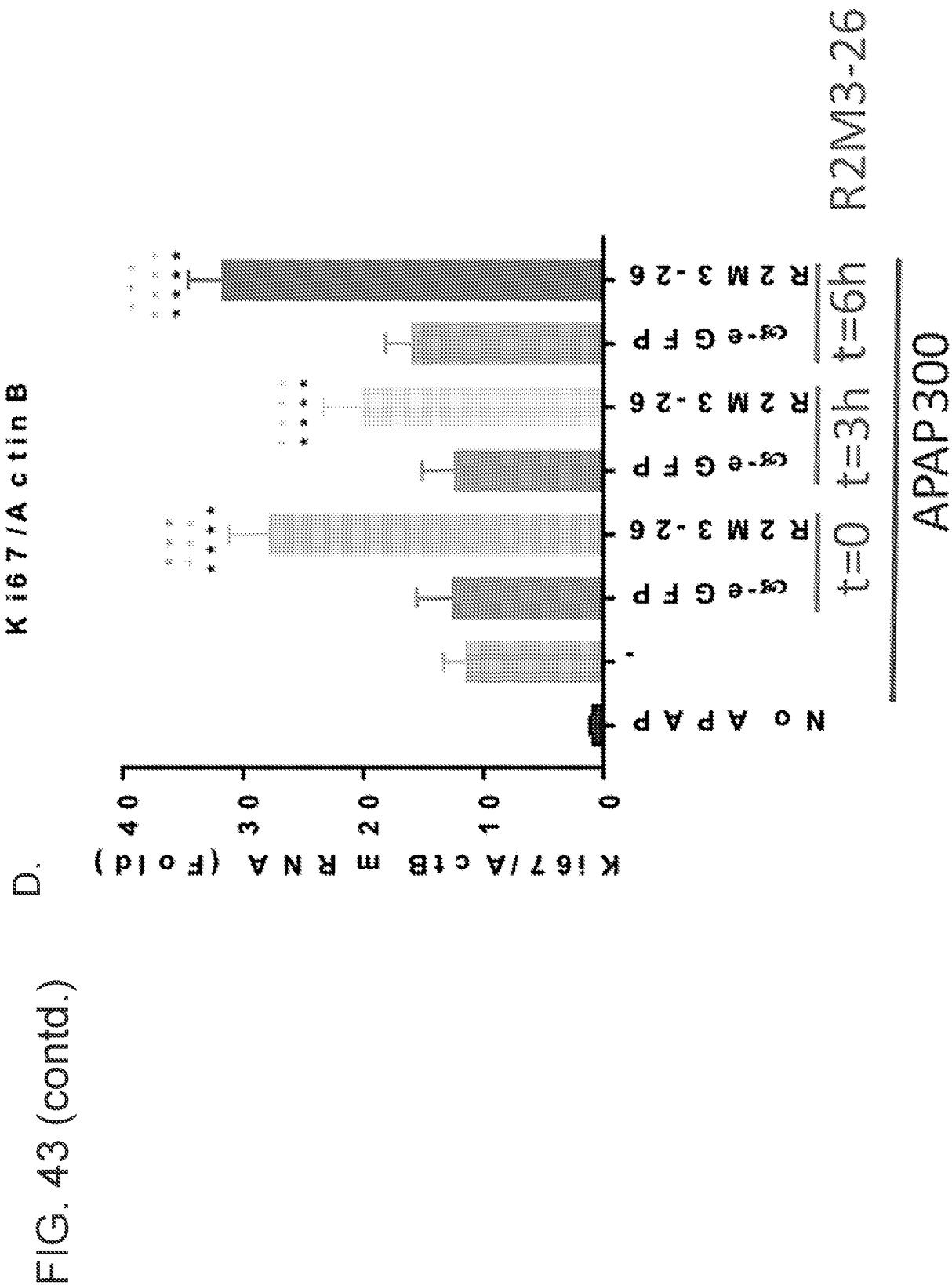
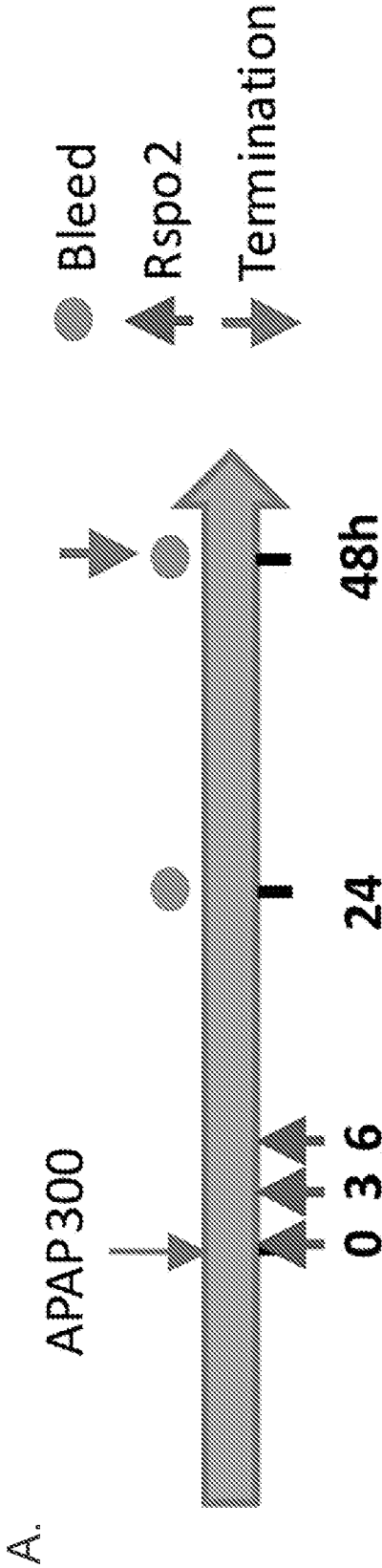


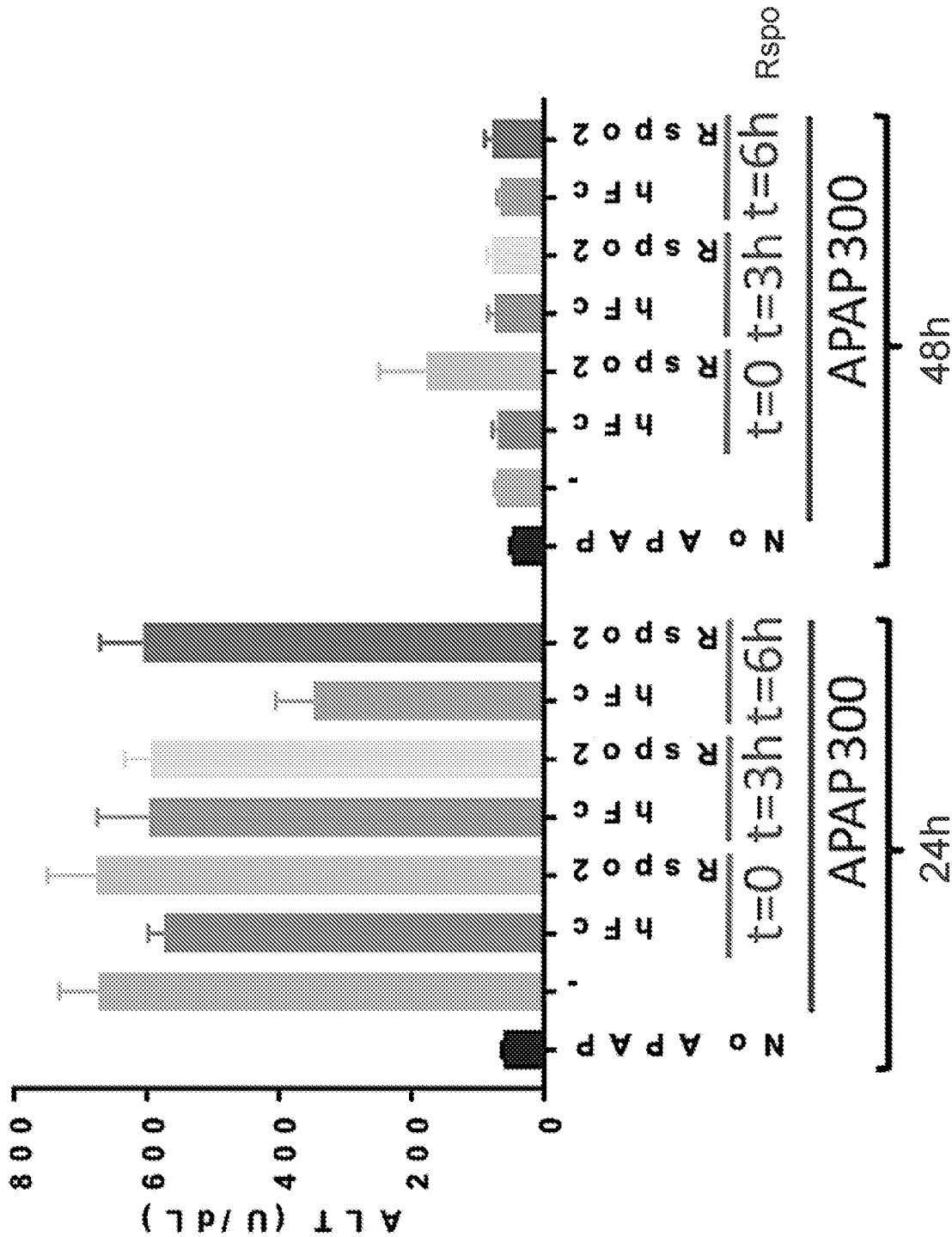
FIG. 43 (contd.)

FIG. 44



ALT

FIG. 44 (contd.) B.



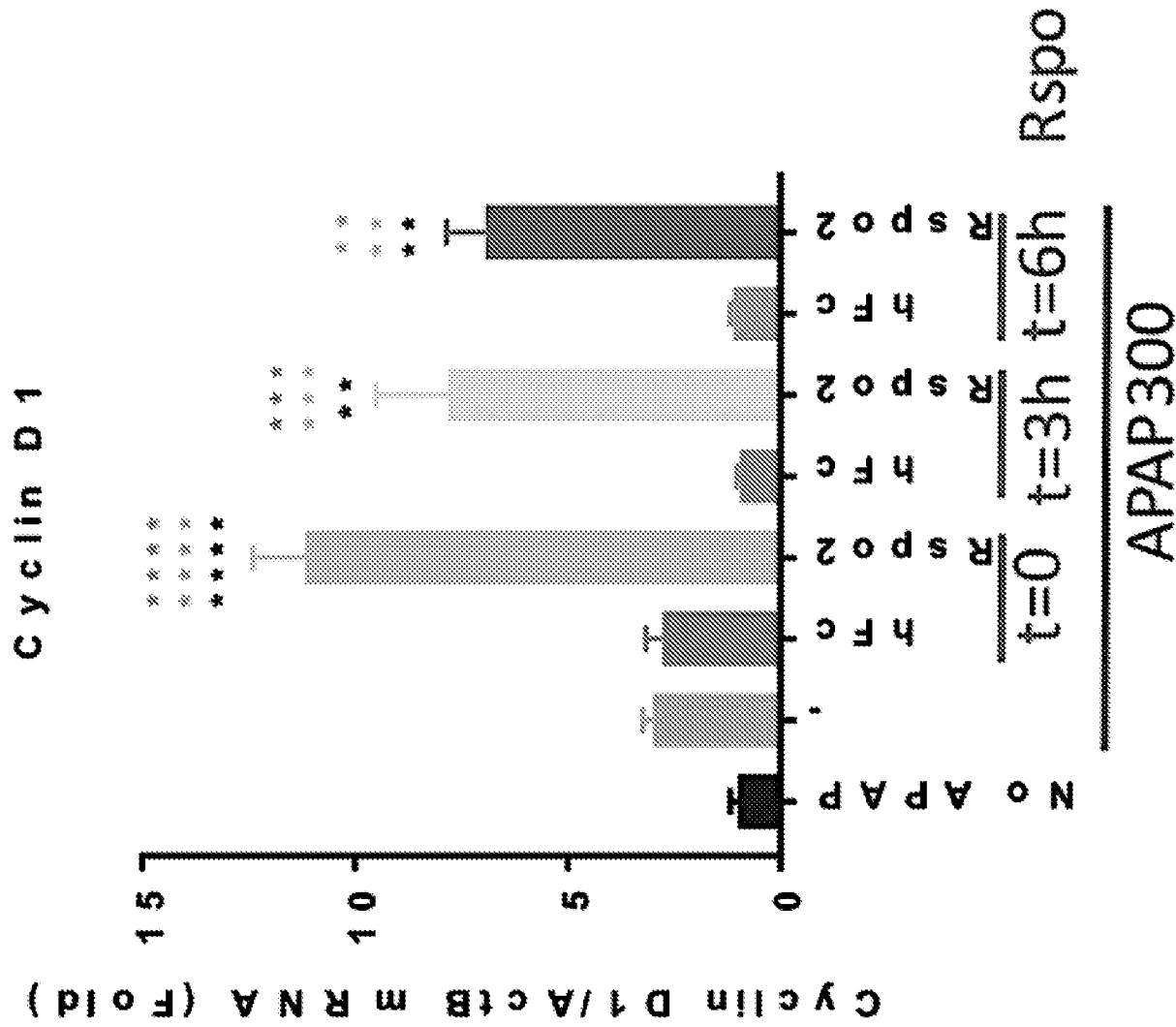


FIG. 44 (contd.) C.

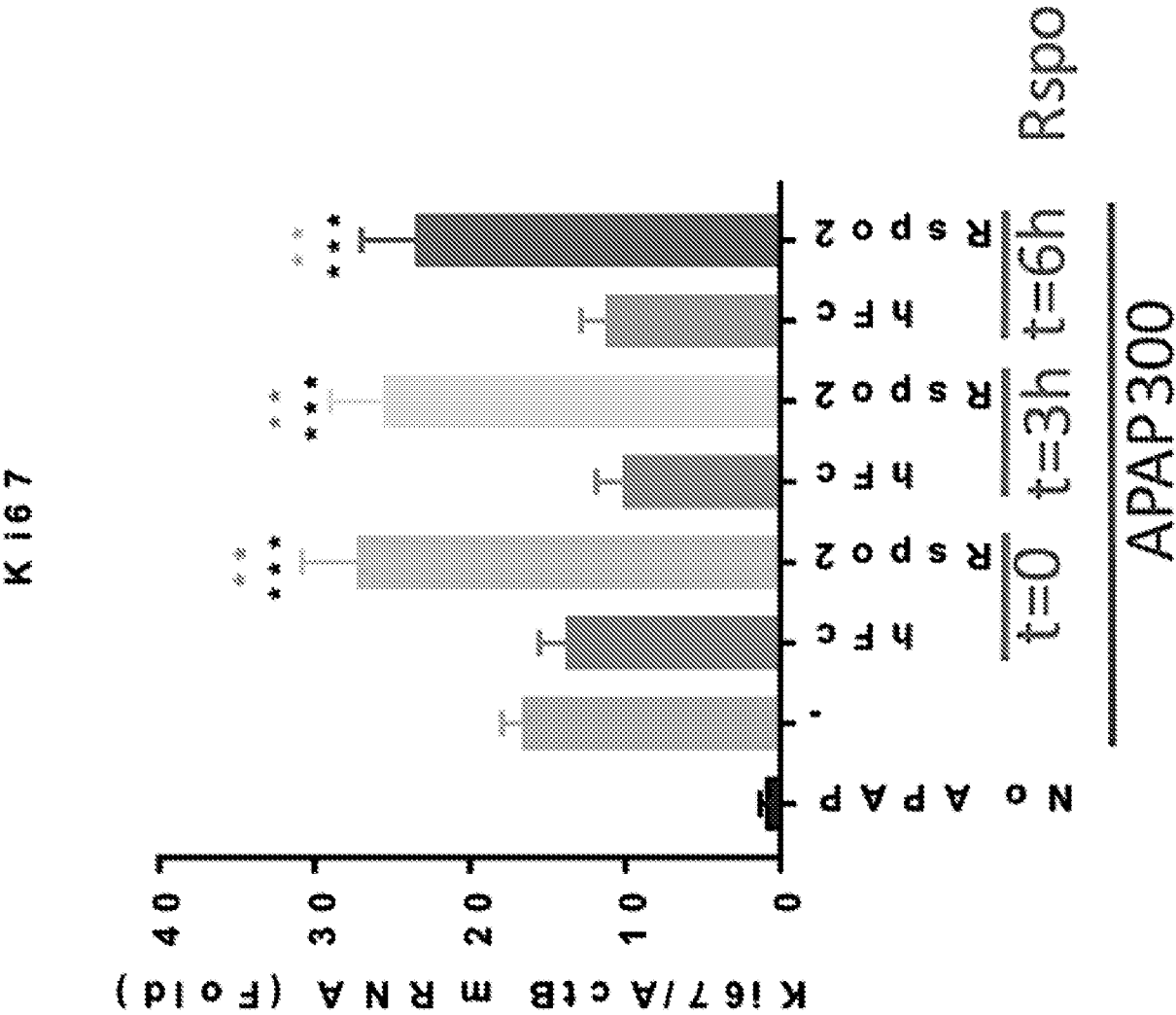


FIG. 44 (contd.) D.

FIG. 45

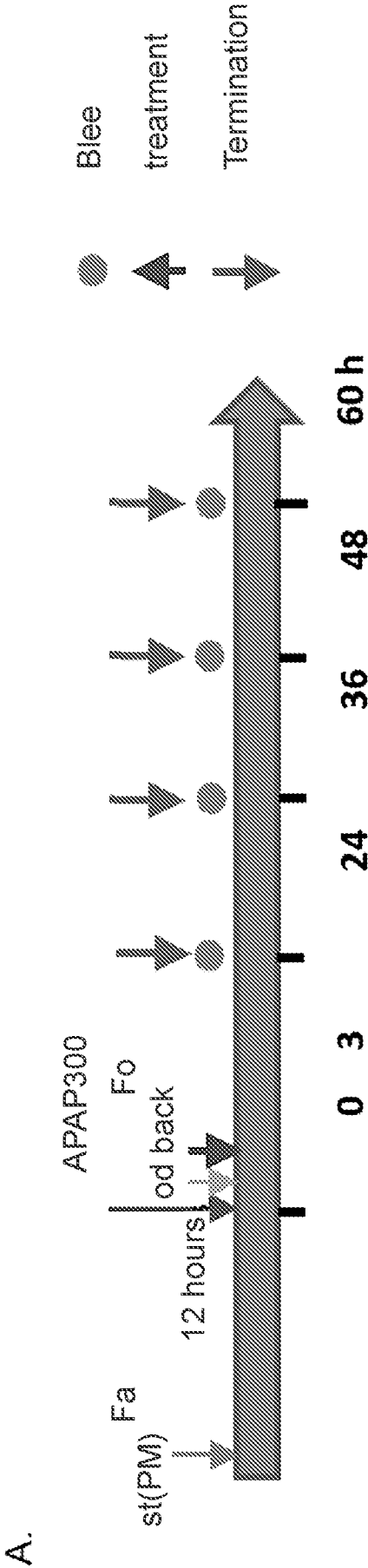
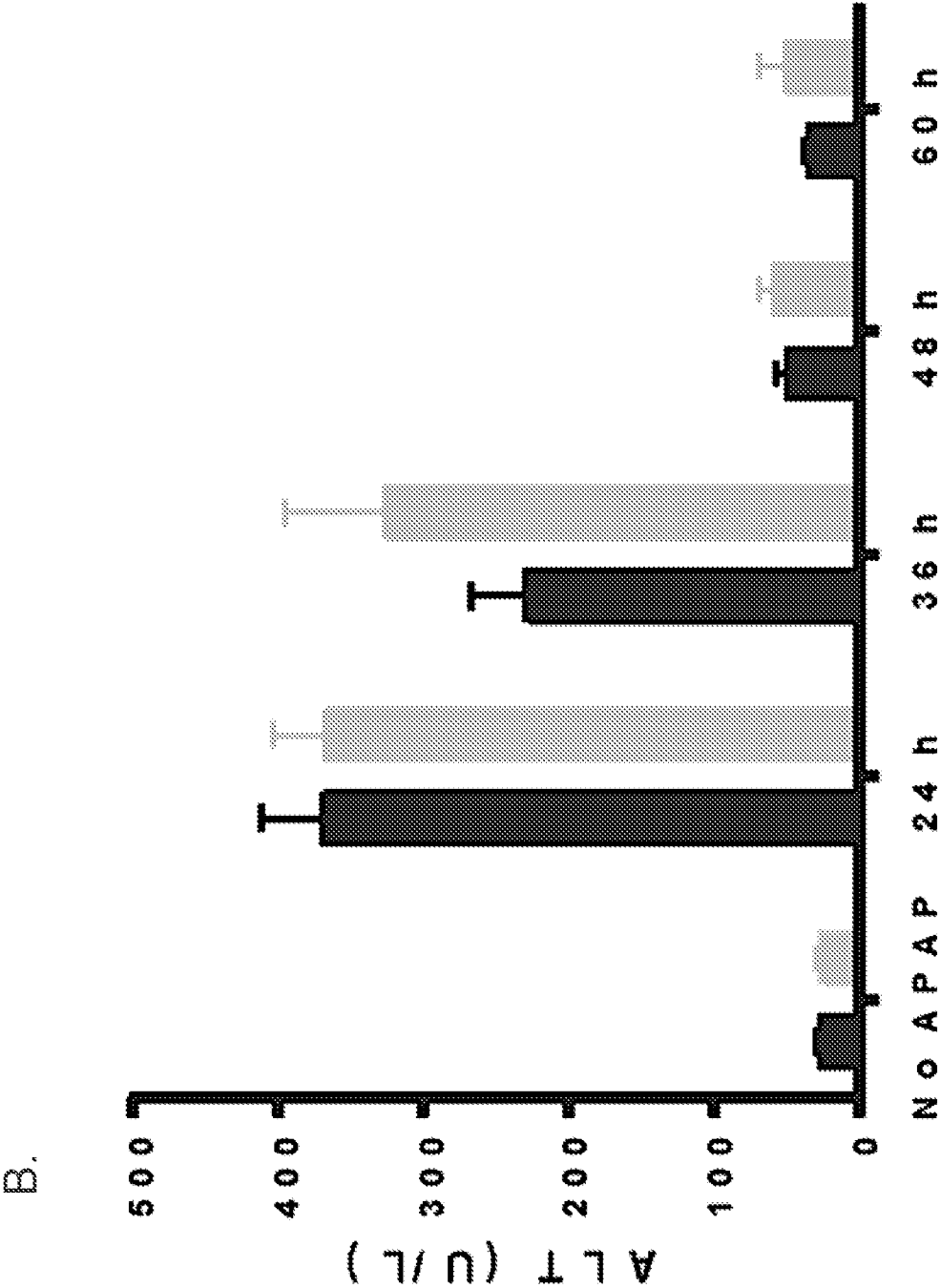


FIG. 45 (contd.)



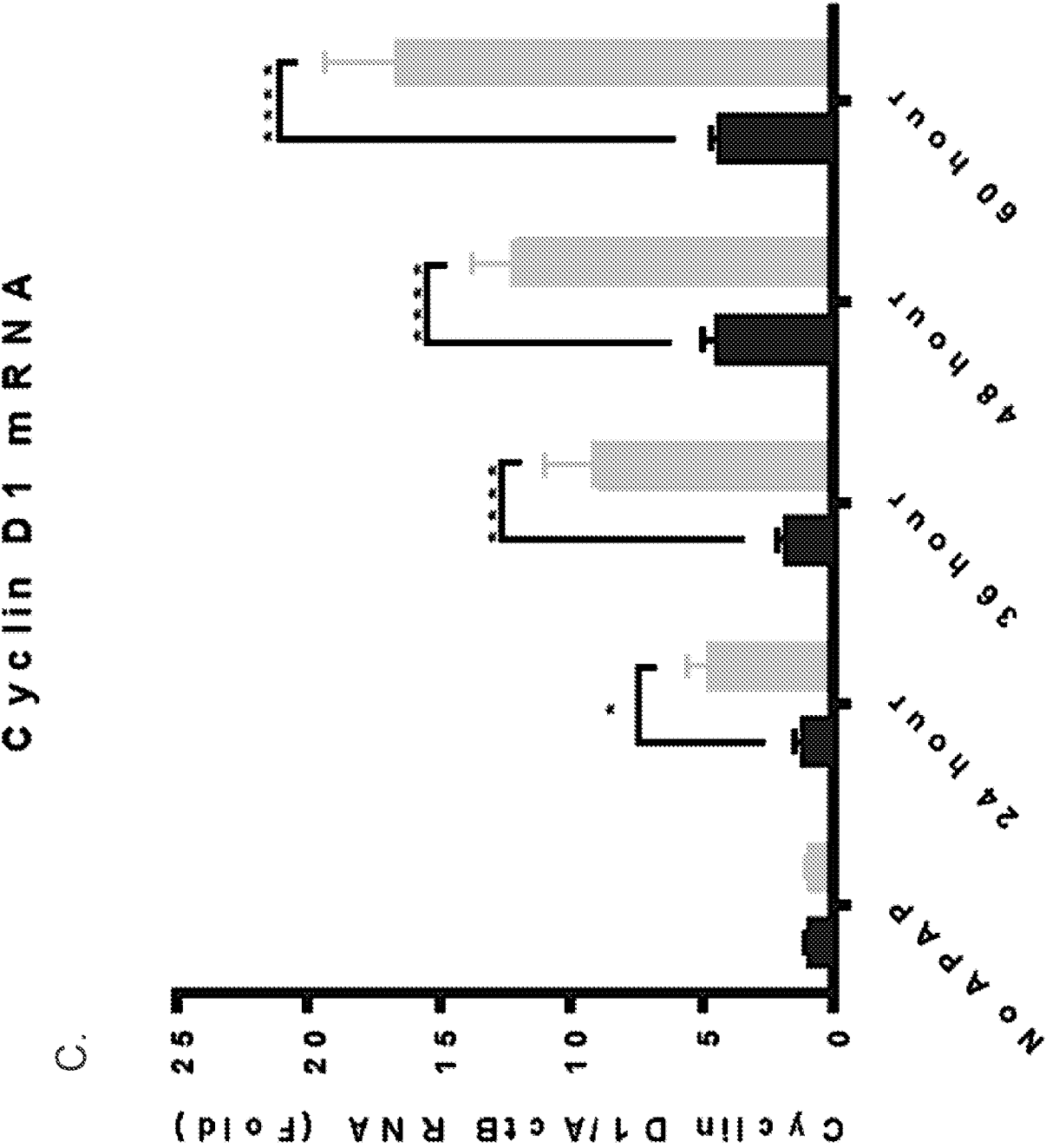


FIG. 45 (contd.)

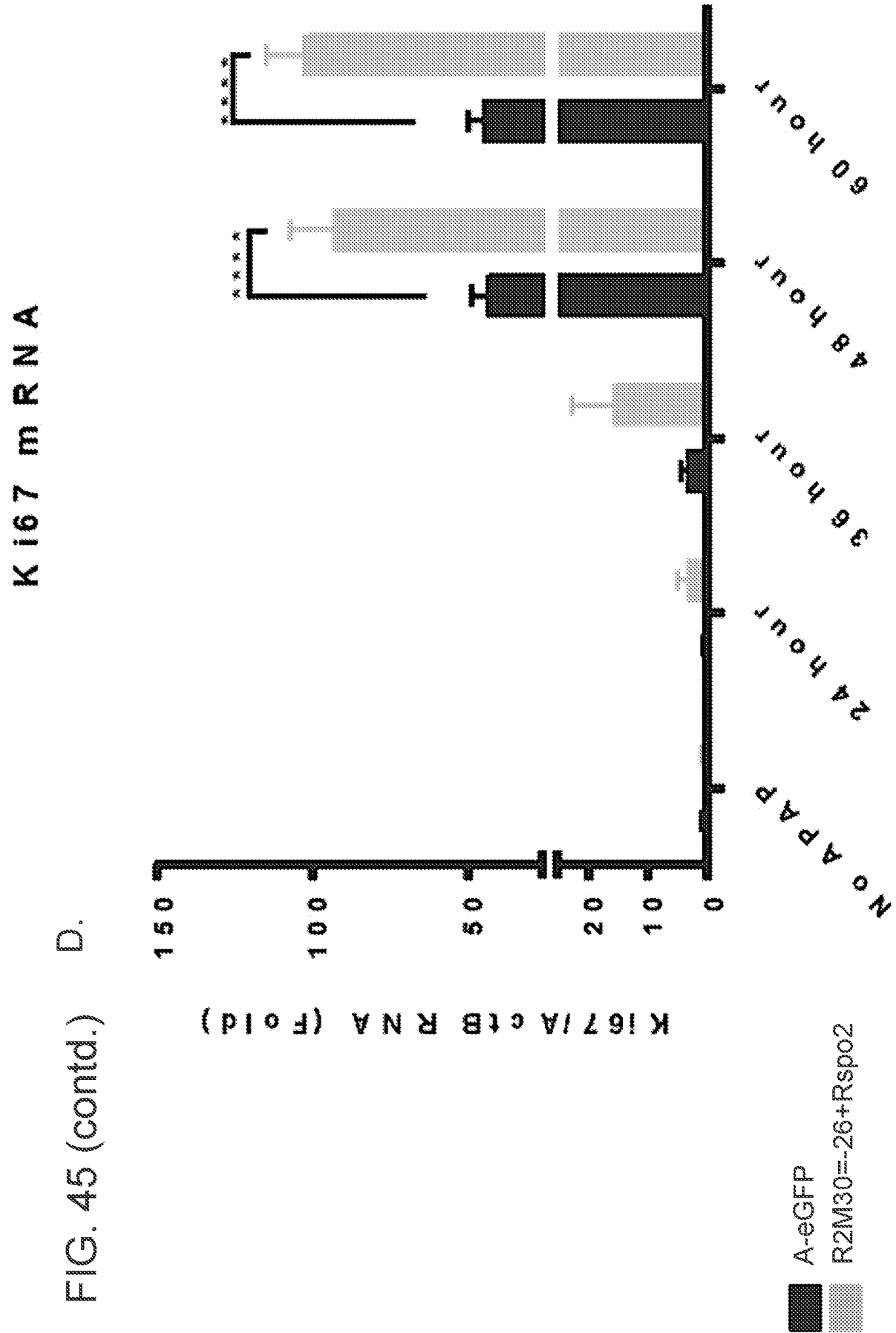


FIG. 45 (contd.)

FIG. 46

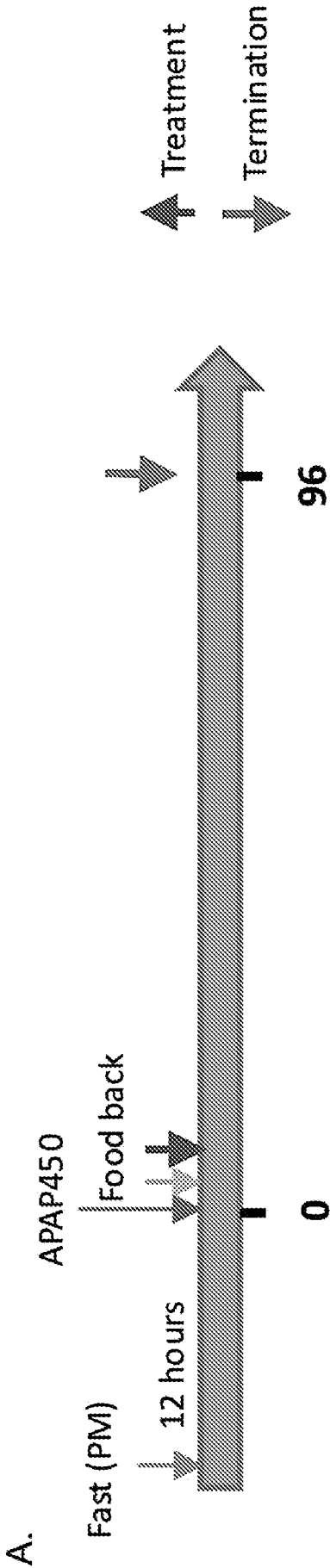


FIG. 46 (contd.)

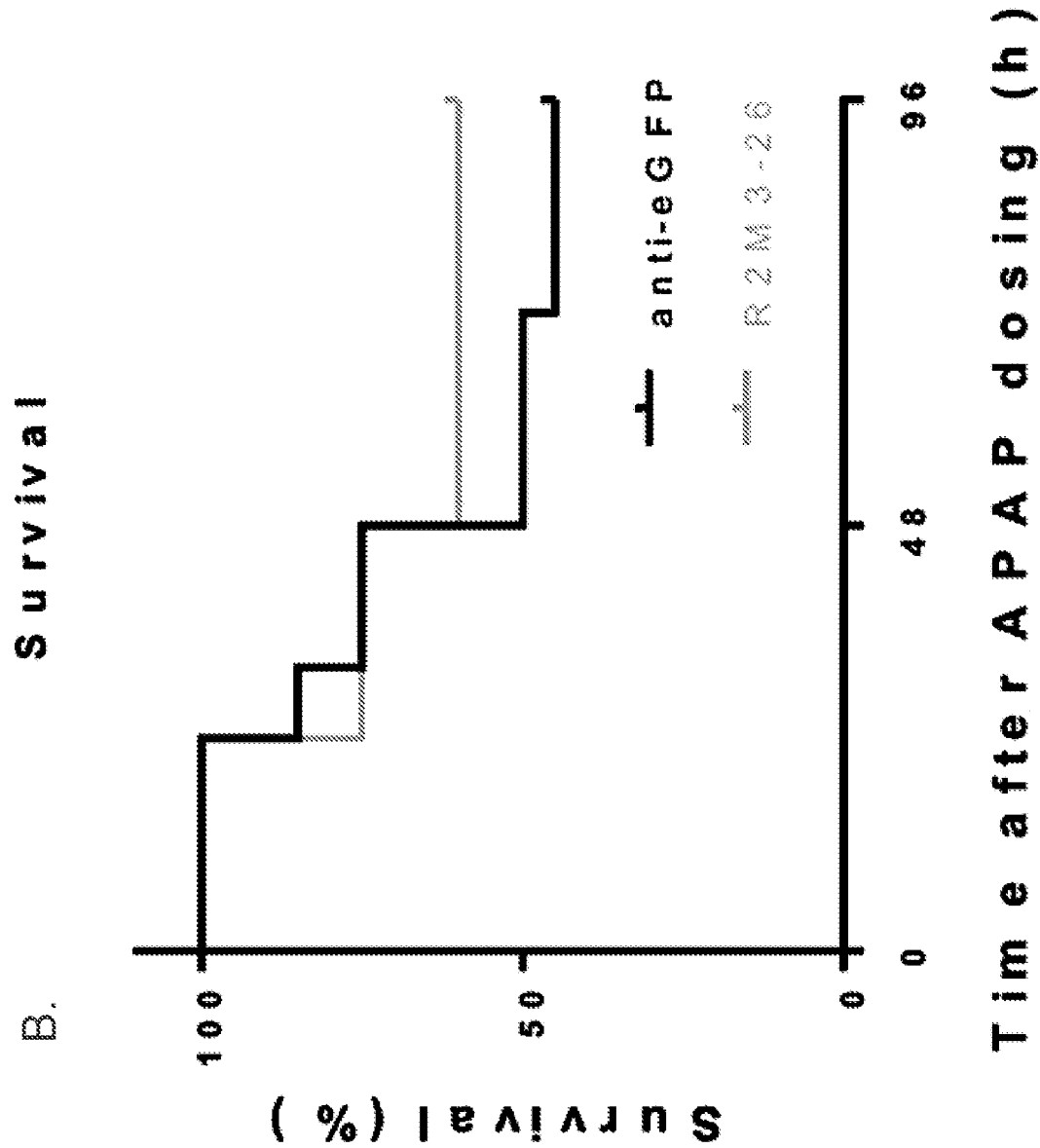


FIG. 46 (contd.)

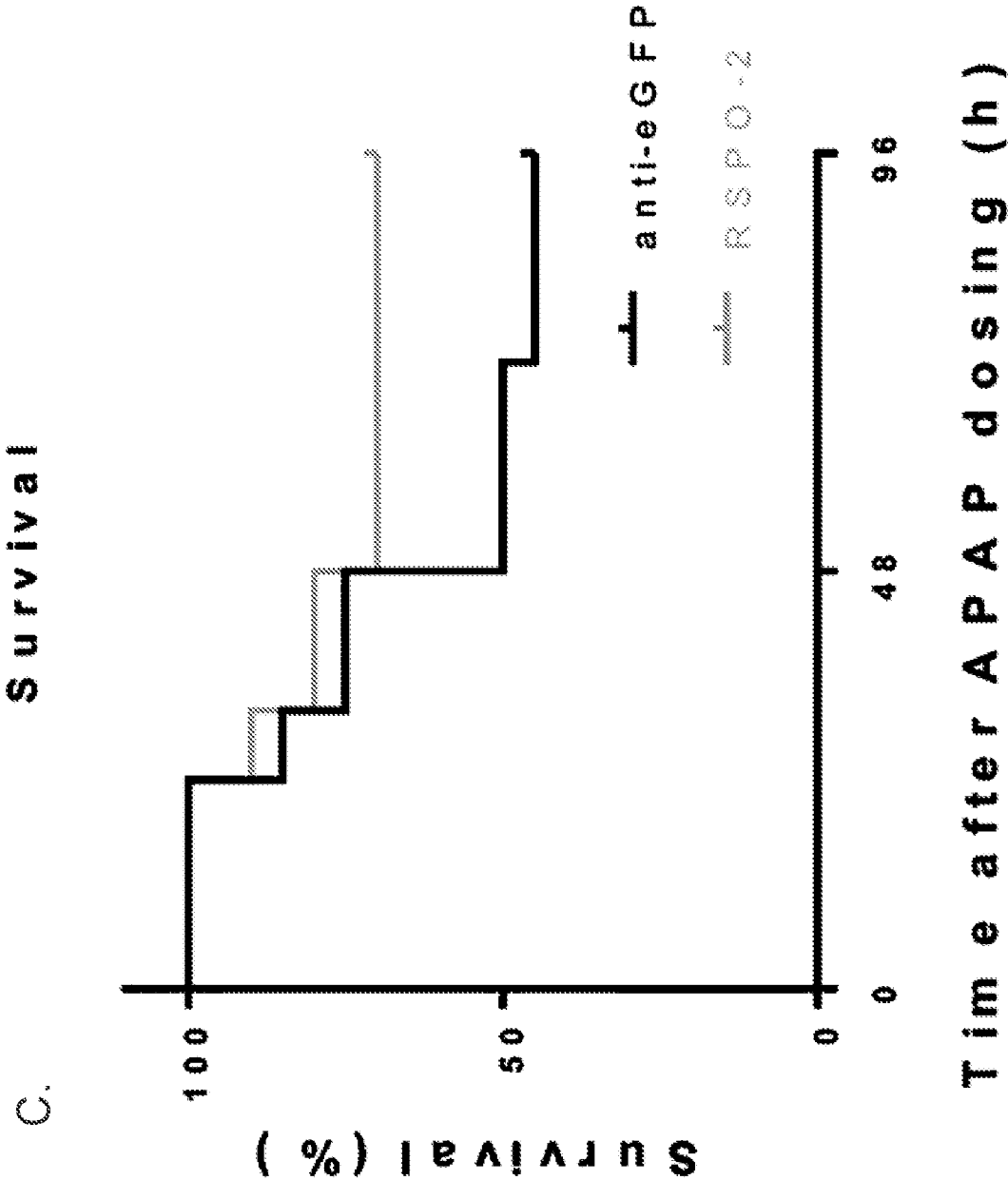
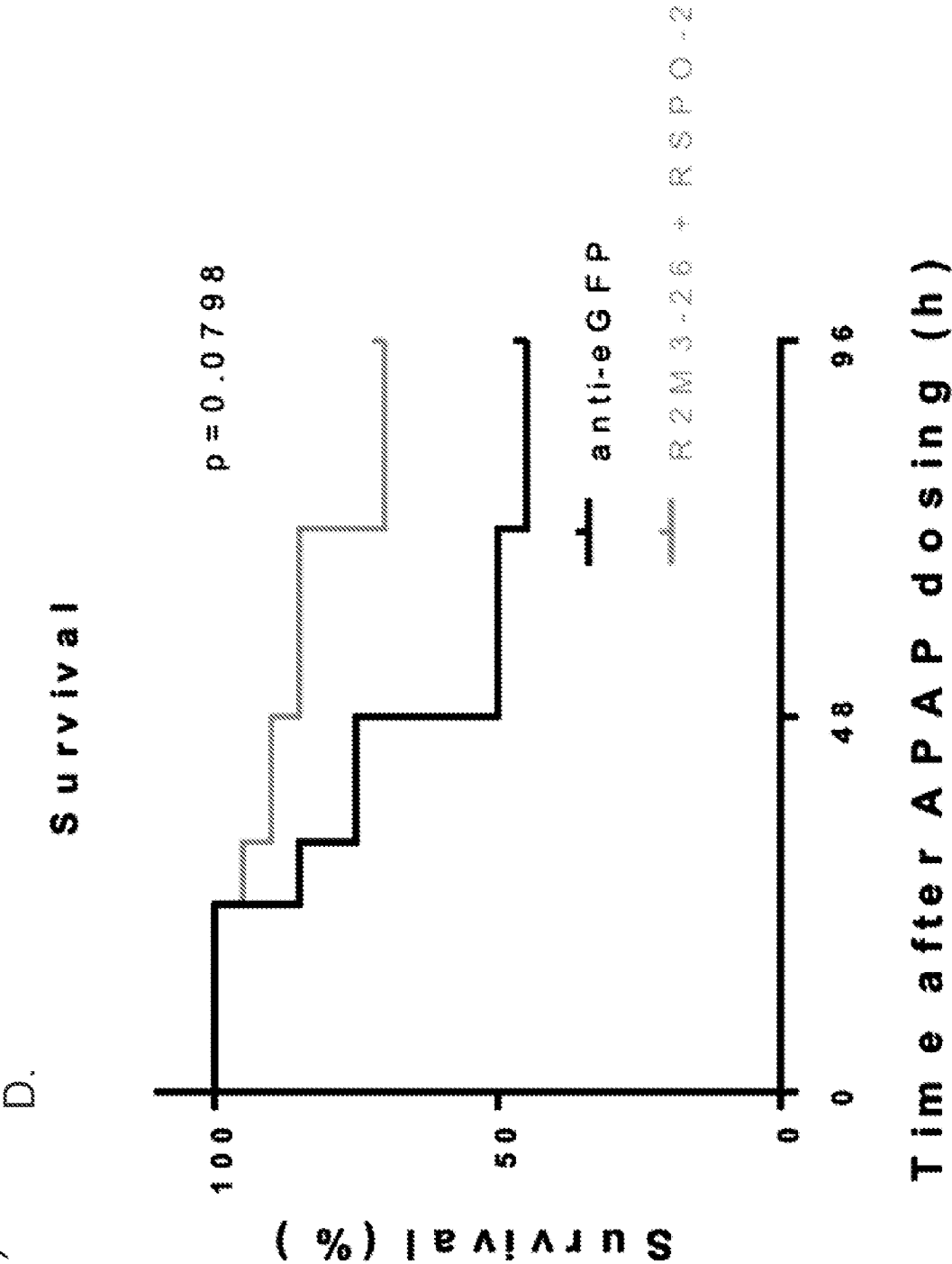


FIG. 46 (contd.)



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/66616

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-70
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
---Please see continuation in first extra sheet -----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, limited to CDRH1 SEQ ID NO: 391, CDRH2 SEQ ID NO: 570, and CDRH3 SEQ ID NO: 752

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/66616

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/28, C07K 16/30, A61K 39/00 (2019.01)

CPC - C07K 16/2863, C07K 16/28, C07K 16/30, C07K 2317/565, C07K 2317/569, C07K 2319/00, C07K 2318/20, C07K 2317/622, C07K 2317/21, C07K 2317/31, A61K 2039/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- A	US 2017/0306029 A1 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY et al.) 26 October 2017 (26.10.2017) Claim 4; Claim 14; Claim 22; para [0011]; para [0030]	1-4 ----- 5
A	WO 2016/023019 A2 (ALECTOR LLC) 11 February 2016 (11.02.2016) Claim 49; SEQ ID NO:12	5
A	WO 2015/109212 A1 (PFIZER et al.) 23 July 2015 (23.07.2015) p120; SEQ ID 51	5
A	WO 2008/084402 A2 (UNIV MARBURG PHILIPPS et al.) 17 July 2008 (17.07.2008) Claim 7; SEQ ID NO:60	5

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 April 2019

Date of mailing of the international search report

01 MAY 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/66616

Continuation of Box No. III. Observations where unity of invention is lacking.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+, Claims 1-5, directed to a soluble, multivalent, multispecific Wnt surrogate molecule comprising one or more Fzd binding regions and one or more LRP5/6 binding regions.

The Wnt surrogate molecule will be searched to the extent that the Wnt surrogate molecule encompasses anti-Fzd antibody clone 0015-A01 heavy chain CDRs comprising CDRH1 of SEQ ID NO:391, CDRH2 of SEQ ID NO:570, CDRH3 of SEQ ID NO:752 (note, clone 0015-A01 is the first claimed antibody clone in Table 1A).

It is believed that claims 1-5 encompass this first named invention, and thus these claims will be searched without fee to the extent that the Wnt surrogate molecule encompasses Wnt surrogate molecule comprising the CDRH1, CDRH2 and CDRH3 sequences of anti-Fzd Antibody clone 0015-A01, as detailed above. Additional Wnt surrogate molecule(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected Wnt surrogate molecule(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched.

An exemplary election would be a Wnt surrogate molecule comprising anti-Fzd antibody clone 0015-A01 light chain CDRs comprising CDRL1 of SEQ ID NO:1156, CDRL2 of SEQ ID NO:1256 and CDRL3 of SEQ ID NO:1265 (claims 1-5).

The inventions listed as Group I+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

The inventions of Group I+ each include the special technical feature of a unique amino acid sequence. Each amino acid sequence is a unique peptide, and is considered a distinct technical feature.

Common technical features

The inventions of Group I+ share the common technical feature of a soluble, multivalent, multispecific Wnt surrogate molecule comprising one or more Fzd binding regions and one or more LRP5/6 binding regions.

However, these shared technical features are previously disclosed by US 2017/0306029 A1 to The Board of Trustees of the Leland Stanford Junior University et al., (hereinafter 'Stanford').

Stanford teaches a soluble, multivalent, multispecific Wnt surrogate molecule comprising a Fzd binding regions and a LRP5/6 binding region (para [0011] - 'Wnt signaling agonist molecules and methods for their use are provided. The molecules of the invention are water soluble; bind with high affinity to both (i) frizzled (Fzd) proteins and (ii) Lrp5/6; and directly activate canonical wnt pathway signaling'; Claim 4 - 'The wnt signaling agonist of claim 3, wherein the polypeptide comprises a binding domain having a high affinity for one or more Fzd proteins; and a binding domain having high affinity to one or both of Lrp5 and Lrp6 protein.'; para [0030] - 'FIG. 5. Provides the amino acid sequence (SEQ ID NO:10) of an exemplary surrogate wnt agonist, depicting the scFv domain, and the Lrp5/6 binding domain.').

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+ inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, continuation of Item 4 above: claims 6-70 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).