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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 March 2022 (03.03.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/046944 A2

(51) International Patent Classification:
C07K 16/28 (2006.01)

(21) International Application Number:
PCT/US2021/047616

(22) International Filing Date:
25 August 2021 (25.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/070,734 26 August 2020 (26.08.2020) US
63/081,801 22 September 2020 (22.09.2020) US

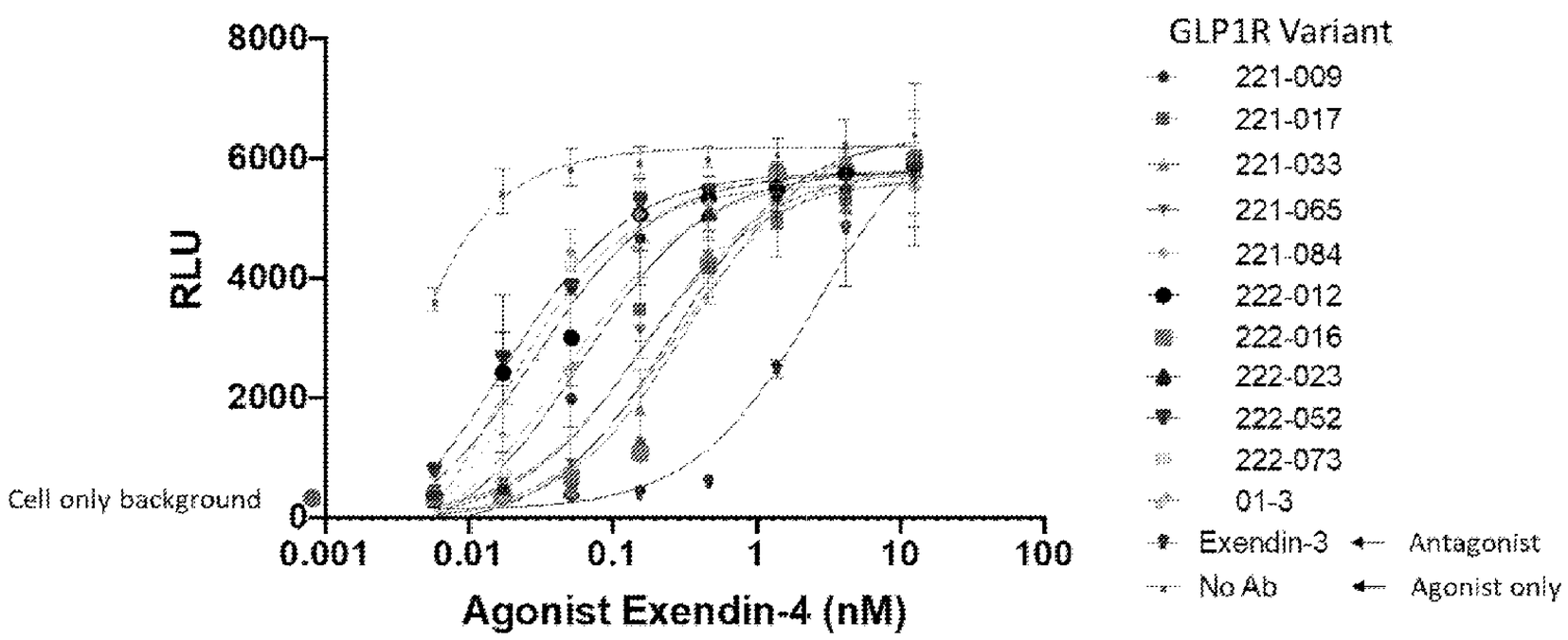
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) Title: METHODS AND COMPOSITIONS RELATING TO GLP1R VARIANTS



IC50 (nM)	221-009	221-017	221-033	221-065	221-084	222-012	222-016	222-023	222-052	222-073	01-3
to agonist	0.06177	0.183	0.2601	0.162	0.01574	0.0285	0.3353	0.267	0.01773	0.02394	0.04982

FIG. 26

(57) **Abstract:** Provided herein are methods and compositions relating to glucagon-like peptide-1 receptor (GLP1R) libraries having nucleic acids encoding for immunoglobulins that bind to GLP1R. Libraries described herein include variegated libraries comprising nucleic acids each encoding for a predetermined variant of at least one predetermined reference nucleic acid sequence. Further described herein are protein libraries generated when the nucleic acid libraries are translated. Further described herein are cell libraries expressing variegated nucleic acid libraries described herein.

[Continued on next page]

WO 2022/046944 A2

(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:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

METHODS AND COMPOSITIONS RELATING TO GLP1R VARIANTS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/070,734 filed on August 26, 2020, and U.S. Provisional Patent Application No. 63/081,801 filed on September 22, 2020, each of which is incorporated by reference in its entirety.

BACKGROUND

[0002] G protein-coupled receptors (GPCRs) are implicated in a wide variety of diseases. Raising antibodies to GPCRs has been difficult due to problems in obtaining suitable antigens because GPCRs are often expressed at low levels in cells and are very unstable when purified. Thus, there is a need for improved agents for therapeutic intervention which target GPCRs.

INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0004] Provided herein are antibodies or antibody fragments that binds GLP1R, comprising an immunoglobulin heavy chain and an immunoglobulin light chain: (a) wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in Table 9; and (b) wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in Table 10. Further provided herein are antibodies or antibody fragments, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment thereof is chimeric or humanized. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP

assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an agonist of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an antagonist of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the allosteric modulator of GLP1R is a negative allosteric modulator.

[0005] Provided herein are methods of treating a metabolic disease or disorder comprising administering an antibody or antibody fragment that binds GLP1R, wherein the antibody or antibody fragment comprises a sequence set forth in Tables 7-13. Further provided herein are methods, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof. Further provided herein are methods, wherein the antibody or antibody fragment thereof is chimeric or humanized. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment is an agonist of GLP1R. Further provided herein are methods, wherein the antibody or antibody fragment is an antagonist of GLP1R. Further provided herein are methods, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R. Further provided herein are methods, wherein the allosteric modulator of GLP1R is a negative allosteric modulator. Further provided herein are methods, wherein the antibody or antibody fragment is an allosteric modulator. Further provided herein are methods, wherein the antibody or antibody fragment is a negative allosteric modulator. Further provided herein are methods, wherein the metabolic disease or disorder is Type II diabetes or obesity.

[0006] Provided herein are antibodies or antibody fragments comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347. Further provided herein are antibodies or antibody fragments, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment thereof is chimeric or humanized. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an agonist of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an antagonist of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R. Further provided herein are antibodies or antibody fragments, wherein the allosteric modulator of GLP1R is a negative allosteric modulator. Further provided herein are antibodies or antibody fragments, wherein the VH comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 58-77. Further provided herein are antibodies or antibody fragments, wherein the VH comprises a sequence of any one of SEQ ID NOs: 58-77. Further provided herein are antibodies or antibody fragments, wherein the VL comprises a sequence at least about 90% identical to any one

of SEQ ID NOs: 92-111. Further provided herein are antibodies or antibody fragments, wherein the VL comprises a sequence of any one of SEQ ID NOs: 92-111.

[0007] Provided herein are methods of treating a metabolic disease or disorder comprising administering an antibody or antibody fragment that binds GLP1R comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347. Further provided herein are methods, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof. Further provided herein are methods, wherein the antibody or antibody fragment thereof is chimeric or humanized. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay. Further provided herein are methods, wherein the antibody or antibody fragment is an agonist of GLP1R. Further provided herein are methods, wherein the antibody or antibody fragment is an antagonist of GLP1R. Further provided herein are methods, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R. Further provided herein are methods, wherein the allosteric modulator of GLP1R is a negative allosteric modulator. Further provided herein are methods, wherein the antibody or antibody fragment is an allosteric modulator. Further provided herein are methods, wherein the antibody or antibody fragment is a negative allosteric modulator. Further provided herein are methods, wherein the VH comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 58-77. Further provided herein

are methods, wherein the VH comprises a sequence of any one of SEQ ID NOs: 58-77. Further provided herein are methods, wherein the VL comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 92-111. Further provided herein are methods, wherein the VL comprises a sequence of any one of SEQ ID NOs: 92-111. Further provided herein are methods, wherein the metabolic disease or disorder is Type II diabetes or obesity.

[0008] Provided herein are nucleic acid compositions comprising: a) a first nucleic acid encoding a variable domain, heavy chain region (VH) comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein (i) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (ii) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (iii) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; b) a second nucleic acid encoding a variable domain, light chain region (VL) comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (i) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (ii) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (iii) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347.

[0009] Provided herein are nucleic acid compositions comprising: a) a first nucleic acid encoding a variable domain, heavy chain region (VH) comprising an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 58-77; b) a second nucleic acid encoding a variable domain, light chain region (VL) comprising at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 92-111; and an excipient. Further provided herein are nucleic acid compositions, wherein the VH comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 58-77. Further provided herein are nucleic acid compositions, wherein the VL comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 92-111. Further provided herein are nucleic acid compositions, wherein the VH comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 58-77, and wherein the VL comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 92-111.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1A** depicts a first schematic of an immunoglobulin.

[0011] **Figure 1B** depicts a second schematic of an immunoglobulin.

[0012] **Figure 2** depicts a schematic of a motif for placement in an immunoglobulin.

[0013] **Figure 3** presents a diagram of steps demonstrating an exemplary process workflow for gene synthesis as disclosed herein.

[0014] **Figure 4** illustrates an example of a computer system.

[0015] **Figure 5** is a block diagram illustrating an architecture of a computer system.

[0016] **Figure 6** is a diagram demonstrating a network configured to incorporate a plurality of computer systems, a plurality of cell phones and personal data assistants, and Network Attached Storage (NAS).

[0017] **Figure 7** is a block diagram of a multiprocessor computer system using a shared virtual address memory space.

[0018] **Figure 8A** depicts a schematic of an immunoglobulin comprising a VH domain attached to a VL domain using a linker.

[0019] **Figure 8B** depicts a schematic of a full-domain architecture of an immunoglobulin comprising a VH domain attached to a VL domain using a linker, a leader sequence, and pIII sequence.

[0020] **Figure 8C** depicts a schematic of four framework elements (FW1, FW2, FW3, FW4) and the variable 3 CDR (L1, L2, L3) elements for a VL or VH domain.

[0021] **Figure 9A** depicts a structure of Glucagon-like peptide 1 (GLP-1, cyan) in complex with GLP-1 receptor (GLP-1R, grey), PDB entry 5VAI.

[0022] **Figure 9B** depicts a crystal structure of CXCR4 chemokine receptor (grey) in complex with a cyclic peptide antagonist CVX15 (blue), PDB entry 3OR0.

[0023] **Figure 9C** depicts a crystal structure of human smoothened receptor with the transmembrane domain in grey and extracellular domain (ECD) in orange, PDB entry 5L7D. The ECD contacts the TMD through extracellular loop 3 (ECL3).

[0024] **Figure 9D** depicts a structure of GLP-1R (grey) in complex with a Fab (magenta), PDB entry 6LN2.

[0025] **Figure 9E** depicts a crystal structure of CXCR4 (grey) in complex with a viral chemokine antagonist Viral macrophage inflammatory protein 2 (vMIP-II, green), PDB entry 4RWS.

[0026] **Figure 10** depicts a schema of the GPCR focused library design. Two germline heavy chain VH1-69 and VH3-30; 4 germline light chain IGKV1-39 and IGKV3-15, and IGLV1-51 and IGLV2-14.

[0027] **Figure 11** depicts a graph of HCDR3 length distribution in the GPCR-focused library compared to the HCDR3 length distribution in B-cell populations from three healthy adult donors. In total, 2,444,718 unique VH sequences from the GPCR library and 2,481,511 unique VH sequences from human B-cell repertoire were analyzed to generate the length distribution plot.

[0028] **Figure 12A** depicts the design of the over-expressing GLP-1R CHO cells for the phage antibody library selection. GLP-1R expression was confirmed by the gating of double detection of GFP green fluorescence and the surface expression of Flag tag on the cell surface.

[0029] **Figure 12B** depicts a cell-based panning process.

[0030] **Figure 13** depicts a graph of percent unique HCDR3 in the output pools of the five GLP-1R panning rounds.

[0031] **Figure 14** depicts a graph of binding plots of the 13 unique GLP-1R Hits, compared to the parental CHO cell binding.

[0032] **Figure 15** depicts HCDR3 loop sequences of the 13 unique GLP1R binders. Six of the clones have a GLP-1 motif, four of the clones have a GLP-2 motif, and three clones do not have a GLP-1 or GLP-2 motif. For the clones that have the GLP-1 or GLP-2 motif, residues that are similar to the GLP-1 sequence or the GLP-2 sequence are colored in black and the residues that are different are colored red. Functional antagonists in the cAMP assay are highlighted in yellow.

[0033] **Figure 16A** depicts a graph of orthosteric inhibition of GLP1R-3 binding in the absence and presence of GLP-1 (7-36).

[0034] **Figure 16B** depicts a graph of effects of GLP1R-3 on GLP-1 activation in the cAMP assay.

[0035] **Figure 16C** depicts a graph of effects of GLP1R-3 on GLP-1 induced β-arrestin recruitment.

[0036] **Figure 17** depicts a design of GLP1R-59-2. The GLP1 (7-36) peptide was linked to the N-terminal of light chain of the functionally inactive GLP-1R binding antibody GLP1R-2.

[0037] **Figure 18A** depicts a graph of GLP1R-59-2 binding specifically to the GLP-1R with an EC50 of 15.5 nM.

[0038] **Figure 18B** depicts a graph of GLP1R-59-2 in the cAMP assay with a similar EC50 as the GLP-1 7-36 peptide.

[0039] **Figure 18C** depicts a graph of GLP1R-59-2 on inducing the β-arrestin recruitment in GLP-1R expression cells.

[0040] **Figures 19A-19B** depict *in vivo* pharmacokinetic (PK) and pharmacodynamic (PD) effects of GLP1R-3 and GLP1R-59-2. Based on the beta phase calculation, GLP1R-3 has a 1-week half-life in rat (**Figure 19A**). GLP1R-59-2 has a 2-day half-life in rat (**Figure 19B**).

[0041] **Figure 20A** depicts a graph of GLP1R-59-2 on glucose after glucose challenge.

[0042] **Figure 20B** depicts a graph of Area Under the Curve (AUC) in a glucose tolerance test (GTT).

[0043] **Figure 21A** depicts a graph of GLP1R-3 and GLP-1 peptide Exendin 9-39 treatment, 19+2 hour dosing regimen

[0044] **Figure 21B** depicts a graph of Area Under the Curve (AUC) in an insulin tolerance test (ITT).

[0045] **Figure 22A** depicts a graph of GLP1R-3 treatment, single 6 hour dosing regimen after insulin challenge, as compared to GLP-1 peptide Exendin 9-39 (1.0 or 0.23 mg/kg dose) or control.

[0046] **Figure 22B** depicts a graph of Area Under the Curve (AUC) of GLP1R-3 (20mg/kg) treatment at 6 hours in an ITT.

[0047] **Figure 23A** depicts a graph of GLP1R-3 treatment, single 6 hour dosing regimen after insulin challenge, as compared to GLP1R-226-1, GLP1R-226-2, or control.

[0048] **Figure 23B** depicts a graph Area Under the Curve (AUC) of GLP1R-3 treatment, single 6 hour dosing regimen after insulin challenge, as compared to GLP1R-226-1, GLP1R-226-2, or control.

[0049] **Figures 24A-24B** are schemas of panning strategy for GLP1R-221 and GLP1R-222 variants.

[0050] **Figures 25A-25B** are graphs of competition data for GLP1R-221 and GLP1R-222 variants.

[0051] **Figure 26** is a graph of GLP1R-221 and GLP1R-222 variants in a cAMP assay.

DETAILED DESCRIPTION

[0052] The present disclosure employs, unless otherwise indicated, conventional molecular biology techniques, which are within the skill of the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art.

[0053] **Definitions**

[0054] Throughout this disclosure, various embodiments are presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of any embodiments. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range to the tenth of the unit of the lower limit unless the context clearly dictates otherwise. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual values within that range, for example, 1.1, 2, 2.3, 5, and 5.9. This applies regardless of the breadth of the

range. The upper and lower limits of these intervening ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure, unless the context clearly dictates otherwise.

[0055] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of any embodiment. As used herein, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, components, and/or groups, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items.

[0056] Unless specifically stated or obvious from context, as used herein, the term "about" in reference to a number or range of numbers is understood to mean the stated number and numbers +/- 10% thereof, or 10% below the lower listed limit and 10% above the higher listed limit for the values listed for a range.

[0057] Unless specifically stated, as used herein, the term "nucleic acid" encompasses double- or triple-stranded nucleic acids, as well as single-stranded molecules. In double- or triple-stranded nucleic acids, the nucleic acid strands need not be coextensive (i.e., a double-stranded nucleic acid need not be double-stranded along the entire length of both strands). Nucleic acid sequences, when provided, are listed in the 5' to 3' direction, unless stated otherwise. Methods described herein provide for the generation of isolated nucleic acids. Methods described herein additionally provide for the generation of isolated and purified nucleic acids. A "nucleic acid" as referred to herein can comprise at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, or more bases in length. Moreover, provided herein are methods for the synthesis of any number of polypeptide-segments encoding nucleotide sequences, including sequences encoding non-ribosomal peptides (NRPs), sequences encoding non-ribosomal peptide-synthetase (NRPS) modules and synthetic variants, polypeptide segments of other modular proteins, such as antibodies, polypeptide segments from other protein families, including non-coding DNA or RNA, such as regulatory sequences e.g. promoters, transcription factors, enhancers, siRNA, shRNA, RNAi, miRNA, small nucleolar RNA derived from microRNA, or any functional or structural DNA or RNA unit of interest. The following are non-limiting examples of

polynucleotides: coding or non-coding regions of a gene or gene fragment, intergenic DNA, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, short interfering RNA (siRNA), short-hairpin RNA (shRNA), micro-RNA (miRNA), small nucleolar RNA, ribozymes, complementary DNA (cDNA), which is a DNA representation of mRNA, usually obtained by reverse transcription of messenger RNA (mRNA) or by amplification; DNA molecules produced synthetically or by amplification, genomic DNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. cDNA encoding for a gene or gene fragment referred herein may comprise at least one region encoding for exon sequences without an intervening intron sequence in the genomic equivalent sequence.

[0058] GPCR Libraries for GLP1 Receptor

[0059] Provided herein are methods and compositions relating to G protein-coupled receptor (GPCR) binding libraries for glucagon-like peptide-1 receptor (GLP1R) comprising nucleic acids encoding for an immunoglobulin comprising a GPCR binding domain. Immunoglobulins as described herein can stably support a GPCR binding domain. The GPCR binding domain may be designed based on surface interactions of a GLP1R ligand and GLP1R. Libraries as described herein may be further variegated to provide for variant libraries comprising nucleic acids each encoding for a predetermined variant of at least one predetermined reference nucleic acid sequence. Further described herein are protein libraries that may be generated when the nucleic acid libraries are translated. In some instances, nucleic acid libraries as described herein are transferred into cells to generate a cell library. Also provided herein are downstream applications for the libraries synthesized using methods described herein. Downstream applications include identification of variant nucleic acids or protein sequences with enhanced biologically relevant functions, e.g., improved stability, affinity, binding, functional activity, and for the treatment or prevention of a disease state associated with GPCR signaling.

[0060] Provided herein are libraries comprising nucleic acids encoding for an immunoglobulin. In some instances, the immunoglobulin is an antibody. As used herein, the term antibody will be understood to include proteins having the characteristic two-armed, Y-shape of a typical antibody molecule as well as one or more fragments of an antibody that retain the ability to specifically bind to an antigen. Exemplary antibodies include, but are not limited to, a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv) (including fragments in which the VL and VH are joined using recombinant methods by a synthetic or natural linker that enables them to be made as a single

protein chain in which the VL and VH regions pair to form monovalent molecules, including single chain Fab and scFab), a single chain antibody, a Fab fragment (including monovalent fragments comprising the VL, VH, CL, and CH1 domains), a F(ab′)2 fragment (including bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge region), a Fd fragment (including fragments comprising the VH and CH1 fragment), a Fv fragment (including fragments comprising the VL and VH domains of a single arm of an antibody), a single-domain antibody (dAb or sdAb) (including fragments comprising a VH domain), an isolated complementarity determining region (CDR), a diabody (including fragments comprising bivalent dimers such as two VL and VH domains bound to each other and recognizing two different antigens), a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof. In some instances, the libraries disclosed herein comprise nucleic acids encoding for an immunoglobulin, wherein the immunoglobulin is a Fv antibody, including Fv antibodies comprised of the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. In some embodiments, the Fv antibody consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association, and the three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. In some embodiments, the six hypervariable regions confer antigen-binding specificity to the antibody. In some embodiments, a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen, including single domain antibodies isolated from camelid animals comprising one heavy chain variable domain such as VHH antibodies or nanobodies) has the ability to recognize and bind antigen. In some instances, the libraries disclosed herein comprise nucleic acids encoding for an immunoglobulin, wherein the immunoglobulin is a single-chain Fv or scFv, including antibody fragments comprising a VH, a VL, or both a VH and VL domain, wherein both domains are present in a single polypeptide chain. In some embodiments, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains allowing the scFv to form the desired structure for antigen binding. In some instances, a scFv is linked to the Fc fragment or a VHH is linked to the Fc fragment (including minibodies). In some instances, the antibody comprises immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, e.g., molecules that contain an antigen binding site. Immunoglobulin molecules are of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG 1, IgG 2, IgG 3, IgG 4, IgA 1 and IgA 2), or subclass.

[0061] In some embodiments, libraries comprise immunoglobulins that are adapted to the species of an intended therapeutic target. Generally, these methods include “mammalization” and

comprise methods for transferring donor antigen-binding information to a less immunogenic mammal antibody acceptor to generate useful therapeutic treatments. In some instances, the mammal is mouse, rat, equine, sheep, cow, primate (*e.g.,* chimpanzee, baboon, gorilla, orangutan, monkey), dog, cat, pig, donkey, rabbit, or human. In some instances, provided herein are libraries and methods for felinization and caninization of antibodies.

[0062] "Humanized" forms of non-human antibodies can be chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human antibody (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody). The donor antibody can be any suitable non-human antibody, such as a mouse, rat, rabbit, chicken, or non-human primate antibody having a desired specificity, affinity, or biological effect. In some instances, selected framework region residues of the recipient antibody are replaced by the corresponding framework region residues from the donor antibody. Humanized antibodies may also comprise residues that are not found in either the recipient antibody or the donor antibody. In some instances, these modifications are made to further refine antibody performance.

[0063] "Caninization" can comprise a method for transferring non-canine antigen-binding information from a donor antibody to a less immunogenic canine antibody acceptor to generate treatments useful as therapeutics in dogs. In some instances, caninized forms of non-canine antibodies provided herein are chimeric antibodies that contain minimal sequence derived from non-canine antibodies. In some instances, caninized antibodies are canine antibody sequences ("acceptor" or "recipient" antibody) in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-canine species ("donor" antibody) such as mouse, rat, rabbit, cat, dogs, goat, chicken, bovine, horse, llama, camel, dromedaries, sharks, non-human primates, human, humanized, recombinant sequence, or an engineered sequence having the desired properties. In some instances, framework region (FR) residues of the canine antibody are replaced by corresponding non-canine FR residues. In some instances, caninized antibodies include residues that are not found in the recipient antibody or in the donor antibody. In some instances, these modifications are made to further refine antibody performance. The caninized antibody may also comprise at least a portion of an immunoglobulin constant region (Fc) of a canine antibody.

[0064] "Felinization" can comprise a method for transferring non-feline antigen-binding information from a donor antibody to a less immunogenic feline antibody acceptor to generate treatments useful as therapeutics in cats. In some instances, felinized forms of non-feline antibodies provided herein are chimeric antibodies that contain minimal sequence derived from non-feline antibodies. In some instances, felinized antibodies are feline antibody sequences

("acceptor" or "recipient" antibody) in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-feline species ("donor" antibody) such as mouse, rat, rabbit, cat, dogs, goat, chicken, bovine, horse, llama, camel, dromedaries, sharks, non-human primates, human, humanized, recombinant sequence, or an engineered sequence having the desired properties. In some instances, framework region (FR) residues of the feline antibody are replaced by corresponding non-feline FR residues. In some instances, felinized antibodies include residues that are not found in the recipient antibody or in the donor antibody. In some instances, these modifications are made to further refine antibody performance. The felinized antibody may also comprise at least a portion of an immunoglobulin constant region (Fc) of a felinize antibody.

[0065] Provided herein are libraries comprising nucleic acids encoding for a non-immunoglobulin. For example, the non-immunoglobulin is an antibody mimetic. Exemplary antibody mimetics include, but are not limited to, anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, atrimers, DARPins, fynomers, Kunitz domain-based proteins, monobodies, anticalins, knottins, armadillo repeat protein-based proteins, and bicyclic peptides.

[0066] Libraries described herein comprising nucleic acids encoding for an immunoglobulin comprising variations in at least one region of the immunoglobulin. Exemplary regions of the antibody for variation include, but are not limited to, a complementarity-determining region (CDR), a variable domain, or a constant domain. In some instances, the CDR is CDR1, CDR2, or CDR3. In some instances, the CDR is a heavy domain including, but not limited to, CDRH1, CDRH2, and CDRH3. In some instances, the CDR is a light domain including, but not limited to, CDRL1, CDRL2, and CDRL3. In some instances, the variable domain is variable domain, light chain (VL) or variable domain, heavy chain (VH). In some instances, the VL domain comprises kappa or lambda chains. In some instances, the constant domain is constant domain, light chain (CL) or constant domain, heavy chain (CH).

[0067] Methods described herein provide for synthesis of libraries comprising nucleic acids encoding for an immunoglobulin, wherein each nucleic acid encodes for a predetermined variant of at least one predetermined reference nucleic acid sequence. In some cases, the predetermined reference sequence is a nucleic acid sequence encoding for a protein, and the variant library comprises sequences encoding for variation of at least a single codon such that a plurality of different variants of a single residue in the subsequent protein encoded by the synthesized nucleic acid are generated by standard translation processes. In some instances, the variant library comprises varied nucleic acids collectively encoding variations at multiple positions. In some instances, the variant library comprises sequences encoding for variation of at least a single codon of a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, or VH domain. In some instances,

the variant library comprises sequences encoding for variation of multiple codons of a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, or VH domain. In some instances, the variant library comprises sequences encoding for variation of multiple codons of framework element 1 (FW1), framework element 2 (FW2), framework element 3 (FW3), or framework element 4 (FW4). An exemplary number of codons for variation include, but are not limited to, at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 225, 250, 275, 300, or more than 300 codons.

[0068] In some instances, the at least one region of the immunoglobulin for variation is from heavy chain V-gene family, heavy chain D-gene family, heavy chain J-gene family, light chain V-gene family, or light chain J-gene family. In some instances, the light chain V-gene family comprises immunoglobulin kappa (IGK) gene or immunoglobulin lambda (IGL). Exemplary genes include, but are not limited to, IGHV1-18, IGHV1-69, IGHV1-8, IGHV3-21, IGHV3-23, IGHV3-30/33rn, IGHV3-28, IGHV1-69, IGHV3-74, IGHV4-39, IGHV4-59/61, IGKV1-39, IGKV1-9, IGKV2-28, IGKV3-11, IGKV3-15, IGKV3-20, IGKV4-1, IGLV1-51, IGLV2-14, IGLV1-40, and IGLV3-1. In some instances, the gene is IGHV1-69, IGHV3-30, IGHV3-23, IGHV3, IGHV1-46, IGHV3-7, IGHV1, or IGHV1-8. In some instances, the gene is IGHV1-69 and IGHV3-30. In some instances, the gene is IGHJ3, IGHJ6, IGHJ, IGHJ4, IGHJ5, IGHJ2, or IGH1. In some instances, the gene is IGHJ3, IGHJ6, IGHJ, or IGHJ4.

[0069] Provided herein are libraries comprising nucleic acids encoding for immunoglobulins, wherein the libraries are synthesized with various numbers of fragments. In some instances, the fragments comprise the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, or VH domain. In some instances, the fragments comprise framework element 1 (FW1), framework element 2 (FW2), framework element 3 (FW3), or framework element 4 (FW4). In some instances, the immunoglobulin libraries are synthesized with at least or about 2 fragments, 3 fragments, 4 fragments, 5 fragments, or more than 5 fragments. The length of each of the nucleic acid fragments or average length of the nucleic acids synthesized may be at least or about 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, or more than 600 base pairs. In some instances, the length is about 50 to 600, 75 to 575, 100 to 550, 125 to 525, 150 to 500, 175 to 475, 200 to 450, 225 to 425, 250 to 400, 275 to 375, or 300 to 350 base pairs.

[0070] Libraries comprising nucleic acids encoding for immunoglobulins as described herein comprise various lengths of amino acids when translated. In some instances, the length of each of the amino acid fragments or average length of the amino acid synthesized may be at least or about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130,

135, 140, 145, 150, or more than 150 amino acids. In some instances, the length of the amino acid is about 15 to 150, 20 to 145, 25 to 140, 30 to 135, 35 to 130, 40 to 125, 45 to 120, 50 to 115, 55 to 110, 60 to 110, 65 to 105, 70 to 100, or 75 to 95 amino acids. In some instances, the length of the amino acid is about 22 amino acids to about 75 amino acids. In some instances, the immunoglobulins comprise at least or about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, or more than 5000 amino acids.

[0071] A number of variant sequences for the at least one region of the immunoglobulin for variation are de novo synthesized using methods as described herein. In some instances, a number of variant sequences is de novo synthesized for CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, VH, or combinations thereof. In some instances, a number of variant sequences is de novo synthesized for framework element 1 (FW1), framework element 2 (FW2), framework element 3 (FW3), or framework element 4 (FW4). The number of variant sequences may be at least or about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, or more than 500 sequences. In some instances, the number of variant sequences is at least or about 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, or more than 8000 sequences. In some instances, the number of variant sequences is about 10 to 500, 25 to 475, 50 to 450, 75 to 425, 100 to 400, 125 to 375, 150 to 350, 175 to 325, 200 to 300, 225 to 375, 250 to 350, or 275 to 325 sequences.

[0072] Variant sequences for the at least one region of the immunoglobulin, in some instances, vary in length or sequence. In some instances, the at least one region that is de novo synthesized is for CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, VH, or combinations thereof. In some instances, the at least one region that is de novo synthesized is for framework element 1 (FW1), framework element 2 (FW2), framework element 3 (FW3), or framework element 4 (FW4). In some instances, the variant sequence comprises at least or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, or more than 50 variant nucleotides or amino acids as compared to wild-type. In some instances, the variant sequence comprises at least or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 additional nucleotides or amino acids as compared to wild-type. In some instances, the variant sequence comprises at least or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, or 50 less nucleotides or amino acids as compared to wild-type. In some instances, the libraries comprise at least or about 10^1, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, or more than 10^{10} variants.

[0073] Following synthesis of libraries described herein, libraries may be used for screening and analysis. For example, libraries are assayed for library displayability and panning. In some instances, displayability is assayed using a selectable tag. Exemplary tags include, but are not

limited to, a radioactive label, a fluorescent label, an enzyme, a chemiluminescent tag, a colorimetric tag, an affinity tag or other labels or tags that are known in the art. In some instances, the tag is histidine, polyhistidine, myc, hemagglutinin (HA), or FLAG. In some instances, libraries are assayed by sequencing using various methods including, but not limited to, single-molecule real-time (SMRT) sequencing, Polony sequencing, sequencing by ligation, reversible terminator sequencing, proton detection sequencing, ion semiconductor sequencing, nanopore sequencing, electronic sequencing, pyrosequencing, Maxam-Gilbert sequencing, chain termination (e.g., Sanger) sequencing, +S sequencing, or sequencing by synthesis.

[0074] In some instances, the libraries are assayed for functional activity, structural stability (e.g., thermal stable or pH stable), expression, specificity, or a combination thereof. In some instances, the libraries are assayed for immunoglobulin (e.g., an antibody) capable of folding. In some instances, a region of the antibody is assayed for functional activity, structural stability, expression, specificity, folding, or a combination thereof. For example, a VH region or VL region is assayed for functional activity, structural stability, expression, specificity, folding, or a combination thereof.

[0075] *GLP1R Libraries*

[0076] Provided herein are GLP1R binding libraries comprising nucleic acids encoding for immunoglobulins (e.g., antibodies) that bind to GLP1R. In some instances, the immunoglobulin sequences for GLP1R binding domains are determined by interactions between the GLP1R binding domains and the GLP1R.

[0077] Provided herein are libraries comprising nucleic acids encoding immunoglobulins comprising GLP1R binding domains, wherein the GLP1R binding domains are designed based on surface interactions on GLP1R. In some instances, the GLP1R comprises a sequence as defined by SEQ ID NO: 1. In some instances, the GLP1R binding domains interact with the amino- or carboxy-terminus of the GLP1R. In some instances, the GLP1R binding domains interact with at least one transmembrane domain including, but not limited to, transmembrane domain 1 (TM1), transmembrane domain 2 (TM2), transmembrane domain 3 (TM3), transmembrane domain 4 (TM4), transmembrane domain 5 (TM5), transmembrane domain 6 (TM6), and transmembrane domain 7 (TM7). In some instances, the GLP1R binding domains interact with an intracellular surface of the GLP1R. For example, the GLP1R binding domains interact with at least one intracellular loop including, but not limited to, intracellular loop 1 (ICL1), intracellular loop 2 (ICL2), and intracellular loop 3 (ICL3). In some instances, the GLP1R binding domains interact with an extracellular surface of the GLP1R. For example, the GLP1R binding domains interact with at least one extracellular domain (ECD) or extracellular loop (ECL) of the GLP1R. The

extracellular loops include, but are not limited to, extracellular loop 1 (ECL1), extracellular loop 2 (ECL2), and extracellular loop 3 (ECL3).

[0078] Described herein are GLP1R binding domains, wherein the GLP1R binding domains are designed based on surface interactions between a GLP1R ligand and the GLP1R. In some instances, the ligand is a peptide. In some instances, the ligand is glucagon, glucagon-like peptide 1-(7-36) amide, glucagon-like peptide 1-(7-37), liraglutide, exendin-4, lixisenatide, T-0632, GLP1R0017, or BETP. In some instances, the ligand is a GLP1R agonist. In some instances, the ligand is a GLP1R antagonist. In some instances, the ligand is a GLP1R allosteric modulator. In some instances, the allosteric modulator is a negative allosteric modulator. In some instances, the allosteric modulator is a positive allosteric modulator.

[0079] Sequences of GLP1R binding domains based on surface interactions between a GLP1R ligand and the GLP1R are analyzed using various methods. For example, multispecies computational analysis is performed. In some instances, a structure analysis is performed. In some instances, a sequence analysis is performed. Sequence analysis can be performed using a database known in the art. Non-limiting examples of databases include, but are not limited to, NCBI BLAST (blast.ncbi.nlm.nih.gov/Blast.cgi), UCSC Genome Browser (genome.ucsc.edu/), UniProt (www.uniprot.org/), and IUPHAR/BPS Guide to PHARMACOLOGY (guidetopharmacology.org/).

[0080] Described herein are GLP1R binding domains designed based on sequence analysis among various organisms. For example, sequence analysis is performed to identify homologous sequences in different organisms. Exemplary organisms include, but are not limited to, mouse, rat, equine, sheep, cow, primate (*e.g.*, chimpanzee, baboon, gorilla, orangutan, monkey), dog, cat, pig, donkey, rabbit, fish, fly, and human.

[0081] Following identification of GLP1R binding domains, libraries comprising nucleic acids encoding for the GLP1R binding domains may be generated. In some instances, libraries of GLP1R binding domains comprise sequences of GLP1R binding domains designed based on conformational ligand interactions, peptide ligand interactions, small molecule ligand interactions, extracellular domains of GLP1R, or antibodies that target GLP1R. In some instances, libraries of GLP1R binding domains comprise sequences of GLP1R binding domains designed based on peptide ligand interactions. Libraries of GLP1R binding domains may be translated to generate protein libraries. In some instances, libraries of GLP1R binding domains are translated to generate peptide libraries, immunoglobulin libraries, derivatives thereof, or combinations thereof. In some instances, libraries of GLP1R binding domains are translated to generate protein libraries that are further modified to generate peptidomimetic libraries. In some instances, libraries of GLP1R

binding domains are translated to generate protein libraries that are used to generate small molecules.

[0082] Methods described herein provide for synthesis of libraries of GLP1R binding domains comprising nucleic acids each encoding for a predetermined variant of at least one predetermined reference nucleic acid sequence. In some cases, the predetermined reference sequence is a nucleic acid sequence encoding for a protein, and the variant library comprises sequences encoding for variation of at least a single codon such that a plurality of different variants of a single residue in the subsequent protein encoded by the synthesized nucleic acid are generated by standard translation processes. In some instances, the libraries of GLP1R binding domains comprise varied nucleic acids collectively encoding variations at multiple positions. In some instances, the variant library comprises sequences encoding for variation of at least a single codon in a GLP1R binding domain. In some instances, the variant library comprises sequences encoding for variation of multiple codons in a GLP1R binding domain. An exemplary number of codons for variation include, but are not limited to, at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 225, 250, 275, 300, or more than 300 codons.

[0083] Methods described herein provide for synthesis of libraries comprising nucleic acids encoding for the GLP1R binding domains, wherein the libraries comprise sequences encoding for variation of length of the GLP1R binding domains. In some instances, the library comprises sequences encoding for variation of length of at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 225, 250, 275, 300, or more than 300 codons less as compared to a predetermined reference sequence. In some instances, the library comprises sequences encoding for variation of length of at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, or more than 300 codons more as compared to a predetermined reference sequence.

[0084] Following identification of GLP1R binding domains, the GLP1R binding domains may be placed in immunoglobulins as described herein. In some instances, the GLP1R binding domains are placed in the CDRH3 region. GPCR binding domains that may be placed in immunoglobulins can also be referred to as a motif. Immunoglobulins comprising GLP1R binding domains may be designed based on binding, specificity, stability, expression, folding, or downstream activity. In some instances, the immunoglobulins comprising GLP1R binding domains enable contact with the GLP1R. In some instances, the immunoglobulins comprising GLP1R binding domains enables high affinity binding with the GLP1R. An exemplary amino acid sequence of GLP1R binding domain is described in **Table 1**.

Table 1. GLP1R amino acid sequences

SEQ ID NO	GPCR	Amino Acid Sequence
1352	GLP1R	RPQGATVSLWETVQKWREYRRQCQRSLTEDPPPATDLFCNRTFDEYA CWPDGEPGSFVNVSCPWYLPWASSVPQGHVYRFCTAEGLWLQKDNS SLPWRDLSECEESKRGERSSPEEQLLFLYIIYTVGYALSFSALVIASAIL LGFRHLHCTRNYIHLNLFASFILRALSVFIKDAALKWMYSTAAQQHQ WDGLLSYQDSLSCRLVFLLMQYCVAANYYWLLVEGVYLYTLLAFSV LSEQWIFRLYVSIGWGVPLLFVVPWGIVKYLYEDEGCWTRNSNMNY WLIIRLPILFAIGVNFLIFVRVICIVVSKLKANLMCKTDIKCRLAKSTLT LIPLLGTHEVIFAFVMDEHARGTLRFIKLFTELSFTSFQGLMVAILYCF VNNEVQLEFRKSWERWRLEHLHIQRDSSMKPLKCPTSSLSSGATAGS SMYTATCQASCS

[0085] Provided herein are immunoglobulins comprising GLP1R binding domains, wherein the sequences of the GLP1R binding domains support interaction with GLP1R. The sequence may be homologous or identical to a sequence of a GLP1R ligand. In some instances, the GLP1R binding domain sequence comprises at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 1. In some instances, the GLP1R binding domain sequence comprises at least or about 95% homology to SEQ ID NO: 1. In some instances, the GLP1R binding domain sequence comprises at least or about 97% homology to SEQ ID NO: 1. In some instances, the GLP1R binding domain sequence comprises at least or about 99% homology to SEQ ID NO: 1. In some instances, the GLP1R binding domain sequence comprises at least or about 100% homology to SEQ ID NO: 1. In some instances, the GLP1R binding domain sequence comprises at least a portion having at least or about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, or more than 400 amino acids of SEQ ID NO: 1.

[0086] The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as EMBOSS MATCHER, EMBOSS WATER, EMBOSS STRETCHER, EMBOSS

NEEDLE, EMBOSS LALIGN, BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0087] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y, where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0088] The term “homology” or “similarity” between two proteins is determined by comparing the amino acid sequence and its conserved amino acid substitutes of one protein sequence to the second protein sequence. Similarity may be determined by procedures which are well-known in the art, for example, a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information).

[0001] The terms “complementarity determining region,” and “CDR,” which are synonymous with “hypervariable region” or “HVR,” are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDRH1, CDRH2, CDRH3) and three CDRs in each light chain variable region (CDRL1, CDRL2, CDRL3). “Framework regions” and “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4). The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 (“Chothia”

numbering scheme); MacCallum et al., J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745." ("Contact" numbering scheme); Lefranc MP et al., "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp Immunol, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme); Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," J Mol Biol, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme); and Whitelegg NR and Rees AR, "WAM: an improved algorithm for modelling antibodies on the WEB," Protein Eng. 2000 Dec;13(12):819-24 ("AbM" numbering scheme. In certain embodiments the CDRs of the antibodies described herein can be defined by a method selected from Kabat, Chothia, IMGT, Aho, AbM, or combinations thereof.

[0089] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based on structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, "30a," and deletions appearing in some antibodies. The two schemes place certain insertions and deletions ("indels") at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0090] Provided herein are GLP1R binding libraries comprising nucleic acids encoding for immunoglobulins comprising GLP1R binding domains comprise variation in domain type, domain length, or residue variation. In some instances, the domain is a region in the immunoglobulin comprising the GLP1R binding domains. For example, the region is the VH, CDRH3, or VL domain. In some instances, the domain is the GLP1R binding domain.

[0091] Methods described herein provide for synthesis of a GLP1R binding library of nucleic acids each encoding for a predetermined variant of at least one predetermined reference nucleic acid sequence. In some cases, the predetermined reference sequence is a nucleic acid sequence encoding for a protein, and the variant library comprises sequences encoding for variation of at least a single codon such that a plurality of different variants of a single residue in the subsequent protein encoded by the synthesized nucleic acid are generated by standard translation processes. In some instances, the GLP1R binding library comprises varied nucleic acids collectively encoding variations at multiple positions. In some instances, the variant library comprises sequences encoding for variation of at least a single codon of a VH, CDRH3, or VL domain. In some instances, the variant library comprises sequences encoding for variation of at least a single codon

in a GLP1R binding domain. For example, at least one single codon of a GLP1R binding domain as listed in **Table 1** is varied. In some instances, the variant library comprises sequences encoding for variation of multiple codons of a VH, CDRH3, or VL domain. In some instances, the variant library comprises sequences encoding for variation of multiple codons in a GLP1R binding domain. An exemplary number of codons for variation include, but are not limited to, at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 225, 250, 275, 300, or more than 300 codons.

[0092] Methods described herein provide for synthesis of a GLP1R binding library of nucleic acids each encoding for a predetermined variant of at least one predetermined reference nucleic acid sequence, wherein the GLP1R binding library comprises sequences encoding for variation of length of a domain. In some instances, the domain is VH, CDRH3, or VL domain. In some instances, the domain is the GLP1R binding domain. In some instances, the library comprises sequences encoding for variation of length of at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 225, 250, 275, 300, or more than 300 codons less as compared to a predetermined reference sequence. In some instances, the library comprises sequences encoding for variation of length of at least or about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, or more than 300 codons more as compared to a predetermined reference sequence.

[0093] Provided herein are GLP1R binding libraries comprising nucleic acids encoding for immunoglobulins comprising GLP1R binding domains, wherein the GLP1R binding libraries are synthesized with various numbers of fragments. In some instances, the fragments comprise the VH, CDRH3, or VL domain. In some instances, the GLP1R binding libraries are synthesized with at least or about 2 fragments, 3 fragments, 4 fragments, 5 fragments, or more than 5 fragments. The length of each of the nucleic acid fragments or average length of the nucleic acids synthesized may be at least or about 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, or more than 600 base pairs. In some instances, the length is about 50 to 600, 75 to 575, 100 to 550, 125 to 525, 150 to 500, 175 to 475, 200 to 450, 225 to 425, 250 to 400, 275 to 375, or 300 to 350 base pairs.

[0094] GLP1R binding libraries comprising nucleic acids encoding for immunoglobulins comprising GLP1R binding domains as described herein comprise various lengths of amino acids when translated. In some instances, the length of each of the amino acid fragments or average length of the amino acid synthesized may be at least or about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, or more than 150 amino acids. In some instances, the length of the amino acid is about 15 to 150, 20 to 145, 25 to

140, 30 to 135, 35 to 130, 40 to 125, 45 to 120, 50 to 115, 55 to 110, 60 to 110, 65 to 105, 70 to 100, or 75 to 95 amino acids. In some instances, the length of the amino acid is about 22 to about 75 amino acids.

[0095] GLP1R binding libraries comprising de novo synthesized variant sequences encoding for immunoglobulins comprising GLP1R binding domains comprise a number of variant sequences. In some instances, a number of variant sequences is de novo synthesized for a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3, VL, VH, or a combination thereof. In some instances, a number of variant sequences is de novo synthesized for framework element 1 (FW1), framework element 2 (FW2), framework element 3 (FW3), or framework element 4 (FW4). In some instances, a number of variant sequences is de novo synthesized for a GPCR binding domain. For example, the number of variant sequences is about 1 to about 10 sequences for the VH domain, about 10^8 sequences for the GLP1R binding domain, and about 1 to about 44 sequences for the VK domain. The number of variant sequences may be at least or about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, or more than 500 sequences. In some instances, the number of variant sequences is about 10 to 300, 25 to 275, 50 to 250, 75 to 225, 100 to 200, or 125 to 150 sequences.

[0096] Described herein are antibodies or antibody fragments thereof that binds GLP1R. In some embodiments, the antibody or antibody fragment thereof comprises a sequence as set forth in **Tables 7-13**. In some embodiments, the antibody or antibody fragment thereof comprises a sequence that is at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence as set forth in **Tables 7-13**.

[0097] In some instances, an antibody or antibody fragment described herein comprises a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, an antibody or antibody fragment described herein comprises a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances,

an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, an antibody or antibody fragment described herein comprises a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977.

[0098] In some instances, an antibody or antibody fragment described herein comprises a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, an antibody or antibody fragment described herein comprises a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, an antibody or antibody fragment described

herein comprises a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 80% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 85% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 90% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, an antibody or antibody fragment described herein comprises a sequence that is at least 95% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347.

[0099] In some embodiments, the antibody or antibody fragment comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347. In some embodiments, the antibody or antibody fragment comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 1169-1347.

[00100] Described herein, in some embodiments, are antibodies or antibody fragments comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein the VH comprises an amino acid sequence at least about 90% identical to a sequence

as set forth in any one of SEQ ID NOs: 58-77, and wherein the VL comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 92-111. In some instances, the antibodies or antibody fragments comprise VH comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 58-77, and VL comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 92-111.

[00101] The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. Typically, techniques for determining sequence identity include comparing two nucleotide or amino acid sequences and the determining their percent identity. Sequence comparisons, such as for the purpose of assessing identities, may be performed by any suitable alignment algorithm, including but not limited to the Needleman-Wunsch algorithm (see, e.g., the EMBOSS Needle aligner available at www.ebi.ac.uk/Tools/psa/emboss_needle/, optionally with default settings), the BLAST algorithm (see, e.g., the BLAST alignment tool available at blast.ncbi.nlm.nih.gov/Blast.cgi, optionally with default settings), and the Smith-Waterman algorithm (see, e.g., the EMBOSS Water aligner available at www.ebi.ac.uk/Tools/psa/emboss_water/, optionally with default settings). Optimal alignment may be assessed using any suitable parameters of a chosen algorithm, including default parameters. The "percent identity", also referred to as "percent homology", between two sequences may be calculated as the number of exact matches between two optimally aligned sequences divided by the length of the reference sequence and multiplied by 100. Percent identity may also be determined, for example, by comparing sequence information using the advanced BLAST computer program, including version 2.2.9, available from the National Institutes of Health. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul, et al., J. Mol. Biol. 215:403-410 (1990); Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997). Briefly, the BLAST program defines identity as the number of identical aligned symbols (i.e., nucleotides or amino acids), divided by the total number of symbols in the shorter of

the two sequences. The program may be used to determine percent identity over the entire length of the sequences being compared. Default parameters are provided to optimize searches with short query sequences, for example, with the blastp program. The program also allows use of an SEG filter to mask-off segments of the query sequences as determined by the SEG program of Wootton and Federhen, Computers and Chemistry 17: 149-163 (1993). High sequence identity generally includes ranges of sequence identity of approximately 80% to 100% and integer values there between.

[00102] GLP1R binding libraries comprising de novo synthesized variant sequences encoding for immunoglobulins comprising GLP1R binding domains comprise improved diversity. For example, variants are generated by placing GLP1R binding domain variants in immunoglobulins comprising N-terminal CDRH3 variations and C-terminal CDRH3 variations. In some instances, variants include affinity maturation variants. Alternatively or in combination, variants include variants in other regions of the immunoglobulin including, but not limited to, CDRH1, CDRH2, CDRL1, CDRL2, and CDRL3. In some instances, the number of variants of the GLP1R binding libraries is at least or about 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} non-identical sequences. For example, a library comprising about 10 variant sequences for a VH region, about 237 variant sequences for a CDRH3 region, and about 43 variant sequences for a VL and CDRL3 region comprises 10^5 non-identical sequences (10 x 237 x 43).

[00103] In some instances, the at least one region of the antibody for variation is from heavy chain V-gene family, heavy chain D-gene family, heavy chain J-gene family, light chain V-gene family, or light chain J-gene family. In some instances, the light chain V-gene family comprises immunoglobulin kappa (IGK) gene or immunoglobulin lambda (IGL). Exemplary regions of the antibody for variation include, but are not limited to, IGHV1-18, IGHV1-69, IGHV1-8, IGHV3-21, IGHV3-23, IGHV3-30/33rn, IGHV3-28, IGHV1-69, IGHV3-74, IGHV4-39, IGHV4-59/61, IGKV1-39, IGKV1-9, IGKV2-28, IGKV3-11, IGKV3-15, IGKV3-20, IGKV4-1, IGLV1-51, IGLV2-14, IGLV1-40, and IGLV3-1. In some instances, the gene is IGHV1-69, IGHV3-30, IGHV3-23, IGHV3, IGHV1-46, IGHV3-7, IGHV1, or IGHV1-8. In some instances, the gene is IGHV1-69 and IGHV3-30. In some instances, the region of the antibody for variation is IGHJ3, IGHJ6, IGHJ, IGHJ4, IGHJ5, IGHJ2, or IGH1. In some instances, the region of the antibody for variation is IGHJ3, IGHJ6, IGHJ, or IGHJ4. In some instances, the at least one region of the antibody for variation is IGHV1-69, IGHV3-23, IGKV3-20, IGKV1-39, or combinations thereof. In some instances, the at least one region of the antibody for variation is IGHV1-69 and IGKV3-20, In some instances, the at least one region of the antibody for variation is IGHV1-69 and IGKV1-39.

In some instances, the at least one region of the antibody for variation is IGHV3-23 and IGKV3-20. In some instances, the at least one region of the antibody for variation is IGHV3-23 and IGKV1-39.

[00104] Provided herein are libraries comprising nucleic acids encoding for a GLP1R antibody comprising variation in at least one region of the antibody, wherein the region is the CDR region. In some instances, the GLP1R antibody is a single domain antibody comprising one heavy chain variable domain such as a VHH antibody. In some instances, the VHH antibody comprises variation in one or more CDR regions. In some instances, libraries described herein comprise at least or about 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2400, 2600, 2800, 3000, or more than 3000 sequences of a CDR1, CDR2, or CDR3. In some instances, libraries described herein comprise at least or about 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} sequences of a CDR1, CDR2, or CDR3. For example, the libraries comprise at least 2000 sequences of a CDR1, at least 1200 sequences for CDR2, and at least 1600 sequences for CDR3. In some instances, each sequence is non-identical.

[00105] In some instances, the CDR1, CDR2, or CDR3 is of a variable domain, light chain (VL). CDR1, CDR2, or CDR3 of a variable domain, light chain (VL) can be referred to as CDRL1, CDRL2, or CDRL3, respectively. In some instances, libraries described herein comprise at least or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2400, 2600, 2800, 3000, or more than 3000 sequences of a CDR1, CDR2, or CDR3 of the VL. In some instances, libraries described herein comprise at least or about 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} sequences of a CDR1, CDR2, or CDR3 of the VL. For example, the libraries comprise at least 20 sequences of a CDR1 of the VL, at least 4 sequences of a CDR2 of the VL, and at least 140 sequences of a CDR3 of the VL. In some instances, the libraries comprise at least 2 sequences of a CDR1 of the VL, at least 1 sequence of CDR2 of the VL, and at least 3000 sequences of a CDR3 of the VL. In some instances, the VL is IGKV1-39, IGKV1-9, IGKV2-28, IGKV3-11, IGKV3-15, IGKV3-20, IGKV4-1, IGLV1-51, IGLV2-14, IGLV1-40, or IGLV3-1. In some instances, the VL is IGKV2-28. In some instances, the VL is IGLV1-51.

[00106] In some instances, the CDR1, CDR2, or CDR3 is of a variable domain, heavy chain (VH). CDR1, CDR2, or CDR3 of a variable domain, heavy chain (VH) can be referred to as CDRH1, CDRH2, or CDRH3, respectively. In some instances, libraries described herein comprise at least or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2400, 2600, 2800, 3000, or more than 3000 sequences of a CDR1, CDR2, or CDR3 of the VH. In some instances, libraries described

herein comprise at least or about 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} sequences of a CDR1, CDR2, or CDR3 of the VH. For example, the libraries comprise at least 30 sequences of a CDR1 of the VH, at least 570 sequences of a CDR2 of the VH, and at least 10^8 sequences of a CDR3 of the VH. In some instances, the libraries comprise at least 30 sequences of a CDR1 of the VH, at least 860 sequences of a CDR2 of the VH, and at least 10^7 sequences of a CDR3 of the VH. In some instances, the VH is IGHV1-18, IGHV1-69, IGHV1-8 IGHV3-21, IGHV3-23, IGHV3-30/33rn, IGHV3-28, IGHV3-74, IGHV4-39, or IGHV4-59/61. In some instances, the VH is IGHV1-69, IGHV3-30, IGHV3-23, IGHV3, IGHV1-46, IGHV3-7, IGHV1, or IGHV1-8. In some instances, the VH is IGHV1-69 or IGHV3-30. In some instances, the VH is IGHV3-23.

[00107] Libraries as described herein, in some embodiments, comprise varying lengths of a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3. In some instances, the length of the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3 comprises at least or about 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, 40, 50, 60, 70, 80, 90, or more than 90 amino acids in length. For example, the CDRH3 comprises at least or about 12, 15, 16, 17, 20, 21, or 23 amino acids in length. In some instances, the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3 comprises a range of about 1 to about 10, about 5 to about 15, about 10 to about 20, or about 15 to about 30 amino acids in length.

[00108] Libraries comprising nucleic acids encoding for antibodies having variant CDR sequences as described herein comprise various lengths of amino acids when translated. In some instances, the length of each of the amino acid fragments or average length of the amino acid synthesized may be at least or about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, or more than 150 amino acids. In some instances, the length of the amino acid is about 15 to 150, 20 to 145, 25 to 140, 30 to 135, 35 to 130, 40 to 125, 45 to 120, 50 to 115, 55 to 110, 60 to 110, 65 to 105, 70 to 100, or 75 to 95 amino acids. In some instances, the length of the amino acid is about 22 amino acids to about 75 amino acids. In some instances, the antibodies comprise at least or about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, or more than 5000 amino acids.

[00109] Ratios of the lengths of a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3 may vary in libraries described herein. In some instances, a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3 comprising at least or about 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, 40, 50, 60, 70, 80, 90, or more than 90 amino acids in length comprises about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 90% of the library. For example, a CDRH3 comprising about 23 amino acids in length is present in the

library at 40%, a CDRH3 comprising about 21 amino acids in length is present in the library at 30%, a CDRH3 comprising about 17 amino acids in length is present in the library at 20%, and a CDRH3 comprising about 12 amino acids in length is present in the library at 10%. In some instances, a CDRH3 comprising about 20 amino acids in length is present in the library at 40%, a CDRH3 comprising about 16 amino acids in length is present in the library at 30%, a CDRH3 comprising about 15 amino acids in length is present in the library at 20%, and a CDRH3 comprising about 12 amino acids in length is present in the library at 10%.

[00110] Libraries as described herein encoding for a VHH antibody comprise variant CDR sequences that are shuffled to generate a library with a theoretical diversity of at least or about 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} sequences. In some instances, the library has a final library diversity of at least or about 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, or more than 10^{20} sequences.

[00111] Provided herein are GLP1R binding libraries encoding for an immunoglobulin. In some instances, the GLP1R immunoglobulin is an antibody. In some instances, the GLP1R immunoglobulin is a VHH antibody. In some instances, the GLP1R immunoglobulin comprises a binding affinity (e.g., kD) to GLP1R of less than 1 nM, less than 1.2 nM, less than 2 nM, less than 5 nM, less than 10 nM, less than 11 nm, less than 13.5 nM, less than 15 nM, less than 20 nM, less than 25 nM, or less than 30 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 1 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 1.2 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 2 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 5 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 10 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 13.5 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 15 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 20 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 25 nM. In some instances, the GLP1R immunoglobulin comprises a kD of less than 30 nM.

[00112] In some instances, the GLP1R immunoglobulin is a GLP1R agonist. In some instances, the GLP1R immunoglobulin is a GLP1R antagonist. In some instances, the GLP1R immunoglobulin is a GLP1R allosteric modulator. In some instances, the allosteric modulator is a negative allosteric modulator. In some instances, the allosteric modulator is a positive allosteric modulator. In some instances, the GLP1R immunoglobulin results in agonistic, antagonistic, or allosteric effects at a concentration of at least or about 1 nM, 2 nM, 4 nM, 6 nM, 8 nM, 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 120 nM, 140 nM, 160 nM, 180

nM, 200 nM, 300 nM, 400 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM, 1000 nM, or more than 1000 nM. In some instances, the GLP1R immunoglobulin is a negative allosteric modulator. In some instances, the GLP1R immunoglobulin is a negative allosteric modulator at a concentration of at least or about 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1 nM, 2 nM, 4 nM, 6 nM, 8 nM, 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, or more than 100 nM. In some instances, the GLP1R immunoglobulin is a negative allosteric modulator at a concentration in a range of about 0.001 to about 100, 0.01 to about 90, about 0.1 to about 80, 1 to about 50, about 10 to about 40 nM, or about 1 to about 10 nM. In some instances, the GLP1R immunoglobulin comprises an EC50 or IC50 of at least or about 0.001, 0.0025, 0.005, 0.01, 0.025, 0.05, 0.06, 0.07, 0.08, 0.9, 0.1, 0.5, 1, 2, 3, 4, 5, 6, or more than 6 nM. In some instances, the GLP1R immunoglobulin comprises an EC50 or IC50 of at least or about 1 nM, 2 nM, 4 nM, 6 nM, 8 nM, 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, or more than 100 nM.

[00113] Provided herein are GLP1R binding libraries encoding for an immunoglobulin, wherein the immunoglobulin comprises a long half-life. In some instances, the half-life of the GLP1R immunoglobulin is at least or about 12 hours, 24 hours 36 hours, 48 hours, 60 hours, 72 hours, 84 hours, 96 hours, 108 hours, 120 hours, 140 hours, 160 hours, 180 hours, 200 hours, or more than 200 hours. In some instances, the half-life of the GLP1R immunoglobulin is in a range of about 12 hours to about 300 hours, about 20 hours to about 280 hours, about 40 hours to about 240 hours, or about 60 hours to about 200 hours.

[00114] GLP1R immunoglobulins as described herein may comprise improved properties. In some instances, the GLP1R immunoglobulins are monomeric. In some instances, the GLP1R immunoglobulins are not prone to aggregation. In some instances, at least or about 70%, 75%, 80%, 85%, 90%, 95%, or 99% of the GLP1R immunoglobulins are monomeric. In some instances, the GLP1R immunoglobulins are thermostable. In some instances, the GLP1R immunoglobulins result in reduced non-specific binding.

[00115] Following synthesis of GLP1R binding libraries comprising nucleic acids encoding immunoglobulins comprising GLP1R binding domains, libraries may be used for screening and analysis. For example, libraries are assayed for library displayability and panning. In some instances, displayability is assayed using a selectable tag. Exemplary tags include, but are not limited to, a radioactive label, a fluorescent label, an enzyme, a chemiluminescent tag, a colorimetric tag, an affinity tag or other labels or tags that are known in the art. In some instances, the tag is histidine, polyhistidine, myc, hemagglutinin (HA), or FLAG. In some instances, the GLP1R binding libraries comprises nucleic acids encoding immunoglobulins comprising GPCR

binding domains with multiple tags such as GFP, FLAG, and Lucy as well as a DNA barcode. In some instances, libraries are assayed by sequencing using various methods including, but not limited to, single-molecule real-time (SMRT) sequencing, Polony sequencing, sequencing by ligation, reversible terminator sequencing, proton detection sequencing, ion semiconductor sequencing, nanopore sequencing, electronic sequencing, pyrosequencing, Maxam-Gilbert sequencing, chain termination (e.g., Sanger) sequencing, +S sequencing, or sequencing by synthesis.

[00116] *Expression Systems*

[00117] Provided herein are libraries comprising nucleic acids encoding for immunoglobulins comprising GLP1R binding domains, wherein the libraries have improved specificity, stability, expression, folding, or downstream activity. In some instances, libraries described herein are used for screening and analysis.

[00118] Provided herein are libraries comprising nucleic acids encoding for immunoglobulins comprising GLP1R binding domains, wherein the nucleic acid libraries are used for screening and analysis. In some instances, screening and analysis comprise *in vitro*, in *vivo*, or *ex vivo* assays. Cells for screening include primary cells taken from living subjects or cell lines. Cells may be from prokaryotes (e.g., bacteria and fungi) or eukaryotes (e.g., animals and plants). Exemplary animal cells include, without limitation, those from a mouse, rabbit, primate, and insect. In some instances, cells for screening include a cell line including, but not limited to, Chinese Hamster Ovary (CHO) cell line, human embryonic kidney (HEK) cell line, or baby hamster kidney (BHK) cell line. In some instances, nucleic acid libraries described herein may also be delivered to a multicellular organism. Exemplary multicellular organisms include, without limitation, a plant, a mouse, rabbit, primate, and insect.

[00119] Nucleic acid libraries or protein libraries encoded thereof described herein may be screened for various pharmacological or pharmacokinetic properties. In some instances, the libraries are screened using *in vitro* assays, *in vivo* assays, or *ex vivo* assays. For example, *in vitro* pharmacological or pharmacokinetic properties that are screened include, but are not limited to, binding affinity, binding specificity, and binding avidity. Exemplary *in vivo* pharmacological or pharmacokinetic properties of libraries described herein that are screened include, but are not limited to, therapeutic efficacy, activity, preclinical toxicity properties, clinical efficacy properties, clinical toxicity properties, immunogenicity, potency, and clinical safety properties.

[00120] Pharmacological or pharmacokinetic properties that may be screened include, but are not limited to, cell binding affinity and cell activity. For example, cell binding affinity assays or cell activity assays are performed to determine agonistic, antagonistic, or allosteric effects of

libraries described herein. In some instances, the cell activity assay is a cAMP assay. In some instances, libraries as described herein are compared to cell binding or cell activity of ligands of GLP1R.

[00121] Libraries as described herein may be screened in cell-based assays or in non-cell-based assays. Examples of non-cell-based assays include, but are not limited to, using viral particles, using *in vitro* translation proteins, and using protealiposomes with GLP1R.

[00122] Nucleic acid libraries as described herein may be screened by sequencing. In some instances, next generation sequence is used to determine sequence enrichment of GLP1R binding variants. In some instances, V gene distribution, J gene distribution, V gene family, CDR3 counts per length, or a combination thereof is determined. In some instances, clonal frequency, clonal accumulation, lineage accumulation, or a combination thereof is determined. In some instances, number of sequences, sequences with VH clones, clones, clones greater than 1, clonotypes, clonotypes greater than 1, lineages, simpsons, or a combination thereof is determined. In some instances, a percentage of non-identical CDR3s is determined. For example, the percentage of non-identical CDR3s is calculated as the number of non-identical CDR3s in a sample divided by the total number of sequences that had a CDR3 in the sample.

[00123] Provided herein are nucleic acid libraries, wherein the nucleic acid libraries may be expressed in a vector. Expression vectors for inserting nucleic acid libraries disclosed herein may comprise eukaryotic or prokaryotic expression vectors. Exemplary expression vectors include, without limitation, mammalian expression vectors: pSF-CMV-NEO-NH2-PPT-3XFLAG, pSF-CMV-NEO-COOH-3XFLAG, pSF-CMV-PURO-NH2-GST-TEV, pSF-OXB20-COOH-TEV-FLAG(R)-6His, pCEP4 pDEST27, pSF-CMV-Ub-KrYFP, pSF-CMV-FMDV-daGFP, pEF1a-mCherry-N1 Vector, pEF1a-tdTomato Vector, pSF-CMV-FMDV-Hygro, pSF-CMV-PGK-Puro, pMCP-tag(m), and pSF-CMV-PURO-NH2-CMYC; bacterial expression vectors: pSF-OXB20-BetaGal,pSF-OXB20-Fluc, pSF-OXB20, and pSF-Tac; plant expression vectors: pRI 101-AN DNA and pCambia2301; and yeast expression vectors: pTYB21 and pKLAC2, and insect vectors: pAc5.1/V5-His A and pDEST8. In some instances, the vector is pcDNA3 or pcDNA3.1.

[00124] Described herein are nucleic acid libraries that are expressed in a vector to generate a construct comprising an immunoglobulin comprising sequences of GLP1R binding domains. In some instances, a size of the construct varies. In some instances, the construct comprises at least or about 500, 600, 700, 800, 900, 1000, 1100, 1300, 1400, 1500, 1600, 1700, 1800, 2000, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, 4000, 4200,4400, 4600, 4800, 5000, 6000, 7000, 8000, 9000, 10000, or more than 10000 bases. In some instances, a the construct comprises a range of about 300 to 1,000, 300 to 2,000, 300 to 3,000, 300 to 4,000, 300 to 5,000, 300 to 6,000, 300 to 7,000,

300 to 8,000, 300 to 9,000, 300 to 10,000, 1,000 to 2,000, 1,000 to 3,000, 1,000 to 4,000, 1,000 to 5,000, 1,000 to 6,000, 1,000 to 7,000, 1,000 to 8,000, 1,000 to 9,000, 1,000 to 10,000, 2,000 to 3,000, 2,000 to 4,000, 2,000 to 5,000, 2,000 to 6,000, 2,000 to 7,000, 2,000 to 8,000, 2,000 to 9,000, 2,000 to 10,000, 3,000 to 4,000, 3,000 to 5,000, 3,000 to 6,000, 3,000 to 7,000, 3,000 to 8,000, 3,000 to 9,000, 3,000 to 10,000, 4,000 to 5,000, 4,000 to 6,000, 4,000 to 7,000, 4,000 to 8,000, 4,000 to 9,000, 4,000 to 10,000, 5,000 to 6,000, 5,000 to 7,000, 5,000 to 8,000, 5,000 to 9,000, 5,000 to 10,000, 6,000 to 7,000, 6,000 to 8,000, 6,000 to 9,000, 6,000 to 10,000, 7,000 to 8,000, 7,000 to 9,000, 7,000 to 10,000, 8,000 to 9,000, 8,000 to 10,000, or 9,000 to 10,000 bases.

[00125] Provided herein are libraries comprising nucleic acids encoding for immunoglobulins comprising GPCR binding domains, wherein the nucleic acid libraries are expressed in a cell. In some instances, the libraries are synthesized to express a reporter gene. Exemplary reporter genes include, but are not limited to, acetohydroxyacid synthase (AHAS), alkaline phosphatase (AP), beta galactosidase (LacZ), beta glucoronidase (GUS), chloramphenicol acetyltransferase (CAT), green fluorescent protein (GFP), red fluorescent protein (RFP), yellow fluorescent protein (YFP), cyan fluorescent protein (CFP), cerulean fluorescent protein, citrine fluorescent protein, orange fluorescent protein , cherry fluorescent protein, turquoise fluorescent protein, blue fluorescent protein, horseradish peroxidase (HRP), luciferase (Luc), nopaline synthase (NOS), octopine synthase (OCS), luciferase, and derivatives thereof. Methods to determine modulation of a reporter gene are well known in the art, and include, but are not limited to, fluorometric methods (*e.g.* fluorescence spectroscopy, Fluorescence Activated Cell Sorting (FACS), fluorescence microscopy), and antibiotic resistance determination.

[00126] Diseases and Disorders

[00127] Provided herein are GLP1R binding libraries comprising nucleic acids encoding for immunoglobulins (e.g., antibodies) comprising GLP1R binding domains that may have therapeutic effects. In some instances, the GLP1R binding libraries result in protein when translated that is used to treat a disease or disorder. In some instances, the protein is an immunoglobulin. In some instances, the protein is a peptidomimetic.

[00128] GLP1R libraries as described herein may comprise modulators of GLP1R. In some instances, the modulator of GLP1R is an inhibitor. In some instances, the modulator of GLP1R is an activator. In some instances, the GLP1R inhibitor is a GLP1R antagonist. In some instances, the GLP1R antagonist is GLP1R-3. Modulators of GLP1R, in some instances, are used for treating various diseases or disorders.

[00129] Exemplary diseases include, but are not limited to, cancer, inflammatory diseases or disorders, a metabolic disease or disorder, a cardiovascular disease or disorder, a respiratory disease

or disorder, pain, a digestive disease or disorder, a reproductive disease or disorder, an endocrine disease or disorder, or a neurological disease or disorder. In some instances, the cancer is a solid cancer or a hematologic cancer. In some instances, a modulator of GLP1R as described herein is used for treatment of weight gain (or for inducing weight loss), treatment of obesity, or treatment of Type II diabetes. In some instances, the GLP1R modulator is used for treating hypoglycemia. In some instances, the GLP1R modulator is used for treating post-bariatric hypoglycemia. In some instances, the GLP1R modulator is used for treating severe hypoglycemia. In some instances, the GLP1R modulator is used for treating hyperinsulinism. In some instances, the GLP1R modulator is used for treating congenital hyperinsulinism.

[00130] In some instances, the subject is a mammal. In some instances, the subject is a mouse, rabbit, dog, or human. Subjects treated by methods described herein may be infants, adults, or children. Pharmaceutical compositions comprising antibodies or antibody fragments as described herein may be administered intravenously or subcutaneously.

[00131] Described herein are pharmaceutical compositions comprising antibodies or antibody fragment thereof that binds GLP1R. In some embodiments, the antibody or antibody fragment thereof comprises a sequence as set forth in **Tables 7-13**. In some embodiments, the antibody or antibody fragment thereof comprises a sequence that is at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence as set forth in **Tables 7-13**.

[00132] In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRH1 sequence of any one of SEQ ID NOs: 441-619. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRH2

sequence of any one of SEQ ID NOs: 620-798. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRH2 sequence of any one of SEQ ID NOs: 620-798. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRH3 sequence of any one of SEQ ID NOs: 799-977.

[00133] In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRL1 sequence of any one of SEQ ID NOs: 978-1156. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRL2

sequence of any one of SEQ ID NOs: 1157-1168. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRL2 sequence of any one of SEQ ID NOs: 1157-1168. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 80% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 85% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 90% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347. In some instances, a pharmaceutical composition comprises an antibody or antibody fragment described herein comprising a sequence that is at least 95% identical to a CDRL3 sequence of any one of SEQ ID NOs: 1169-1347.

[00134] In some embodiments, the antibody or antibody fragment comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347. In some embodiments, the antibody or antibody fragment comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 441-619; (b) an amino

acid sequence of CDRH2 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is at least or about 80%, 85%, 90%, or 95% identical to any one of SEQ ID NOs: 1169-1347.

Described herein, in some embodiments, are antibodies or antibody fragments comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein the VH comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 58-77, and wherein the VL comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 92-111. In some instances, the antibodies or antibody fragments comprise VH comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 58-77, and VL comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 92-111.

[00135] Described herein are pharmaceutical compositions comprising antibodies or antibody fragment thereof that binds GLP1R that comprise various dosages of the antibodies or antibody fragment. In some instances, the dosage is ranging from about 1 to 80 mg/kg, from about 1 to about 100 mg/kg, from about 5 to about 100 mg/kg, from about 5 to about 80 mg/kg, from about 5 to about 60 mg/kg, from about 5 to about 50 mg/kg or from about 5 to about 500 mg/kg which can be administered in single or multiple doses. In some instances, the dosage is administered in an amount of about 0.01 mg/kg, about 0.05 mg/kg, about 0.10 mg/kg, about 0.25 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 105 mg/kg, about 110 mg/kg, about 115 mg/kg, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, about 200, about 205, about 210, about 215, about 220, about 225, about 230, about 240, about 250, about 260, about 270, about 275, about 280, about 290, about 300, about 310, about 320, about 330, about 340, about 350, about 360 mg/kg, about 370 mg/kg, about 380 mg/kg, about 390 mg/kg, about 400 mg/kg, 410 mg/kg, about 420 mg/kg, about 430 mg/kg, about 440 mg/kg, about 450

mg/kg, about 460 mg/kg, about 470 mg/kg, about 480 mg/kg, about 490 mg/kg, or about 500 mg/kg.

[00136] Variant Libraries

[00137] *Codon variation*

[00138] Variant nucleic acid libraries described herein may comprise a plurality of nucleic acids, wherein each nucleic acid encodes for a variant codon sequence compared to a reference nucleic acid sequence. In some instances, each nucleic acid of a first nucleic acid population contains a variant at a single variant site. In some instances, the first nucleic acid population contains a plurality of variants at a single variant site such that the first nucleic acid population contains more than one variant at the same variant site. The first nucleic acid population may comprise nucleic acids collectively encoding multiple codon variants at the same variant site. The first nucleic acid population may comprise nucleic acids collectively encoding up to 19 or more codons at the same position. The first nucleic acid population may comprise nucleic acids collectively encoding up to 60 variant triplets at the same position, or the first nucleic acid population may comprise nucleic acids collectively encoding up to 61 different triplets of codons at the same position. Each variant may encode for a codon that results in a different amino acid during translation. **Table 2** provides a listing of each codon possible (and the representative amino acid) for a variant site.

Table 2. List of codons and amino acids

Amino Acids	One letter code	Three letter code	Codons			
Alanine	A	Ala	GCA	GCC	GCG	GCT
Cysteine	C	Cys	TGC	TGT		
Aspartic acid	D	Asp	GAC	GAT		
Glutamic acid	E	Glu	GAA	GAG		
Phenylalanine	F	Phe	TTC	TTT		
Glycine	G	Gly	GGA	GGC	GGG	GGT
Histidine	H	His	CAC	CAT		
Isoleucine	I	Iso	ATA	ATC	ATT	

Lysine	K	Lys	AAA	AAG				
Leucine	L	Leu	TTA	TTG	CTA	CTC	CTG	CTT
Methionine	M	Met	ATG					
Asparagine	N	Asn	AAC	AAT				
Proline	P	Pro	CCA	CCC	CCG	CCT		
Glutamine	Q	Gln	CAA	CAG				
Arginine	R	Arg	AGA	AGG	CGA	CGC	CGG	CGT
Serine	S	Ser	AGC	AGT	TCA	TCC	TCG	TCT
Threonine	T	Thr	ACA	ACC	ACG	ACT		
Valine	V	Val	GTA	GTC	GTG	GTT		
Tryptophan	W	Trp	TGG					
Tyrosine	Y	Tyr	TAC	TAT				

[00139] A nucleic acid population may comprise varied nucleic acids collectively encoding up to 20 codon variations at multiple positions. In such cases, each nucleic acid in the population comprises variation for codons at more than one position in the same nucleic acid. In some instances, each nucleic acid in the population comprises variation for codons at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more codons in a single nucleic acid. In some instances, each variant long nucleic acid comprises variation for codons at 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 codons in a single long nucleic acid. In some instances, the variant nucleic acid population comprises variation for codons at 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 codons in a single nucleic acid. In some instances, the variant nucleic acid population comprises variation for codons in at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more codons in a single long nucleic acid.

[00140] **Highly Parallel Nucleic Acid Synthesis**

[00141] Provided herein is a platform approach utilizing miniaturization, parallelization, and vertical integration of the end-to-end process from polynucleotide synthesis to gene assembly

within nanowells on silicon to create a revolutionary synthesis platform. Devices described herein provide, with the same footprint as a 96-well plate, a silicon synthesis platform capable of increasing throughput by a factor of up to 1,000 or more compared to traditional synthesis methods, with production of up to approximately 1,000,000 or more polynucleotides, or 10,000 or more genes in a single highly-parallelized run.

[00142] With the advent of next-generation sequencing, high resolution genomic data has become an important factor for studies that delve into the biological roles of various genes in both normal biology and disease pathogenesis. At the core of this research is the central dogma of molecular biology and the concept of "residue-by-residue transfer of sequential information." Genomic information encoded in the DNA is transcribed into a message that is then translated into the protein that is the active product within a given biological pathway.

[00143] Another exciting area of study is on the discovery, development and manufacturing of therapeutic molecules focused on a highly-specific cellular target. High diversity DNA sequence libraries are at the core of development pipelines for targeted therapeutics. Gene mutants are used to express proteins in a design, build, and test protein engineering cycle that ideally culminates in an optimized gene for high expression of a protein with high affinity for its therapeutic target. As an example, consider the binding pocket of a receptor. The ability to test all sequence permutations of all residues within the binding pocket simultaneously will allow for a thorough exploration, increasing chances of success. Saturation mutagenesis, in which a researcher attempts to generate all possible mutations at a specific site within the receptor, represents one approach to this development challenge. Though costly and time- and labor-intensive, it enables each variant to be introduced into each position. In contrast, combinatorial mutagenesis, where a few selected positions or short stretch of DNA may be modified extensively, generates an incomplete repertoire of variants with biased representation.

[00144] To accelerate the drug development pipeline, a library with the desired variants available at the intended frequency in the right position available for testing – in other words, a precision library – enables reduced costs as well as turnaround time for screening. Provided herein are methods for synthesizing nucleic acid synthetic variant libraries which provide for precise introduction of each intended variant at the desired frequency. To the end user, this translates to the ability to not only thoroughly sample sequence space but also be able to query these hypotheses in an efficient manner, reducing cost and screening time. Genome-wide editing can elucidate important pathways, libraries where each variant and sequence permutation can be tested for optimal functionality, and thousands of genes can be used to reconstruct entire pathways and genomes to re-engineer biological systems for drug discovery.

[00145] In a first example, a drug itself can be optimized using methods described herein. For example, to improve a specified function of an antibody, a variant polynucleotide library encoding for a portion of the antibody is designed and synthesized. A variant nucleic acid library for the antibody can then be generated by processes described herein (e.g., PCR mutagenesis followed by insertion into a vector). The antibody is then expressed in a production cell line and screened for enhanced activity. Example screens include examining modulation in binding affinity to an antigen, stability, or effector function (e.g., ADCC, complement, or apoptosis). Exemplary regions to optimize the antibody include, without limitation, the Fc region, Fab region, variable region of the Fab region, constant region of the Fab region, variable domain of the heavy chain or light chain (V_H or V_L), and specific complementarity-determining regions (CDRs) of V_H or V_L.

[00146] Nucleic acid libraries synthesized by methods described herein may be expressed in various cells associated with a disease state. Cells associated with a disease state include cell lines, tissue samples, primary cells from a subject, cultured cells expanded from a subject, or cells in a model system. Exemplary model systems include, without limitation, plant and animal models of a disease state.

[00147] To identify a variant molecule associated with prevention, reduction or treatment of a disease state, a variant nucleic acid library described herein is expressed in a cell associated with a disease state, or one in which a cell a disease state can be induced. In some instances, an agent is used to induce a disease state in cells. Exemplary tools for disease state induction include, without limitation, a Cre/Lox recombination system, LPS inflammation induction, and streptozotocin to induce hypoglycemia. The cells associated with a disease state may be cells from a model system or cultured cells, as well as cells from a subject having a particular disease condition. Exemplary disease conditions include a bacterial, fungal, viral, autoimmune, or proliferative disorder (e.g., cancer). In some instances, the variant nucleic acid library is expressed in the model system, cell line, or primary cells derived from a subject, and screened for changes in at least one cellular activity. Exemplary cellular activities include, without limitation, proliferation, cycle progression, cell death, adhesion, migration, reproduction, cell signaling, energy production, oxygen utilization, metabolic activity, and aging, response to free radical damage, or any combination thereof.

[00148] Substrates

[00149] Devices used as a surface for polynucleotide synthesis may be in the form of substrates which include, without limitation, homogenous array surfaces, patterned array surfaces, channels, beads, gels, and the like. Provided herein are substrates comprising a plurality of clusters, wherein each cluster comprises a plurality of loci that support the attachment and synthesis of polynucleotides. In some instances, substrates comprise a homogenous array surface. For

example, the homogenous array surface is a homogenous plate. The term "locus" as used herein refers to a discrete region on a structure which provides support for polynucleotides encoding for a single predetermined sequence to extend from the surface. In some instances, a locus is on a two-dimensional surface, *e.g.*, a substantially planar surface. In some instances, a locus is on a three-dimensional surface, *e.g.*, a well, microwell, channel, or post. In some instances, a surface of a locus comprises a material that is actively functionalized to attach to at least one nucleotide for polynucleotide synthesis, or preferably, a population of identical nucleotides for synthesis of a population of polynucleotides. In some instances, polynucleotide refers to a population of polynucleotides encoding for the same nucleic acid sequence. In some cases, a surface of a substrate is inclusive of one or a plurality of surfaces of a substrate. The average error rates for polynucleotides synthesized within a library described here using the systems and methods provided are often less than 1 in 1000, less than about 1 in 2000, less than about 1 in 3000 or less often without error correction.

[00150] Provided herein are surfaces that support the parallel synthesis of a plurality of polynucleotides having different predetermined sequences at addressable locations on a common support. In some instances, a substrate provides support for the synthesis of more than 50, 100, 200, 400, 600, 800, 1000, 1200, 1400, 1600, 1800, 2,000; 5,000; 10,000; 20,000; 50,000; 100,000; 200,000; 300,000; 400,000; 500,000; 600,000; 700,000; 800,000; 900,000; 1,000,000; 1,200,000; 1,400,000; 1,600,000; 1,800,000; 2,000,000; 2,500,000; 3,000,000; 3,500,000; 4,000,000; 4,500,000; 5,000,000; 10,000,000 or more non-identical polynucleotides. In some cases, the surfaces provide support for the synthesis of more than 50, 100, 200, 400, 600, 800, 1000, 1200, 1400, 1600, 1800, 2,000; 5,000; 10,000; 20,000; 50,000; 100,000; 200,000; 300,000; 400,000; 500,000; 600,000; 700,000; 800,000; 900,000; 1,000,000; 1,200,000; 1,400,000; 1,600,000; 1,800,000; 2,000,000; 2,500,000; 3,000,000; 3,500,000; 4,000,000; 4,500,000; 5,000,000; 10,000,000 or more polynucleotides encoding for distinct sequences. In some instances, at least a portion of the polynucleotides have an identical sequence or are configured to be synthesized with an identical sequence. In some instances, the substrate provides a surface environment for the growth of polynucleotides having at least 80, 90, 100, 120, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 bases or more.

[00151] Provided herein are methods for polynucleotide synthesis on distinct loci of a substrate, wherein each locus supports the synthesis of a population of polynucleotides. In some cases, each locus supports the synthesis of a population of polynucleotides having a different sequence than a population of polynucleotides grown on another locus. In some instances, each polynucleotide sequence is synthesized with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more redundancy across different loci within

the same cluster of loci on a surface for polynucleotide synthesis. In some instances, the loci of a substrate are located within a plurality of clusters. In some instances, a substrate comprises at least 10, 500, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 11000, 12000, 13000, 14000, 15000, 20000, 30000, 40000, 50000 or more clusters. In some instances, a substrate comprises more than 2,000; 5,000; 10,000; 100,000; 200,000; 300,000; 400,000; 500,000; 600,000; 700,000; 800,000; 900,000; 1,000,000; 1,100,000; 1,200,000; 1,300,000; 1,400,000; 1,500,000; 1,600,000; 1,700,000; 1,800,000; 1,900,000; 2,000,000; 300,000; 400,000; 500,000; 600,000; 700,000; 800,000; 900,000; 1,000,000; 1,200,000; 1,400,000; 1,600,000; 1,800,000; 2,000,000; 2,500,000; 3,000,000; 3,500,000; 4,000,000; 4,500,000; 5,000,000; or 10,000,000 or more distinct loci. In some instances, a substrate comprises about 10,000 distinct loci. The amount of loci within a single cluster is varied in different instances. In some cases, each cluster includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 130, 150, 200, 300, 400, 500 or more loci. In some instances, each cluster includes about 50-500 loci. In some instances, each cluster includes about 100-200 loci. In some instances, each cluster includes about 100-150 loci. In some instances, each cluster includes about 109, 121, 130 or 137 loci. In some instances, each cluster includes about 19, 20, 61, 64 or more loci. Alternatively or in combination, polynucleotide synthesis occurs on a homogenous array surface.

[00152] In some instances, the number of distinct polynucleotides synthesized on a substrate is dependent on the number of distinct loci available in the substrate. In some instances, the density of loci within a cluster or surface of a substrate is at least or about 1, 10, 25, 50, 65, 75, 100, 130, 150, 175, 200, 300, 400, 500, 1,000 or more loci per mm^2. In some cases, a substrate comprises 10-500, 25-400, 50-500, 100-500, 150-500, 10-250, 50-250, 10-200, or 50-200 mm^2. In some instances, the distance between the centers of two adjacent loci within a cluster or surface is from about 10-500, from about 10-200, or from about 10-100 um. In some instances, the distance between two centers of adjacent loci is greater than about 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 um. In some instances, the distance between the centers of two adjacent loci is less than about 200, 150, 100, 80, 70, 60, 50, 40, 30, 20 or 10 um. In some instances, each locus has a width of about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 um. In some cases, each locus has a width of about 0.5-100, 0.5-50, 10-75, or 0.5-50 um.

[00153] In some instances, the density of clusters within a substrate is at least or about 1 cluster per 100 mm^2, 1 cluster per 10 mm^2, 1 cluster per 5 mm^2, 1 cluster per 4 mm^2, 1 cluster per 3 mm^2, 1 cluster per 2 mm^2, 1 cluster per 1 mm^2, 2 clusters per 1 mm^2, 3 clusters per 1 mm^2, 4 clusters per 1 mm^2, 5 clusters per 1 mm^2, 10 clusters per 1 mm^2, 50 clusters per 1 mm^2 or more. In some instances, a substrate comprises from about 1 cluster per 10 mm^2 to about 10 clusters per 1 mm^2.

In some instances, the distance between the centers of two adjacent clusters is at least or about 50, 100, 200, 500, 1000, 2000, or 5000 um. In some cases, the distance between the centers of two adjacent clusters is between about 50-100, 50-200, 50-300, 50-500, and 100-2000 um. In some cases, the distance between the centers of two adjacent clusters is between about 0.05-50, 0.05-10, 0.05-5, 0.05-4, 0.05-3, 0.05-2, 0.1-10, 0.2-10, 0.3-10, 0.4-10, 0.5-10, 0.5-5, or 0.5-2 mm. In some cases, each cluster has a cross section of about 0.5 to about 2, about 0.5 to about 1, or about 1 to about 2 mm. In some cases, each cluster has a cross section of about 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9 or 2 mm. In some cases, each cluster has an interior cross section of about 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.15, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9 or 2 mm.

[00154] In some instances, a substrate is about the size of a standard 96 well plate, for example between about 100 and about 200 mm by between about 50 and about 150 mm. In some instances, a substrate has a diameter less than or equal to about 1000, 500, 450, 400, 300, 250, 200, 150, 100 or 50 mm. In some instances, the diameter of a substrate is between about 25-1000, 25-800, 25-600, 25-500, 25-400, 25-300, or 25-200 mm. In some instances, a substrate has a planar surface area of at least about 100; 200; 500; 1,000; 2,000; 5,000; 10,000; 12,000; 15,000; 20,000; 30,000; 40,000; 50,000 mm^2 or more. In some instances, the thickness of a substrate is between about 50-2000, 50- 1000, 100-1000, 200-1000, or 250-1000 mm.

[00155] *Surface materials*

[00156] Substrates, devices, and reactors provided herein are fabricated from any variety of materials suitable for the methods, compositions, and systems described herein. In certain instances, substrate materials are fabricated to exhibit a low level of nucleotide binding. In some instances, substrate materials are modified to generate distinct surfaces that exhibit a high level of nucleotide binding. In some instances, substrate materials are transparent to visible and/or UV light. In some instances, substrate materials are sufficiently conductive, *e.g.*, are able to form uniform electric fields across all or a portion of a substrate. In some instances, conductive materials are connected to an electric ground. In some instances, the substrate is heat conductive or insulated. In some instances, the materials are chemical resistant and heat resistant to support chemical or biochemical reactions, for example polynucleotide synthesis reaction processes. In some instances, a substrate comprises flexible materials. For flexible materials, materials can include, without limitation: nylon, both modified and unmodified, nitrocellulose, polypropylene, and the like. In some instances, a substrate comprises rigid materials. For rigid materials, materials can include, without limitation: glass; fuse silica; silicon, plastics (for example polytetraflouroethylene, polypropylene, polystyrene, polycarbonate, and blends thereof, and the like); and metals (for example, gold, platinum, and the like). The substrate, solid support or reactors

can be fabricated from a material selected from the group consisting of silicon, polystyrene, agarose, dextran, cellulosic polymers, polyacrylamides, polydimethylsiloxane (PDMS), and glass. The substrates/solid supports or the microstructures/reactors therein may be manufactured with a combination of materials listed herein or any other suitable material known in the art.

[00157] Surface Architecture

[00158] Provided herein are substrates for the methods, compositions, and systems described herein, wherein the substrates have a surface architecture suitable for the methods, compositions, and systems described herein. In some instances, a substrate comprises raised and/or lowered features. One benefit of having such features is an increase in surface area to support polynucleotide synthesis. In some instances, a substrate having raised and/or lowered features is referred to as a three-dimensional substrate. In some cases, a three-dimensional substrate comprises one or more channels. In some cases, one or more loci comprise a channel. In some cases, the channels are accessible to reagent deposition via a deposition device such as a material deposition device. In some cases, reagents and/or fluids collect in a larger well in fluid communication one or more channels. For example, a substrate comprises a plurality of channels corresponding to a plurality of loci with a cluster, and the plurality of channels are in fluid communication with one well of the cluster. In some methods, a library of polynucleotides is synthesized in a plurality of loci of a cluster.

[00159] Provided herein are substrates for the methods, compositions, and systems described herein, wherein the substrates are configured for polynucleotide synthesis. In some instances, the structure is configured to allow for controlled flow and mass transfer paths for polynucleotide synthesis on a surface. In some instances, the configuration of a substrate allows for the controlled and even distribution of mass transfer paths, chemical exposure times, and/or wash efficacy during polynucleotide synthesis. In some instances, the configuration of a substrate allows for increased sweep efficiency, for example by providing sufficient volume for a growing polynucleotide such that the excluded volume by the growing polynucleotide does not take up more than 50, 45, 40, 35, 30, 25, 20, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1%, or less of the initially available volume that is available or suitable for growing the polynucleotide. In some instances, a three-dimensional structure allows for managed flow of fluid to allow for the rapid exchange of chemical exposure.

[00160] Provided herein are substrates for the methods, compositions, and systems described herein, wherein the substrates comprise structures suitable for the methods, compositions, and systems described herein. In some instances, segregation is achieved by physical structure. In some instances, segregation is achieved by differential functionalization of the surface generating active and passive regions for polynucleotide synthesis. In some instances, differential

functionalization is achieved by alternating the hydrophobicity across the substrate surface, thereby creating water contact angle effects that cause beading or wetting of the deposited reagents. Employing larger structures can decrease splashing and cross-contamination of distinct polynucleotide synthesis locations with reagents of the neighboring spots. In some cases, a device, such as a material deposition device, is used to deposit reagents to distinct polynucleotide synthesis locations. Substrates having three-dimensional features are configured in a manner that allows for the synthesis of a large number of polynucleotides (*e.g.*, more than about 10,000) with a low error rate (*e.g.*, less than about 1:500, 1:1000, 1:1500, 1:2,000, 1:3,000, 1:5,000, or 1:10,000). In some cases, a substrate comprises features with a density of about or greater than about 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400 or 500 features per mm^2.

[00161] A well of a substrate may have the same or different width, height, and/or volume as another well of the substrate. A channel of a substrate may have the same or different width, height, and/or volume as another channel of the substrate. In some instances, the diameter of a cluster or the diameter of a well comprising a cluster, or both, is between about 0.05-50, 0.05-10, 0.05-5, 0.05-4, 0.05-3, 0.05-2, 0.05-1, 0.05-0.5, 0.05-0.1, 0.1-10, 0.2-10, 0.3-10, 0.4-10, 0.5-10, 0.5-5, or 0.5-2 mm. In some instances, the diameter of a cluster or well or both is less than or about 5, 4, 3, 2, 1, 0.5, 0.1, 0.09, 0.08, 0.07, 0.06, or 0.05 mm. In some instances, the diameter of a cluster or well or both is between about 1.0 and 1.3 mm. In some instances, the diameter of a cluster or well, or both is about 1.150 mm. In some instances, the diameter of a cluster or well, or both is about 0.08 mm. The diameter of a cluster refers to clusters within a two-dimensional or three-dimensional substrate.

[00162] In some instances, the height of a well is from about 20-1000, 50-1000, 100- 1000, 200-1000, 300-1000, 400-1000, or 500-1000 um. In some cases, the height of a well is less than about 1000, 900, 800, 700, or 600 um.

[00163] In some instances, a substrate comprises a plurality of channels corresponding to a plurality of loci within a cluster, wherein the height or depth of a channel is 5-500, 5-400, 5-300, 5-200, 5-100, 5-50, or 10-50 um. In some cases, the height of a channel is less than 100, 80, 60, 40, or 20 um.

[00164] In some instances, the diameter of a channel, locus (*e.g.*, in a substantially planar substrate) or both channel and locus (*e.g.*, in a three-dimensional substrate wherein a locus corresponds to a channel) is from about 1-1000, 1-500, 1-200, 1-100, 5-100, or 10-100 um, for example, to about 90, 80, 70, 60, 50, 40, 30, 20 or 10 um. In some instances, the diameter of a channel, locus, or both channel and locus is less than about 100, 90, 80, 70, 60, 50, 40, 30, 20 or 10

um. In some instances, the distance between the center of two adjacent channels, loci, or channels and loci is from about 1-500, 1-200, 1-100, 5-200, 5-100, 5-50, or 5-30, for example, to about 20 um.

[00165] Surface Modifications

[00166] Provided herein are methods for polynucleotide synthesis on a surface, wherein the surface comprises various surface modifications. In some instances, the surface modifications are employed for the chemical and/or physical alteration of a surface by an additive or subtractive process to change one or more chemical and/or physical properties of a substrate surface or a selected site or region of a substrate surface. For example, surface modifications include, without limitation, (1) changing the wetting properties of a surface, (2) functionalizing a surface, i.e., providing, modifying or substituting surface functional groups, (3) defunctionalizing a surface, i.e., removing surface functional groups, (4) otherwise altering the chemical composition of a surface, *e.g.*, through etching, (5) increasing or decreasing surface roughness, (6) providing a coating on a surface, *e.g.*, a coating that exhibits wetting properties that are different from the wetting properties of the surface, and/or (7) depositing particulates on a surface.

[00167] In some cases, the addition of a chemical layer on top of a surface (referred to as adhesion promoter) facilitates structured patterning of loci on a surface of a substrate. Exemplary surfaces for application of adhesion promotion include, without limitation, glass, silicon, silicon dioxide and silicon nitride. In some cases, the adhesion promoter is a chemical with a high surface energy. In some instances, a second chemical layer is deposited on a surface of a substrate. In some cases, the second chemical layer has a low surface energy. In some cases, surface energy of a chemical layer coated on a surface supports localization of droplets on the surface. Depending on the patterning arrangement selected, the proximity of loci and/or area of fluid contact at the loci are alterable.

[00168] In some instances, a substrate surface, or resolved loci, onto which nucleic acids or other moieties are deposited, *e.g.*, for polynucleotide synthesis, are smooth or substantially planar (*e.g.*, two-dimensional) or have irregularities, such as raised or lowered features (*e.g.*, three-dimensional features). In some instances, a substrate surface is modified with one or more different layers of compounds. Such modification layers of interest include, without limitation, inorganic and organic layers such as metals, metal oxides, polymers, small organic molecules, and the like.

[00169] In some instances, resolved loci of a substrate are functionalized with one or more moieties that increase and/or decrease surface energy. In some cases, a moiety is chemically inert. In some cases, a moiety is configured to support a desired chemical reaction, for example, one or more processes in a polynucleotide synthesis reaction. The surface energy, or hydrophobicity, of a

surface is a factor for determining the affinity of a nucleotide to attach onto the surface. In some instances, a method for substrate functionalization comprises: (a) providing a substrate having a surface that comprises silicon dioxide; and (b) silanizing the surface using a suitable silanizing agent described herein or otherwise known in the art, for example, an organofunctional alkoxysilane molecule. Methods and functionalizing agents are described in U.S. Patent No. 5474796, which is herein incorporated by reference in its entirety.

[00170] In some instances, a substrate surface is functionalized by contact with a derivatizing composition that contains a mixture of silanes, under reaction conditions effective to couple the silanes to the substrate surface, typically via reactive hydrophilic moieties present on the substrate surface. Silanization generally covers a surface through self-assembly with organofunctional alkoxysilane molecules. A variety of siloxane functionalizing reagents can further be used as currently known in the art, *e.g.*, for lowering or increasing surface energy. The organofunctional alkoxysilanes are classified according to their organic functions.

[00171] Polynucleotide Synthesis

[00172] Methods of the current disclosure for polynucleotide synthesis may include processes involving phosphoramidite chemistry. In some instances, polynucleotide synthesis comprises coupling a base with phosphoramidite. Polynucleotide synthesis may comprise coupling a base by deposition of phosphoramidite under coupling conditions, wherein the same base is optionally deposited with phosphoramidite more than once, i.e., double coupling. Polynucleotide synthesis may comprise capping of unreacted sites. In some instances, capping is optional. Polynucleotide synthesis may also comprise oxidation or an oxidation step or oxidation steps. Polynucleotide synthesis may comprise deblocking, detritylation, and sulfurization. In some instances, polynucleotide synthesis comprises either oxidation or sulfurization. In some instances, between one or each step during a polynucleotide synthesis reaction, the device is washed, for example, using tetrazole or acetonitrile. Time frames for any one step in a phosphoramidite synthesis method may be less than about 2 min, 1 min, 50 sec, 40 sec, 30 sec, 20 sec and 10 sec.

[00173] Polynucleotide synthesis using a phosphoramidite method may comprise a subsequent addition of a phosphoramidite building block (*e.g.*, nucleoside phosphoramidite) to a growing polynucleotide chain for the formation of a phosphite triester linkage. Phosphoramidite polynucleotide synthesis proceeds in the 3' to 5' direction. Phosphoramidite polynucleotide synthesis allows for the controlled addition of one nucleotide to a growing nucleic acid chain per synthesis cycle. In some instances, each synthesis cycle comprises a coupling step. Phosphoramidite coupling involves the formation of a phosphite triester linkage between an activated nucleoside phosphoramidite and a nucleoside bound to the substrate, for example, via a

linker. In some instances, the nucleoside phosphoramidite is provided to the device activated. In some instances, the nucleoside phosphoramidite is provided to the device with an activator. In some instances, nucleoside phosphoramidites are provided to the device in a 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100-fold excess or more over the substrate-bound nucleosides. In some instances, the addition of nucleoside phosphoramidite is performed in an anhydrous environment, for example, in anhydrous acetonitrile. Following addition of a nucleoside phosphoramidite, the device is optionally washed. In some instances, the coupling step is repeated one or more additional times, optionally with a wash step between nucleoside phosphoramidite additions to the substrate. In some instances, a polynucleotide synthesis method used herein comprises 1, 2, 3 or more sequential coupling steps. Prior to coupling, in many cases, the nucleoside bound to the device is de-protected by removal of a protecting group, where the protecting group functions to prevent polymerization. A common protecting group is 4,4′-dimethoxytrityl (DMT).

[00174] Following coupling, phosphoramidite polynucleotide synthesis methods optionally comprise a capping step. In a capping step, the growing polynucleotide is treated with a capping agent. A capping step is useful to block unreacted substrate-bound 5′-OH groups after coupling from further chain elongation, preventing the formation of polynucleotides with internal base deletions. Further, phosphoramidites activated with 1H-tetrazole may react, to a small extent, with the O6 position of guanosine. Without being bound by theory, upon oxidation with I_2 /water, this side product, possibly via O6-N7 migration, may undergo depurination. The apurinic sites may end up being cleaved in the course of the final deprotection of the polynucleotide thus reducing the yield of the full-length product. The O6 modifications may be removed by treatment with the capping reagent prior to oxidation with I_2/water. In some instances, inclusion of a capping step during polynucleotide synthesis decreases the error rate as compared to synthesis without capping. As an example, the capping step comprises treating the substrate-bound polynucleotide with a mixture of acetic anhydride and 1-methylimidazole. Following a capping step, the device is optionally washed.

[00175] In some instances, following addition of a nucleoside phosphoramidite, and optionally after capping and one or more wash steps, the device bound growing nucleic acid is oxidized. The oxidation step comprises a phosphite triester which is oxidized into a tetracoordinated phosphate triester, a protected precursor of the naturally occurring phosphate diester internucleoside linkage. In some instances, oxidation of the growing polynucleotide is achieved by treatment with iodine and water, optionally in the presence of a weak base (*e.g.*, pyridine, lutidine, collidine). Oxidation may be carried out under anhydrous conditions using, *e.g.* tert-Butyl hydroperoxide or (1S)-(+)-

(10-camphorsulfonyl)-oxaziridine (CSO). In some methods, a capping step is performed following oxidation. A second capping step allows for device drying, as residual water from oxidation that may persist can inhibit subsequent coupling. Following oxidation, the device and growing polynucleotide are optionally washed. In some instances, the step of oxidation is substituted with a sulfurization step to obtain polynucleotide phosphorothioates, wherein any capping steps can be performed after the sulfurization. Many reagents are capable of the efficient sulfur transfer, including but not limited to 3-(Dimethylaminomethylidene)amino)-3H-1,2,4-dithiazole-3-thione, DDTT, 3H-1,2-benzodithiol-3-one 1,1-dioxide, also known as Beaucage reagent, and N,N,N'N'-Tetraethylthiuram disulfide (TETD).

[00176] In order for a subsequent cycle of nucleoside incorporation to occur through coupling, the protected 5′ end of the device bound growing polynucleotide is removed so that the primary hydroxyl group is reactive with a next nucleoside phosphoramidite. In some instances, the protecting group is DMT and deblocking occurs with trichloroacetic acid in dichloromethane. Conducting detritylation for an extended time or with stronger than recommended solutions of acids may lead to increased depurination of solid support-bound polynucleotide and thus reduces the yield of the desired full-length product. Methods and compositions of the disclosure described herein provide for controlled deblocking conditions limiting undesired depurination reactions. In some instances, the device bound polynucleotide is washed after deblocking. In some instances, efficient washing after deblocking contributes to synthesized polynucleotides having a low error rate.

[00177] Methods for the synthesis of polynucleotides typically involve an iterating sequence of the following steps: application of a protected monomer to an actively functionalized surface (*e.g.*, locus) to link with either the activated surface, a linker or with a previously deprotected monomer; deprotection of the applied monomer so that it is reactive with a subsequently applied protected monomer; and application of another protected monomer for linking. One or more intermediate steps include oxidation or sulfurization. In some instances, one or more wash steps precede or follow one or all of the steps.

[00178] Methods for phosphoramidite-based polynucleotide synthesis comprise a series of chemical steps. In some instances, one or more steps of a synthesis method involve reagent cycling, where one or more steps of the method comprise application to the device of a reagent useful for the step. For example, reagents are cycled by a series of liquid deposition and vacuum drying steps. For substrates comprising three-dimensional features such as wells, microwells, channels and the like, reagents are optionally passed through one or more regions of the device via the wells and/or channels.

[00179] Methods and systems described herein relate to polynucleotide synthesis devices for the synthesis of polynucleotides. The synthesis may be in parallel. For example, at least or about at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 1000, 10000, 50000, 75000, 100000 or more polynucleotides can be synthesized in parallel. The total number polynucleotides that may be synthesized in parallel may be from 2-100000, 3-50000, 4-10000, 5-1000, 6-900, 7-850, 8-800, 9-750, 10-700, 11-650, 12-600, 13-550, 14-500, 15-450, 16-400, 17-350, 18-300, 19-250, 20-200, 21-150,22-100, 23-50, 24-45, 25-40, 30-35. Those of skill in the art appreciate that the total number of polynucleotides synthesized in parallel may fall within any range bound by any of these values, for example 25-100. The total number of polynucleotides synthesized in parallel may fall within any range defined by any of the values serving as endpoints of the range. Total molar mass of polynucleotides synthesized within the device or the molar mass of each of the polynucleotides may be at least or at least about 10, 20, 30, 40, 50, 100, 250, 500, 750, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 25000, 50000, 75000, 100000 picomoles, or more. The length of each of the polynucleotides or average length of the polynucleotides within the device may be at least or about at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200, 300, 400, 500 nucleotides, or more. The length of each of the polynucleotides or average length of the polynucleotides within the device may be at most or about at most 500, 400, 300, 200, 150, 100, 50, 45, 35, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10 nucleotides, or less. The length of each of the polynucleotides or average length of the polynucleotides within the device may fall from 10-500, 9-400, 11-300, 12-200, 13-150, 14-100, 15-50, 16-45, 17-40, 18-35, 19-25. Those of skill in the art appreciate that the length of each of the polynucleotides or average length of the polynucleotides within the device may fall within any range bound by any of these values, for example 100-300. The length of each of the polynucleotides or average length of the polynucleotides within the device may fall within any range defined by any of the values serving as endpoints of the range.

[00180] Methods for polynucleotide synthesis on a surface provided herein allow for synthesis at a fast rate. As an example, at least 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, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 125, 150, 175, 200 nucleotides per hour, or more are synthesized. Nucleotides include adenine, guanine, thymine, cytosine, uridine building blocks, or analogs/modified versions thereof. In some instances, libraries of polynucleotides are synthesized in parallel on substrate. For example, a device comprising about or at least about 100; 1,000; 10,000; 30,000; 75,000; 100,000; 1,000,000; 2,000,000; 3,000,000; 4,000,000; or 5,000,000 resolved loci is able to support the synthesis of at least the same number of

distinct polynucleotides, wherein polynucleotide encoding a distinct sequence is synthesized on a resolved locus. In some instances, a library of polynucleotides is synthesized on a device with low error rates described herein in less than about three months, two months, one month, three weeks, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 days, 24 hours, or less. In some instances, larger nucleic acids assembled from a polynucleotide library synthesized with low error rate using the substrates and methods described herein are prepared in less than about three months, two months, one month, three weeks, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 days, 24 hours, or less.

[00181] In some instances, methods described herein provide for generation of a library of nucleic acids comprising variant nucleic acids differing at a plurality of codon sites. In some instances, a nucleic acid may have 1 site, 2 sites, 3 sites, 4 sites, 5 sites, 6 sites, 7 sites, 8 sites, 9 sites, 10 sites, 11 sites, 12 sites, 13 sites, 14 sites, 15 sites, 16 sites, 17 sites 18 sites, 19 sites, 20 sites, 30 sites, 40 sites, 50 sites, or more of variant codon sites.

[00182] In some instances, the one or more sites of variant codon sites may be adjacent. In some instances, the one or more sites of variant codon sites may not be adjacent but are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more codons.

[00183] In some instances, a nucleic acid may comprise multiple sites of variant codon sites, wherein all the variant codon sites are adjacent to one another, forming a stretch of variant codon sites. In some instances, a nucleic acid may comprise multiple sites of variant codon sites, wherein none the variant codon sites are adjacent to one another. In some instances, a nucleic acid may comprise multiple sites of variant codon sites, wherein some the variant codon sites are adjacent to one another, forming a stretch of variant codon sites, and some of the variant codon sites are not adjacent to one another.

[00184] Referring to the Figures, **FIG. 3** illustrates an exemplary process workflow for synthesis of nucleic acids (e.g., genes) from shorter nucleic acids. The workflow is divided generally into phases: (1) de novo synthesis of a single stranded nucleic acid library, (2) joining nucleic acids to form larger fragments, (3) error correction, (4) quality control, and (5) shipment. Prior to de novo synthesis, an intended nucleic acid sequence or group of nucleic acid sequences is preselected. For example, a group of genes is preselected for generation.

[00185] Once large nucleic acids for generation are selected, a predetermined library of nucleic acids is designed for de novo synthesis. Various suitable methods are known for generating high density polynucleotide arrays. In the workflow example, a device surface layer is provided. In the example, chemistry of the surface is altered in order to improve the polynucleotide synthesis process. Areas of low surface energy are generated to repel liquid while areas of high surface energy are generated to attract liquids. The surface itself may be in the form of a planar surface or

contain variations in shape, such as protrusions or microwells which increase surface area. In the workflow example, high surface energy molecules selected serve a dual function of supporting DNA chemistry, as disclosed in International Patent Application Publication WO/2015/021080, which is herein incorporated by reference in its entirety.

[00186] In situ preparation of polynucleotide arrays is generated on a solid support and utilizes single nucleotide extension process to extend multiple oligomers in parallel. A deposition device, such as a material deposition device, is designed to release reagents in a step-wise fashion such that multiple polynucleotides extend, in parallel, one residue at a time to generate oligomers with a predetermined nucleic acid sequence **302**. In some instances, polynucleotides are cleaved from the surface at this stage. Cleavage includes gas cleavage, *e.g.*, with ammonia or methylamine.

[00187] The generated polynucleotide libraries are placed in a reaction chamber. In this exemplary workflow, the reaction chamber (also referred to as "nanoreactor") is a silicon coated well, containing PCR reagents and lowered onto the polynucleotide library **303**. Prior to or after the sealing **304** of the polynucleotides, a reagent is added to release the polynucleotides from the substrate. In the exemplary workflow, the polynucleotides are released subsequent to sealing of the nanoreactor **305**. Once released, fragments of single stranded polynucleotides hybridize in order to span an entire long-range sequence of DNA. Partial hybridization **305** is possible because each synthesized polynucleotide is designed to have a small portion overlapping with at least one other polynucleotide in the pool.

[00188] After hybridization, a PCA reaction is commenced. During the polymerase cycles, the polynucleotides anneal to complementary fragments and gaps are filled in by a polymerase. Each cycle increases the length of various fragments randomly depending on which polynucleotides find each other. Complementarity amongst the fragments allows for formation of a complete large span of double stranded DNA **306**.

[00189] After PCA is complete, the nanoreactor is separated from the device **307** and positioned for interaction with a device having primers for PCR **308**. After sealing, the nanoreactor is subject to PCR **309** and the larger nucleic acids are amplified. After PCR **310**, the nanochamber is opened **311**, error correction reagents are added **312**, the chamber is sealed **313** and an error correction reaction occurs to remove mismatched base pairs and/or strands with poor complementarity from the double stranded PCR amplification products **314**. The nanoreactor is opened and separated **315**. Error corrected product is next subject to additional processing steps, such as PCR and molecular bar coding, and then packaged **322** for shipment **323**.

[00190] In some instances, quality control measures are taken. After error correction, quality control steps include for example interaction with a wafer having sequencing primers for

amplification of the error corrected product **316**, sealing the wafer to a chamber containing error corrected amplification product **317**, and performing an additional round of amplification **318**. The nanoreactor is opened **319** and the products are pooled **320** and sequenced **321**. After an acceptable quality control determination is made, the packaged product **322** is approved for shipment **323**.

[00191] In some instances, a nucleic acid generated by a workflow such as that in **FIG. 3** is subject to mutagenesis using overlapping primers disclosed herein. In some instances, a library of primers is generated by in situ preparation on a solid support and utilize single nucleotide extension process to extend multiple oligomers in parallel. A deposition device, such as a material deposition device, is designed to release reagents in a step wise fashion such that multiple polynucleotides extend, in parallel, one residue at a time to generate oligomers with a predetermined nucleic acid sequence **302**.

[00192] **Computer systems**

[00193] Any of the systems described herein, may be operably linked to a computer and may be automated through a computer either locally or remotely. In various instances, the methods and systems of the disclosure may further comprise software programs on computer systems and use thereof. Accordingly, computerized control for the synchronization of the dispense/vacuum/refill functions such as orchestrating and synchronizing the material deposition device movement, dispense action and vacuum actuation are within the bounds of the disclosure. The computer systems may be programmed to interface between the user specified base sequence and the position of a material deposition device to deliver the correct reagents to specified regions of the substrate.

[00194] The computer system **400** illustrated in **FIG. 4** may be understood as a logical apparatus that can read instructions from media **411** and/or a network port **405**, which can optionally be connected to server **409** having fixed media **412**. The system, such as shown in **FIG. 4** can include a CPU **401**, disk drives **403**, optional input devices such as keyboard **415** and/or mouse **416** and optional monitor **407**. Data communication can be achieved through the indicated communication medium to a server at a local or a remote location. The communication medium can include any means of transmitting and/or receiving data. For example, the communication medium can be a network connection, a wireless connection or an internet connection. Such a connection can provide for communication over the World Wide Web. It is envisioned that data relating to the present disclosure can be transmitted over such networks or connections for reception and/or review by a party **422** as illustrated in **FIG. 4**.

[00195] **FIG. 5** is a block diagram illustrating a first example architecture of a computer system **500** that can be used in connection with example instances of the present disclosure. As depicted in **FIG. 5**, the example computer system can include a processor **502** for processing instructions.

Non-limiting examples of processors include: Intel Xeon™ processor, AMD Opteron™ processor, Samsung 32-bit RISC ARM 1176JZ(F)-S v1.0™ processor, ARM Cortex-A8 Samsung S5PC100TM processor, ARM Cortex-A8 Apple A4™ processor, Marvell PXA 930™ processor, or a functionally-equivalent processor. Multiple threads of execution can be used for parallel processing. In some instances, multiple processors or processors with multiple cores can also be used, whether in a single computer system, in a cluster, or distributed across systems over a network comprising a plurality of computers, cell phones, and/or personal data assistant devices.

[00196] As illustrated in **FIG. 5**, a high-speed cache **504** can be connected to, or incorporated in, the processor **502** to provide a high speed memory for instructions or data that have been recently, or are frequently, used by the processor **502**. The processor **502** is connected to a north bridge **506** by a processor bus **508**. The north bridge **506** is connected to random access memory (RAM) **510** by a memory bus **512** and manages access to the RAM **510** by the processor **502**. The north bridge **506** is also connected to a south bridge **514** by a chipset bus **516**. The south bridge **514** is, in turn, connected to a peripheral bus **518**. The peripheral bus can be, for example, PCI, PCI-X, PCI Express, or other peripheral bus. The north bridge and south bridge are often referred to as a processor chipset and manage data transfer between the processor, RAM, and peripheral components on the peripheral bus **518**. In some alternative architectures, the functionality of the north bridge can be incorporated into the processor instead of using a separate north bridge chip. In some instances, system **500** can include an accelerator card **522** attached to the peripheral bus **518**. The accelerator can include field programmable gate arrays (FPGAs) or other hardware for accelerating certain processing. For example, an accelerator can be used for adaptive data restructuring or to evaluate algebraic expressions used in extended set processing.

[00197] Software and data are stored in external storage **524** and can be loaded into RAM **510** and/or cache **504** for use by the processor. The system **500** includes an operating system for managing system resources; non-limiting examples of operating systems include: Linux, Windows™, MACOSTM, BlackBerry OSTM, iOS™, and other functionally-equivalent operating systems, as well as application software running on top of the operating system for managing data storage and optimization in accordance with example instances of the present disclosure. In this example, system **500** also includes network interface cards (NICs) **520** and **521** connected to the peripheral bus for providing network interfaces to external storage, such as Network Attached Storage (NAS) and other computer systems that can be used for distributed parallel processing.

[00198] **FIG. 6** is a diagram showing a network **600** with a plurality of computer systems **602a**, and **602b**, a plurality of cell phones and personal data assistants **602c**, and Network Attached Storage (NAS) **604a**, and **604b**. In example instances, systems **602a**, **602b**, and **602c** can manage

data storage and optimize data access for data stored in Network Attached Storage (NAS) **604a** and **604b**. A mathematical model can be used for the data and be evaluated using distributed parallel processing across computer systems **602a**, and **602b**, and cell phone and personal data assistant systems **602c**. Computer systems **602a**, and **602b**, and cell phone and personal data assistant systems **602c** can also provide parallel processing for adaptive data restructuring of the data stored in Network Attached Storage (NAS) **604a** and **604b**. **FIG. 6** illustrates an example only, and a wide variety of other computer architectures and systems can be used in conjunction with the various instances of the present disclosure. For example, a blade server can be used to provide parallel processing. Processor blades can be connected through a back plane to provide parallel processing. Storage can also be connected to the back plane or as Network Attached Storage (NAS) through a separate network interface. In some example instances, processors can maintain separate memory spaces and transmit data through network interfaces, back plane or other connectors for parallel processing by other processors. In other instances, some or all of the processors can use a shared virtual address memory space.

[00199] **FIG. 7** is a block diagram of a multiprocessor computer system **700** using a shared virtual address memory space in accordance with an example instance. The system includes a plurality of processors **702a-f** that can access a shared memory subsystem **704**. The system incorporates a plurality of programmable hardware memory algorithm processors (MAPs) **706a-f** in the memory subsystem **704**. Each MAP **706a-f** can comprise a memory **708a-f** and one or more field programmable gate arrays (FPGAs) **710a-f**. The MAP provides a configurable functional unit and particular algorithms or portions of algorithms can be provided to the FPGAs **710a-f** for processing in close coordination with a respective processor. For example, the MAPs can be used to evaluate algebraic expressions regarding the data model and to perform adaptive data restructuring in example instances. In this example, each MAP is globally accessible by all of the processors for these purposes. In one configuration, each MAP can use Direct Memory Access (DMA) to access an associated memory **708a-f**, allowing it to execute tasks independently of, and asynchronously from the respective microprocessor **702a-f**. In this configuration, a MAP can feed results directly to another MAP for pipelining and parallel execution of algorithms.

[00200] The above computer architectures and systems are examples only, and a wide variety of other computer, cell phone, and personal data assistant architectures and systems can be used in connection with example instances, including systems using any combination of general processors, co-processors, FPGAs and other programmable logic devices, system on chips (SOCs), application specific integrated circuits (ASICs), and other processing and logic elements. In some instances, all or part of the computer system can be implemented in software or hardware. Any

variety of data storage media can be used in connection with example instances, including random access memory, hard drives, flash memory, tape drives, disk arrays, Network Attached Storage (NAS) and other local or distributed data storage devices and systems.

[00201] In example instances, the computer system can be implemented using software modules executing on any of the above or other computer architectures and systems. In other instances, the functions of the system can be implemented partially or completely in firmware, programmable logic devices such as field programmable gate arrays (FPGAs) as referenced in **FIG. 5**, system on chips (SOCs), application specific integrated circuits (ASICs), or other processing and logic elements. For example, the Set Processor and Optimizer can be implemented with hardware acceleration through the use of a hardware accelerator card, such as accelerator card **522** illustrated in **FIG. 5**.

[00202] The following examples are set forth to illustrate more clearly the principle and practice of embodiments disclosed herein to those skilled in the art and are not to be construed as limiting the scope of any claimed embodiments. Unless otherwise stated, all parts and percentages are on a weight basis.

EXAMPLES

[00203] The following examples are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

[00204] Example 1: Functionalization of a device surface

[00205] A device was functionalized to support the attachment and synthesis of a library of polynucleotides. The device surface was first wet cleaned using a piranha solution comprising 90% H_2SO_4 and 10% H_2O_2 for 20 minutes. The device was rinsed in several beakers with DI water, held under a DI water gooseneck faucet for 5 min, and dried with N_2. The device was subsequently soaked in NH_4OH (1:100; 3 mL:300 mL) for 5 min, rinsed with DI water using a handgun, soaked in three successive beakers with DI water for 1 min each, and then rinsed again with DI water using the handgun. The device was then plasma cleaned by exposing the device surface to O_2. A SAMCO PC-300 instrument was used to plasma etch O_2 at 250 watts for 1 min in downstream mode.

[00206] The cleaned device surface was actively functionalized with a solution comprising N-(3-triethoxysilylpropyl)-4-hydroxybutyramide using a YES-1224P vapor deposition oven system with the following parameters: 0.5 to 1 torr, 60 min, 70 °C, 135 °C vaporizer. The device surface was resist coated using a Brewer Science 200X spin coater. SPR™ 3612 photoresist was spin coated on the device at 2500 rpm for 40 sec. The device was pre-baked for 30 min at 90 °C on a Brewer hot plate. The device was subjected to photolithography using a Karl Suss MA6 mask aligner instrument. The device was exposed for 2.2 sec and developed for 1 min in MSF 26A. Remaining developer was rinsed with the handgun and the device soaked in water for 5 min. The device was baked for 30 min at 100 °C in the oven, followed by visual inspection for lithography defects using a Nikon L200. A descum process was used to remove residual resist using the SAMCO PC-300 instrument to O_2 plasma etch at 250 watts for 1 min.

[00207] The device surface was passively functionalized with a 100 µL solution of perfluorooctyltrichlorosilane mixed with 10 µL light mineral oil. The device was placed in a chamber, pumped for 10 min, and then the valve was closed to the pump and left to stand for 10 min. The chamber was vented to air. The device was resist stripped by performing two soaks for 5 min in 500 mL NMP at 70 °C with ultrasonication at maximum power (9 on Crest system). The device was then soaked for 5 min in 500 mL isopropanol at room temperature with ultrasonication at maximum power. The device was dipped in 300 mL of 200 proof ethanol and blown dry with N_2. The functionalized surface was activated to serve as a support for polynucleotide synthesis.

[00208] **Example 2: Synthesis of a 50-mer sequence on an oligonucleotide synthesis device**

[00209] A two-dimensional oligonucleotide synthesis device was assembled into a flowcell, which was connected to a flowcell (Applied Biosystems (ABI394 DNA Synthesizer"). The two-dimensional oligonucleotide synthesis device was uniformly functionalized with N-(3-TRIETHOXYSILYLPROPYL)-4-HYDROXYBUTYRAMIDE (Gelest) which was used to synthesize an exemplary polynucleotide of 50 bp ("50-mer polynucleotide") using polynucleotide synthesis methods described herein.

[00210] The sequence of the 50-mer was as described in SEQ ID NO: 1348.

5'AGACAATCAACCATTTGGGGTGGACAGCCTTGACCTCTAGACTTCGGCAT##TTTTTTT TTT3' (SEQ ID NO.: 1348), where # denotes Thymidine-succinyl hexamide CED phosphoramidite (CLP-2244 from ChemGenes), which is a cleavable linker enabling the release of oligos from the surface during deprotection.

[00211] The synthesis was done using standard DNA synthesis chemistry (coupling, capping, oxidation, and deblocking) according to the protocol in **Table 3** and an ABI synthesizer.

Table 3: Synthesis protocols

	Table 3	
General DNA Synthesis Process Name	**Process Step**	**Time (sec)**
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	23
	N2 System Flush	4
	Acetonitrile System Flush	4
DNA BASE ADDITION (Phosphoramidite + Activator Flow)	Activator Manifold Flush	2
	Activator to Flowcell	6
	Activator + Phosphoramidite to Flowcell	6
	Activator to Flowcell	0.5
	Activator + Phosphoramidite to Flowcell	5
	Activator to Flowcell	0.5
	Activator + Phosphoramidite to Flowcell	5
	Activator to Flowcell	0.5
	Activator + Phosphoramidite to Flowcell	5
	Incubate for 25sec	25
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	15
	N2 System Flush	4
	Acetonitrile System Flush	4
DNA BASE ADDITION (Phosphoramidite + Activator Flow)	Activator Manifold Flush	2
	Activator to Flowcell	5
	Activator + Phosphoramidite to Flowcell	18
	Incubate for 25sec	25
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	15
	N2 System Flush	4
	Acetonitrile System Flush	4
CAPPING (CapA+B, 1:1, Flow)	CapA+B to Flowcell	15
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	15
	Acetonitrile System Flush	4
OXIDATION (Oxidizer Flow)	Oxidizer to Flowcell	18
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	N2 System Flush	4

Table 3		
General DNA Synthesis Process Name	**Process Step**	**Time (sec)**
	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	15
	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	15
	N2 System Flush	4
	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	23
	N2 System Flush	4
	Acetonitrile System Flush	4
DEBLOCKING (Deblock Flow)	Deblock to Flowcell	36
WASH (Acetonitrile Wash Flow)	Acetonitrile System Flush	4
	N2 System Flush	4
	Acetonitrile System Flush	4
	Acetonitrile to Flowcell	18
	N2 System Flush	4.13
	Acetonitrile System Flush	4.13
	Acetonitrile to Flowcell	15

[00212] The phosphoramidite/activator combination was delivered similarly to the delivery of bulk reagents through the flowcell. No drying steps were performed as the environment stays "wet" with reagent the entire time.

[00213] The flow restrictor was removed from the ABI 394 synthesizer to enable faster flow. Without flow restrictor, flow rates for amidites (0.1M in ACN), Activator, (0.25M Benzoylthiotetrazole ("BTT"; 30-3070-xx from GlenResearch) in ACN), and Ox (0.02M I2 in 20% pyridine, 10% water, and 70% THF) were roughly ~100uL/sec, for acetonitrile ("ACN") and capping reagents (1:1 mix of CapA and CapB, wherein CapA is acetic anhydride in THF/Pyridine and CapB is 16% 1-methylimidizole in THF), roughly ~200uL/sec, and for Deblock (3% dichloroacetic acid in toluene), roughly ~300uL/sec (compared to ~50uL/sec for all reagents with flow restrictor). The time to completely push out Oxidizer was observed, the timing for chemical flow times was adjusted accordingly and an extra ACN wash was introduced between different chemicals. After polynucleotide synthesis, the chip was deprotected in gaseous ammonia overnight at 75 psi. Five drops of water were applied to the surface to recover polynucleotides. The recovered polynucleotides were then analyzed on a BioAnalyzer small RNA chip.

[00214] Example 3: Synthesis of a 100-mer sequence on an oligonucleotide synthesis device

[00215] The same process as described in Example 2 for the synthesis of the 50-mer sequence was used for the synthesis of a 100-mer polynucleotide ("100-mer polynucleotide"; 5' CGGGATCCTTATCGTCATCGTCGTACAGATCCCGACCCATTTGCTGTCCACCAGTCATG

CTAGCCATACCATGATGATGATGATGATGAGAACCCCGCAT##TTTTTTTTTT3', where # denotes Thymidine-succinyl hexamide CED phosphoramidite (CLP-2244 from ChemGenes); SEQ ID NO.: 1349) on two different silicon chips, the first one uniformly functionalized with N-(3-TRIETHOXYSILYLPROPYL)-4-HYDROXYBUTYRAMIDE and the second one functionalized with 5/95 mix of 11-acetoxyundecyltriethoxysilane and n-decyltriethoxysilane, and the polynucleotides extracted from the surface were analyzed on a BioAnalyzer instrument.

[00216] All ten samples from the two chips were further PCR amplified using a forward (5'ATGCGGGGTTCTCATCATC3'; SEQ ID NO.: 1350) and a reverse (5'CGGGATCCTTATCGTCATCG3'; SEQ ID NO.: 1351) primer in a 50uL PCR mix (25uL NEB Q5 mastermix, 2.5uL 10uM Forward primer, 2.5uL 10uM Reverse primer, 1uL polynucleotide extracted from the surface, and water up to 50uL) using the following thermalcycling program:

98 ℃, 30 sec

98 ℃, 10 sec; 63 ℃, 10 sec; 72 ℃, 10 sec; repeat 12 cycles

72 ℃, 2 min

[00217] The PCR products were also run on a BioAnalyzer, demonstrating sharp peaks at the 100-mer position. Next, the PCR amplified samples were cloned, and Sanger sequenced. **Table 4** summarizes the results from the Sanger sequencing for samples taken from spots 1-5 from chip 1 and for samples taken from spots 6-10 from chip 2.

Table 4: Sequencing results

Spot	Error rate	Cycle efficiency
1	1/763 bp	99.87%
2	1/824 bp	99.88%
3	1/780 bp	99.87%
4	1/429 bp	99.77%
5	1/1525 bp	99.93%
6	1/1615 bp	99.94%
7	1/531 bp	99.81%
8	1/1769 bp	99.94%
9	1/854 bp	99.88%
10	1/1451 bp	99.93%

[00218] Thus, the high quality and uniformity of the synthesized polynucleotides were repeated on two chips with different surface chemistries. Overall, 89% of the 100-mers that were sequenced were perfect sequences with no errors, corresponding to 233 out of 262.

[00219] **Table 5** summarizes error characteristics for the sequences obtained from the polynucleotide samples from spots 1-10.

Table 5: Error characteristics

Sample ID/Spot no.	OSA_0046/1	OSA_0047/2	OSA_0048/3	OSA_0049/4	OSA_0050/5	OSA_0051/6	OSA_0052/7	OSA_0053/8	OSA_0054/9	OSA_0055/10
Total Sequences	32	32	32	32	32	32	32	32	32	32
Sequencing Quality	25 of 28	27 of 27	26 of 30	21 of 23	25 of 26	29 of 30	27 of 31	29 of 31	28 of 29	25 of 28
Oligo Quality	23 of 25	25 of 27	22 of 26	18 of 21	24 of 25	25 of 29	22 of 27	28 of 29	26 of 28	20 of 25
ROI Match Count	2500	2698	2561	2122	2499	2666	2625	2899	2798	2348
ROI Mutation	2	2	1	3	1	0	2	1	2	1
ROI Multi Base Deletion	0	0	0	0	0	0	0	0	0	0
ROI Small Insertion	1	0	0	0	0	0	0	0	0	0
ROI Single Base Deletion	0	0	0	0	0	0	0	0	0	0
Large Deletion Count	0	0	1	0	0	1	1	0	0	0
Mutation: G>A	2	2	1	2	1	0	2	1	2	1
Mutation: T>C	0	0	0	1	0	0	0	0	0	0
ROI Error Count	3	2	2	3	1	1	3	1	2	1
ROI Error Rate	Err: ~1 in 834	Err: ~1 in 1350	Err: ~1 in 1282	Err: ~1 in 708	Err: ~1 in 2500	Err: ~1 in 2667	Err: ~1 in 876	Err: ~1 in 2900	Err: ~1 in 1400	Err: ~1 in 2349
ROI Minus Primer Error Rate	MP Err: ~1 in 763	MP Err: ~1 in 824	MP Err: ~1 in 780	MP Err: ~1 in 429	MP Err: ~1 in 1525	MP Err: ~1 in 1615	MP Err: ~1 in 531	MP Err: ~1 in 1769	MP Err: ~1 in 854	MP Err: ~1 in 1451

[00220] **Example 4: Functional GLP-1R Antibodies Identified from a Synthetic GPCR-focused Library Demonstrate Potent Blood Glucose Control**

[00221] This example describes the identification of antagonistic and agonistic GLP-1R antibodies with *in vitro* and *in vivo* functional activity.

[00222] **Materials and Method**

[00223] *Stable cell line and phage library generation*

[00224] The full length human GLP-1R gene (UniProt - P43220) with an N-terminal FLAG tag and C-terminal GFP tag cloned into pCDNA3.1(+) vector (ThermoFisher) was transfected into suspension Chinese Hamster Ovary (CHO) cells to generate the stable cell line expressing GLP-1R. Target expression was confirmed by FACS. Cells expressing > 80% of GLP-1R by GFP were then directly used for cell-based selections.

[00225] Germline heavy chain IGHV1-69, IGHV3-30 and germline light chain IGKV1-39, IGKV3-15, IGLV1-51, IGLV2-14 framework combinations were used in the GPCR-focused phage-displayed library, and all six CDR diversities were encoded by oligo pools synthesized similar to Examples 1-3 above. The CDRs were also screened to ensure they did not contain manufacturability liabilities, cryptic splice sites, or commonly used nucleotide restriction sites. The heavy chain variable region (VH) and light chain variable region (VL) were linked by (G4S)3 linker. The resulting scFv (VH-linker-VL) gene library was cloned into a pADL 22-2c (Antibody Design Labs) phage display vector by NotI restriction digestion and electroporated into TG1 electro-competent *E. coli* cells. (Lucigen). The final library has a diversity of 1.1×10^{10} size, which was verified by NGS.

[00226] *Panning and screening strategy used to isolate agonist GLP-1R scFv clones*

[00227] Before panning on GLP-1R expressing CHO cells, phage particles were blocked with 5% BSA/PBS and depleted for non-specific binders on CHO parent cells. For CHO parent cell depletion, the input phage aliquot was rotated at 14 rpm/min with 1×10^8 CHO parent cells for 1 hour at room temperature (RT). The cells were then pelleted by centrifuging at 1,200 rpm for 10 mins in a tabletop Eppendorf centrifuge 5920RS/4x1000 rotor to deplete the non-specific CHO cell binders. The phage supernatant, depleted of CHO cell binders, was then transferred to 1×10^8 GLP-1R expressing CHO cells. The phage supernatant and GLP-1R expressing CHO cells were rotated at 14 rpm/min for 1 hour at RT to select for GLP-1R binders. After incubation, the cells were washed several times with 1x PBS/0.5% Tween to remove non-binding clones. To elute the phage bound to the GLP-1R cells, the cells were incubated with trypsin in PBS buffer for 30 minutes at 37^{O}C. The cells were pelleted by centrifuging at 1,200 rpm for 10 mins. The output supernatant enriched in GLP-1R binding clones was amplified in TG1 *E.coli* cells to use as input phage for the next round of selection. This selection strategy was repeated for five rounds. Every round was depleted against the CHO parent background. Amplified output phage from a round was used as the

input phage for the subsequent round, and the stringency of washes were increased in each subsequent round of selections with more washes. After five rounds of selection, 500 clones from each of round 4 and round 5 were Sanger sequenced to identify unique clones.

[00228] *Next-generation sequencing analysis*

[00229] The phagemid DNA was miniprepped from the output bacterial stocks of all panning rounds. The variable heavy chain (VH) was PCR amplified from the phagemid DNA using the Forward Primer ACAGAATTCATTAAAGAGGAGAAATTAACC and reverse primer TGAACCGCCTCCACCGCTAG. The PCR product was directly used for library preparation using the KAPA HyperPlus Library Preparation Kit (Kapa Biosystems, product # KK8514). To add diversity in the library, the samples were spiked with 15% PhiX Control purchased from Illumina, Inc. (product # FC-110-3001). The library was then loaded onto Illumina's 600 cycle MiSeq Reagent Kit v3 (Illumina, product # MS-102-3003) and run on the MiSeq instrument.

[00230] *Reformatting and High Throughput (HT) IgG purification*

[00231] Expi293 cells were transfected using Expifectamine (ThermoFisher, A14524) with the heavy chain and light chain DNA at a 2:1 ratio and supernatants were harvested 4 days post-transfection before cell viability dropped below 80%. Purifications were undertaken using either King Fisher (ThermoFisher) with protein A magnetic beads or Phynexus protein A column tips (Hamilton). For large scale production of IgG clones that were evaluated in *in vivo* mouse studies, an Akta HPLC purification system (GE) was used.

[00232] *IgG characterization and quality control.* The purified IgGs for the positive GLP-1R binders (hits) were subjected to characterization for their purity by LabChip GXII Touch HT Protein Express high-sensitivity assay. Dithiothreitol (DTT) was used to reduce the IgG into VH and VL. IgG concentrations were measured using Lunatic (UnChain). IgG for in vivo mouse studies were further characterized by HPLC and tested for endotoxin levels (Endosafe® nexgen-PTS™ Endotoxin Testing, Charles River), with less than 5 EU per kg dosing.

[00233] *Binding assays and flow cytometry*

[00234] GLP-1R IgG clones were tested in a binding assay coupled to flow cytometry analysis as follows: FLAG-GLP-1R-GFP expressing CHO cells (CHO-GLP-1R) and CHO-parent cells were incubated with 100 nM IgG for 1 h on ice, washed three times and incubated with Alexa 647 conjugated goat-anti-human antibody (1:200) (Jackson ImmunoResearch Laboratories, 109-605-044) for 30 min on ice, followed by three washes, centrifuging to pellet the cells between each washing step. All incubations and washes were in buffer containing PBS+1% BSA. For titrations, IgG was serially diluted 1:3 starting from 100 nM down to 0.046 nM. Cells were analyzed by flow cytometry and hits (a hit is an IgG that specifically binds to CHO-GLP-1R) were identified by

measuring the GFP signal against the Alexa 647 signal. Flow cytometry data of binding assays with 100 nM IgG are presented as dot plots. Analyses of binding assays with IgG titrations are presented as binding curves plotting IgG concentrations against MFI (mean fluorescence intensity).

[00235] *Ligand competition assay*

[00236] Ligand competition assays involved co-incubating the primary IgG with 1 μM GLP-1 (7-36). For each data point, IgG (600 nM) was prepared in Flow buffer (PBS+1%BSA) and diluted 1:3 down for 8 titration points. Peptide GLP-1 7-36 (2 μM) was prepared similarly with the Flow buffer (PBS+1% BSA). Each well contained 100,000 cells to which 50 μL of IgG and 50μL of peptide (=plus) or buffer alone without peptide (= minus) were added. Cells and IgG/peptide mix were incubated for 1hr on ice, and after washing, secondary antibody (goat anti-human APC, Jackson ImmunoResearch Laboratories, product# 109-605-044) diluted 1:200 in PBS+1%BSA was added. This was incubated on ice for 30 mins (50μL per well), before washing and resuspending in 60μL buffer. Finally, the assay read-out was measured on an Intellicyt® IQue3 Screener at a rate of 4 seconds per well.

[00237] *Cell-based functional assays*

[00238] *cAMP assays*. GLP-1R IgG clones were tested for their potential effects on GLP-1R signaling by performing cAMP assays obtained from Eurofins DiscoverX. The technology involved in detecting cAMP levels is a no wash gain-of-signal competitive immunoassay based on Enzyme Fragment Complementation technology. Experiments were designed to test for either agonist or antagonist activity of the IgG clones. To test for agonist activity of the IgGs, cells were stimulated with IgG incubating for 30 min at 37°C (titrations 1:3 starting from 100nM and diluting down to 0.046 nM with PBS) or with the known agonist GLP-1 7-36 peptide (MedChemExpress, Cat. No.: HY-P005), titrated 1:6 starting from 12.5 nM and diluting down to 0.003 nM with PBS. To test for antagonist activity, cells were incubated with IgG at a fixed concentration of 100 nM for 1 h at room temperature to allow binding, followed by stimulation with GLP1 7-36 peptide (titrations 1:6 starting from 12.5 nM down to 0.003 nM in PBS) for 30 min at 37°C. Intracellular cAMP levels were detected by following the assay kit instructions.

[00239] *Beta arrestin recruitment assy.* β-arrestin recruitment assay was obtained from Eurofins DiscoverX (Cat #93-0300E2) that utilized untagged GLP-1R overexpressing CHO-K1 cells. The experiment is to test if GLP1R-3 has an effect on GLP-1 7-36 agonist induced β-arrestin recruitment upon GLP-1R activation. Expanded cells were seeded into 96 well plates at 5,000 cells/well, and the experiment was performed 48 hours after plating cells. 100 nM IgG was pre-incubated for 1 hour at RT with plated cells in 50 ul volume, and then 5 ul of ligand GLP-1 7-36 was added for a further incubation for 30 min at 37 °C. Add 22.5 uL of detection solution to each

well, tap gently and briefly spin down. Then incubate plates at RT for 1 hour in the dark. The plates were then read by a Chemiluminescence plate reader, Molecular Devices SpectraMax M5, and output relative light units (RLU) data were analyzed using GraphPad Prism.

[00240] *In vivo studies*

[00241] *Animals*. All animal procedures were approved by Institutional Animal Care and Use Committee (IACUC) at the University of California San Francisco and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of laboratory Animals. C57BL/6NHsd (Envigo RMS, LLC) male littermates at 8-10 weeks of age, weighing ~20-28 grams, were used in all the studies described. The mice were housed in a room that was temperature (22-25C) and light controlled (12-h: 12-h light/dark cycle starting at 7AM. The mice were fed with chow diet with 9% fat (PicoLab mouse Diet 20 (#5058), Lab Supply, Fortworth Texas, USA) for the duration of housing at the UCSF animal care facility.

[00242] *Monoclonal Antibodies and Reagents*. Anti-GLP-1 monoclonal antibodies (mAb) in PBS buffer were tested in these studies an agonist mAb, GLP1R-59-2 and one antagonist mAb, GLP1R-3. Mice were dosed prior to a Glucose Tolerance Test (GTT) or an Insulin Tolerance test (ITT) using the following regimen: Agonist GLP1R-59-2 mAb was dosed at 5 or 10 mg/kg at three different administration regimen groups prior to performing a GTT and with four different administration regimen groups in an Insulin Tolerance test (ITT). 1. mAb administered as a single dose, 15 hours prior to GTT and 21 hours prior to ITT. 2. mAb administered as a double dose, 15 hours prior to GTT and 21 hours prior to ITT plus a second mAb dose 2 hours prior to GTT and ITT. 3. mAb single dose 2 hours prior to GTT and ITT. 4. mAb single dose 6 hours prior to ITT only.

[00243] Antagonist GLP1R-3 mAb was dosed at 20 mg/kg at four different administration regimen groups. 1. mAb administered as a single dose, 15 hours prior to GTT and 21 hours prior to ITT. 2. mAb administered as a double dose, 15 hours prior to GTT and 21 hours prior to ITT plus a second mAb dose 2 hours prior to GTT and ITT. 3. mAb as a single dose 6 hours prior to GTT and ITT. 4. mAb single dose 2 hours prior to GTT and ITT.

[00244] Extendin 9-39 Peptide (MedChemExpress, Cat. No.: HY-P0264) were dosed at 1.0 or 0.23 mg/kg at three different administration regimen groups. 1. Extendin administered as a single dose, 21 hours prior to ITT. 2. Extendin administered as a double dose, 21 hours prior to ITT plus a second Extendin dose 2 hours prior to ITT. 3. mAb as a single dose 6 hours prior to ITT.

[00245] *Glucose Tolerance Test*

[00246] A Glucose Tolerance Test (GTT) was used to assess two different anti-GLP1 mAbs (Agonist and Antagonist) effect on glucose tolerance following an acute glucose administration.

Intraperitoneal Glucose Tolerance Test (IP-GTT) was conducted in 8 or 10-week old male mice to assess glucose disposal after a glucose injection and measuring blood glucose level after mice were fasted overnight (14-16 hours). To avoid circadian variations in mouse blood glucose levels this testing was performed at fixed times. Mice were weighed after the overnight fast and baseline blood glucose levels (pre-glucose injection; Time 0 minutes) were measured. Mice were injected, i.p., with a single bolus (10ul/gram body weight) of 30% Dextrose solution (Hospira, Illinois) and blood glucose levels were measured at 15, 30, 60, 120 and 180-minutes post glucose administration. Blood samples were obtained by a tail nick and blood glucose levels were monitored using a OneTouch Ultra 2 glucose monitor (LifeScan, Inc.)

[00247] *Insulin Tolerance Test*

[00248] An Insulin Tolerance Test (ITT) was conducted to assess two different anti-GLP1 mAbs (agonist and antagonist) effect on insulin sensitivity following acute insulin administration. 8 or 10-week old male mice were fasted for 6 hours and body weight was recorded before and after fasting. To avoid circadian variations in mouse blood glucose levels this testing was performed at fixed times. Blood samples were collected by tail nick and baseline glucose was measured prior to insulin injection. Mice were injected, i.p., with a single bolus (0.75U/Kg body weight) of human insulin (Novolin, Novo Nordisk) and blood glucose levels were measured at 15, 30, 45, 60 and 120 minutes after insulin injection. Blood glucose levels were monitored using a OneTouch Ultra 2 glucose monitor (LifeScan, Inc.).

[00249] *ELISA for Pharmacokinetic (PK) Studies.*

[00250] The rat PK study was done at Charles River Laboratories, One Innovation Dr, 3 Biotech, Worcester, MA 01605. 5 Male Sprague-Dawley rats per group were allowed to acclimate after receiving at test facility for a minimum of 3 days before dosing. GLP1R-3 and GLP1R59-2 were dosed at 10 mg/kg by IV in 100mM Hepes, 100mM NaCl, 50mM NaAc, pH 6.0 vehicle. Serial blood samples were collected via jugular vein cannula with ~ 250ul volume at each time point: pre-dose, 0.0833, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 96, 168, 240 and 336 hours post dose. Blood samples were collected into K_2EDTA tubes and stored on wet ice until processed to plasma by centrifugation (3500 rpm for 10 minutes at 5°C) within 30 minutes of collection**.** Plasma samples were then transferred into an appropriate tube containing DPP-4 (3.3µL for 100µL of plasma) and frozen on dry ice. To measure the human IgG in rat plasma samples, sheep anti-Human IgG (1 mg/mL) was used as coating reagent) (The binding site, Lot No. AU003.M), and goat anti-Human IgG, HRP (H&L) (1 mg/mL) was used as detection reagent) (Bethyl, cat# A80-319P) in an ELISA assay. Stock solutions of human IgG standards and QCs were prepared by spiking human IgG into rat plasma. A minimum of two wells were used to analyze each study

samples, QC's, standards, and blank. A 4-parameter logistic (4PL) model was used to fit the sigmoid calibration curve. The semi-logarithmic sigmoid calibration curve was obtained by plotting the absorbance response against concentration. Concentrations of analyte in the test samples were determined by computer interpolation from the plot of the calibration curve.

[00251] **Results**

[00252] *Design of GPCR-focused antibody library is based on GPCR binding motifs and GPCR antibodies*

[00253] All known GPCR interactions, which include interactions of GPCRs with ligands, peptides, antibodies, endogenous extracellular loops and small molecules were analyzed to map the GPCR binding molecular determinants. Crystal structures of almost 150 peptides, ligand or antibodies bound to ECDs of around 50 GPCRs (http://www.gpcrdb.org) were used to identify GPCR binding motifs. Over 1000 GPCR binding motifs were extracted from this analysis. In addition, by analysis of all solved structures of GPCRs (zhanglab.ccmb.med.umich.edu/GPCR-EXP/), over 2000 binding motifs from endogenous extracellular loops of GPCRs were identified. Finally, by analysis of structures of over 100 small molecule ligands bound to GPCR, a reduced amino acid library of 5 amino acids (Tyr, Phe, His, Pro and Gly) that may be able to recapitulate many of the structural contacts of these ligands was identified. A sub-library with this reduced amino acid diversity was placed within a CxxxxxC motif. In total, over 5000 GPCR binding motifs were identified (**Figs. 9A-9E**). These binding motifs were placed in one of five different stem regions: CARDLRELECEEWTxxxxxSRGPCVDPRGVAGSFDVW, CARDMYYDFxxxxxEVVPADDAFDIW, CARDGRGSLPRPKGGPxxxxxYDSSEDSGGAFDIW, CARANQHFxxxxxGYHYYGMDVW, CAKHMSMQxxxxxRADLVGDAFDVW.

[00254] These stem regions were selected from structural antibodies with ultra-long HCDR3s. Antibody germlines were specifically chosen to tolerate these ultra-long HCDR3s. Structure and sequence analysis of human antibodies with longer than 21 amino acids revealed a V-gene bias in antibodies with long CDR3s. Finally, the germline IGHV (IGHV1-69 and IGHV3-30), IGKV (IGKV1-39 and IGKV3-15) and IGLV (IGLV1-51 and IGLV2-14) genes were chosen based on this analysis.

[00255] In addition to HCDR3 diversity, limited diversity was also introduced in the other 5 CDRs. There were 416 HCDR1 and 258 HCDR2 variants in the IGHV1-69 domain; 535 HCDR1 and 416 HCDR2 variants in the IGHV3-30 domain; 490 LCDR1, 420 LCDR2 and 824 LCDR3 variants in the IGKV1-39 domain; 490 LCDR1, 265 LCDR2 and 907 LCDR3 variants in the IGKV3-15 domain; 184 LCDR1, 151 LCDR2 and 824 LCDR3 variants in the IGLV1-51 domain; 967 LCDR1, 535 LCDR2 and 922 LCDR3 variants in the IGLV2-14 domain (**Fig. 10**). These CDR

variants were selected by comparing the germline CDRs with the near-germline space of single, double and triple mutations observed in the CDRs within the V-gene repertoire of at least two out of 12 human donors. All CDRs have were pre-screened to remove manufacturability liabilities, cryptic splice sites or nucleotide restriction sites. The CDRs were synthesized as an oligo pool and incorporated into the selected antibody scaffolds. The heavy chain (VH) and light chain (VL) genes were linked by $(G_4S)_3$ linker. The resulting scFv (VH-linker-VL) gene pool was cloned into a phagemid display vector at the N-terminal of the M13 gene-3 minor coat protein. The final size of the GPCR library is 1×10^{10} in a scFv format. Next-generation sequencing (NGS) was performed on the final phage library to analyze the HCDR3 length distribution in the library for comparison with the HCDR3 length distribution in B-cell populations from three healthy adult donors. The HCDR3 sequences from the three healthy donors used were derived from a publicly available database with over 37 million B-cell receptor sequences[31]. The HCDR3 length in the GPCR library is much longer than the HCDR3 length observed in B-cell repertoire sequences. On average, the median HCDR3 length in the GPCR library (which shows a biphasic pattern of distribution) is two or three times longer (33 to 44 amino acids) than the median lengths observed in natural B-cell repertoire sequences (15 to 17 amino acids) (**Fig. 11**). The biphasic length distribution of HCDR3 in the GPCR library is mainly caused by the two groups of stems (8aa, 9aaxxxxx10aa, 12aa) and (14aa, 16aa xxxxx18aa, 14aa) used to present the motifs within HCDR3.

[00256] *Phage panning against GLP-1R over-expressing cell lines resulted in clonal enrichment*

[00257] A GLP-1R over-expressing CHO stable cell line was created with a FLAG tag presented on the N-terminus of the receptor in order to detect cell surface expression and an EGFP tag on the C-terminus to track total receptor expression. Flow cytometry analysis of these cells confirmed that the majority of the receptor (> 80%) was expressed at the cell surface (**Fig. 12A**). These GLP-1R-expressing CHO cells were used for five rounds of phage panning against the GPCR-focused library. The selection scheme is outlined in **Fig. 12B**. The variable heavy chain (VH) from the output of each panning round was PCR amplified and sequenced by MiSeq. As the percent unique HCDR3 decreases in each round output pool NGS sequencing, significant clonal enrichment was observed from round 1 to round 5 (**Fig. 13**), indicating a target specific clonal selection in the panning process. Approx. 1000 clones in total (from round 4 and round 5) were picked for single clonal NGS sequencing and ~100 unique VH-VL pairs were selected to be reformatted and expressed as full length human IgG2 at 1ml scale.

[00258] *IgG binders directed to GLP-1R contain either GLP-1, GLP-2 or unique HCDR3 motifs identified*

[00259] Purified IgG clones were tested for specific binding to GLP-1R-expressing CHO cells. A single-point flow cytometry analysis using 100nM of IgG concentration revealed that out of 100 IgG unique clones tested, 13 IgG clones bound specifically to GLP-1R-positive cells (GFP+) and not parental CHO cells (GFP-). The binding of these 13 hits was then further evaluated by 8-point titrations of each IgG clone starting from 200nM (30μg/mL) and the cell binding affinities were determined to be in the double-digit nM range. The average CHO parental cell background binding by all 13 IgG clones is shown as a black line and is minimal compared with specific binding to GLP-1R-expressing cells (**Fig. 14**). Full saturation was not observed, the plateau of the binding curve at the highest concentration, 200 nM used in the experiment. **Fig. 15** shows the HCDR3 amino acid sequences of these 13 IgG clones. Six of these were found to include a GLP-1 motif, four included a GLP-2 motif, and three had unknown motif.

[00260] *Eight IgGs of the 13 binders are negative antagonists in GLP-1R mediated cAMP signaling*

[00261] The 13 IgG binders were next assessed for their functional activity in the cAMP signaling pathway by using GLP-1R over-expressing CHO-K1 cells purchased from DiscoverX that are designed and validated for assessing GLP-1R-induced cAMP signaling. In the first instance, the IgG clones were tested for agonist activity as compared with the peptide agonist GLP-1 7-36 in dose titrations. While GLP-1 7-36 stimulation resulted in a cAMP signal, none was observed for the IgG clones, indicating that they are not activating. Subsequently, the panel of IgG clones were tested for antagonist activity by pre-incubating GLP-1R-expressing cells with a fixed concentration of IgG to allow binding to occur and then stimulating the cells with GLP-1 7-36 in a dose dependent manner. This allowed examination of the impact of the presence of IgG on GLP-1 7-36-induced GLP-1R cAMP signaling, thereby potentially revealing any potential competitive effects of the IgG. It was observed that the GLP-1 7-36 dose response curve shifted to the right in the presence of 8 out of the 13 IgG clones, suggesting that they act as negative antagonists of the GLP-1 7-36 response (data not shown). Similar observations were made regarding the effect of the 13 IgG clones on Exendin-4 induced GLP-1R cAMP signaling response (data not shown). The remaining five IgG clones appeared to have no significant effects on GLP-1R cAMP signaling (data not shown).

[00262] *Characterization of mechanisms of action of the antagonist IgG GLP1R-3*

[00263] To determine the mechanism of action of these resulting functional hits, subsequent studies focused one of the GLP-1 motif-containing IgG clones that demonstrated high binding affinity, as well as functionality: GLP1R-3. Ligand competition binding assays, the IgG effects on

the GLP-1 dose response in cAMP signaling, and beta-arrestin recruitment assays were conducted, resulting in characterization of GLP1R-3 as follows:

[00264] *Competition with the endogenous ligand in GLP-1R binding assays.* To determine if GLP1R-3 binds to the orthosteric site on the receptor, N-terminal FLAG-tagged and C terminal GFP-tagged GLP-1R over-expressing CHO cells were incubated with a dose titration of GLP1R-3 starting at 100 nM in the presence or absence of a fixed concentration of the peptide agonist GLP-1 7-36 (1μM). Flow cytometry analysis revealed significantly reduced binding of GLP1R-3 to GLP-1R (GFP+) in the presence of GLP-1 7-36. Whilst the presence of GLP-1 7-36 peptide does not completely ablate GLP1R-3 binding, this observation suggests that the antibody may bind to an overlapping epitope, or GLP1R-3 have stronger binding affinity for GLP-1 7-36 to compete for binding. (**Fig. 16A**).

[00265] *GLP1R-3 antagonizes GLP-1 activated cAMP signaling.* The next step was to determine if GLP1R-3 exhibits competitive antagonism for GLP-1R in a dose-dependent manner. GLP-1 7-36-induced cAMP signaling was examined in the presence of a constant concentration (100 nM) of GLP1R-3 with a dose titration of GLP-1 7-36 starting at 20 nM with a 3-fold down titration, and a clear dose-dependent inhibition of the cAMP signal was observed. The EC50 for GLP-1 7-36 peptide is 0.025 nM without presence of GLP1R-3, and 0.11 nM in the presence of 100 nM GLP1R-3 (**Fig. 16B**), supporting that GLP1R-3 is a competitive antagonist.

[00266] *GLP1R-3 reduces β-arrestin recruitment upon GLP-1R activation.* When a GPCR is activated by an agonist, β-arrestins are recruited to the GPCR from the cytosol, thereby excluding the receptor from further G protein interactions and leading to signal arrest, hence the name "arrestin". To determine if GLP1R-3 had any effects on β-arrestin recruitment by activated GLP-1R, GLP-1R over-expressing CHO-K1 cells (DiscoverX) that are specifically designed and validated for assessing GLP-1R β-arrestin recruitment were employed in the following manner. Cells were pre-incubated with a fixed concentration of GLP1R-3 (100nM) for 1 hr at room temperature to allow binding to occur and then stimulated with GLP-1 7-36. GLP1R-3, showed inhibition of GLP-1 7-36 peptide-induced beta arrestin recruitment to GLP-1R as evidenced by the right shift of GLP-1 7-36 dose response curve for β-arrestin recruitment (**Fig. 16C**). This indicated that GLP1R-3 reduces β-arrestin recruitment to GLP-1R, which is consistent with the observed reduced receptor activation. Thus, these cell-based assays indicate that GLP1R-3 is a competitive antagonist to GLP-1 7-36 for GLP-1R.

[00267] *Design and characterization of a GLP-1R agonist IgG GLP1R-59-2*

[00268] Since none of the 13 IgG hits showed any agonist activity, a GLP-1R agonist antibody (GLP1R-59-2) by linking the native GLP-1 7-36 peptide to the light chain N-terminal of a

functionally inactive but GLP-1R-specific binder GLP1R-2 (**Fig. 17**) was engineered. GLP-1R binding assays, cAMP assays, and β-arrestin recruitment assays were conducted, resulting in characterization of GLP1R-59-2 as described here:

[00269] *GLP1R-59-2 specifically binds to GLP-1R-expressing CHO cells.* Flow cytometry analysis revealed that GLP1R-59-2 bound specifically to GLP-1R-positive cells (GFP+) and not parental CHO cells (GFP-), specific binding was also confirmed by GLP1R-59-2 dose titrations producing an apparent binding EC_{50} of 15.5 nM (**Fig. 18A**).

[00270] *GLP1R-59-2 induces a GLP-1R cAMP response similar to GLP-1 7-36.* GLP1R-59-2 was tested for agonist activity as compared with GLP-1 7-36 for stimulating GLP-1R over-expressing CHO-K1 cells (DiscoverX) with separate dose titration analyses conducted for both ligand and antibody. It was found that both induced similar cAMP signaling profile and their dose response curves had almost overlapping EC_{50} values, 0.042nM for GLP1R-59-2 and 0.085nM for GLP-1 7-36. (**Fig. 18B**) supporting the hypothesis that GLP1R-59-2 can act as an effective agonist for GLP-1R.

[00271] *GLP1R-59-2 is less efficacious for β-arrestin recruitment to GLP-1R than GLP-1 7-36.* To determine if GLP1R-59-2 was able to induce a similar level of β-arrestin recruitment to GLP-1R as GLP-1 7-36, GLP-1R over-expressing CHO-K1 cells (DiscoverX) were stimulated with dose titrations of each. It was found that less β-arrestin recruitment occurred with GLP1R-59-2 stimulation than with GLP-1 7-36 stimulation (**Fig. 18C**). Whilst GLP1R-59-2 is less efficacious than GLP-1 7-36 for the maximal β-arrestin recruitment, it would appear that the agonist IgG is slightly more potent with an EC_{50} of 0.042nM, and 0.085nM for GLP-1 7-36, respectively.

[00272] *In vivo PK and PD testing of GLP1R-3 and GLP1R-59-2*

[00273] Endogenous GLP-1 peptide has a very short serum half-life of only a few minutes, however GLP-1R antibodies can have significantly longer half-lives. This can be a considerable advantage over the current GLP-1 peptide analog therapeutics. An *in vivo* PK rat study was performed to evaluate the half-life of the antagonist GLP1R-3 and agonist GLP1R-59-2 in IgG format. In a 2-week PK study, GLP1R-3 exhibited an antibody-like *in vivo* half-life of ~1-week in rats, while the agonist GLP-1 peptide-antibody fusion, GLP1R-59-2 exhibited > 2-day half-life in rats (**Figs. 19A-19B**). Liraglutide, the approved GLP-1R agonist for the treatment of Type II diabetes has a 13-hour half-life.

[00274] Agonist GLP1R-59-2 was tested for it's *in vivo* pharmacodynamic (PD) effects in Glucose tolerance test (GTT) using wild-type C57BL/6NHsd mouse model, in comparison with the vehicle control. Agonist mAb GLP1R-59-2 treatment, either dose (5 mg/kg and 10 mg/kg) or dosing regimen (2 hrs, 13+2 hrs, and 15 hrs before glucose challenge), significantly stabilized

blood glucose even after a glucose challenge (**Fig. 20A**). Compared to control mice GLP1R-59-2 treatments are all significant ($p<0.001$) at reducing Area Under the Curve (AUC) in an GTT (**Fig. 20B**). However, there is no significant difference between each individual treatment timing or dose.

[00275] Antagonist, GLP1R-3 mAb and GLP-1 peptide Exendin 9-39 treatment, with 19+2 hours dosing regimen before insulin challenge, significantly stabilizes a higher blood glucose in wild-type C57BL/6NHsd mice (**Fig. 21A**). Compared to control mice GLP1R-3 mAb (20mg/kg) and Exendin (1 mg/kg) treatments are both significant ($p<0.0001$) at stabilizing Area Under the Curve (AUC) in an ITT (**Fig. 21B**). However, there is no significant difference between GLP1R-3 and Control vs. Exendin (0.23mg/kg) with 19+2 hour treatment.

[00276] Another experiment using a single 6 hour dosing regimen, antagonist, GLP1R-3 mAb treatment also significantly stabilizes a higher blood glucose after an insulin challenge compared to GLP-1 peptide Exendin 9-39 (1.0 or 0.23 mg/kg dose) or control (**Fig. 22A**). Compared to control mice, GLP1R-3 mAb (20 mg/kg) treatment at 6 hours, significantly ($p<0.05$) stabilizes Area Under the Curve (AUC) in an ITT. However, there is no significant difference between Control vs. Exendin (1.0 and 0.23 mg/kg) with the single 6 hour treatment (**Fig. 22B**).

[00277] GLP1R-3 mAb treatment was also compared to a comparator antibody GLP1R-226-1 and GLP1R-226-2. GLP1R-3 mAb treatment in a single 6 hour dosing regimen significantly stabilized a higher blood glucose after an insulin challenge (at time 0) compared to GLP1R-226-1 (20 mg/kg) or control (**Figs. 23A-23B**). Compared to control mice, GLP1R-3 mAb (20mg/kg) treatment at 6 hours, significantly ($p<0.05$) stabilized Area Under the Curve (AUC) in an ITT. There was no significant difference ($p<0.05$) between control vs. GLP1R-226-1 or GLP1R-226-2 with a single 6 hour treatment.

[00278] **Example 5: GLP1R Variants**

[00279] GLP1R-3 was optimized to generate additional GLP1R variants.

[00280] The panning strategy for GLP1R-221 and GLP1R-222 variants is seen in **Figs. 24A-24B**. 768 clones from Round 4 and Round 5 were picked and sequenced on Miseq. 95 unique clones were reformatted. Data for GLP1R-221 and GLP1R-222 variants is seen in **Tables 6A-6H.** Sequences for the GLP1R-221 and GLP1R-222 variants are seen in **Tables 9-13**.

Table 6A.

IgG	MFI Ratio	Subtraction
GLP1R-3	993.31197	232201
GLP1R-221-065	914.54027	272235

GLP1R-221-075	1174.8495	241813
GLP1R-221-017	1484.8457	240383
GLP1R-221-033	1015.9153	239520
GLP1R-221-076	746.61867	235615.5
GLP1R-221-092	711.73926	231701
GLP1R-221-034	711.15764	222989.5
GLP1R-221-066	927.53542	222368.5
GLP1R-221-084	1067.8986	220848
GLP1R-221-009	1119.868	220417

Table 6B.

IgG	MFI Ratio	Subtraction
GLP1R-3	740.2	223614
GLP1R-222-052	13.70825851	350309.5
GLP1R-222-016	773.9745223	242714
GLP1R-222-023	777.8080645	240810.5
GLP1R-222-014	794.2474916	237181
GLP1R-222-090	525.349537	226519
GLP1R-222-073	983.9519651	225096
GLP1R-222-012	774.5748709	224723.5

GLP1R-222-082	711.0952381	223680
GLP1R-222-081	850.1807692	220787
GLP1R-222-056	946.2456522	217406.5

Table 6C.

Sample	Median RL1-H of Expressing Singlets	Median RL1-H of Parent Singlets	MFI Ratio
GLP1R221-017	240545	162	1484.8
GLP1R221-075	242019	206	1174.8
GLP1R221-009	220614	197	1119.9
GLP1R221-084	221055	207	1067.9
GLP1R221-044	217533.5	209	1040.8
GLP1R221-033	239756	236	1015.9
GLP1R01-3	232435	234	993.3
GLP1R221-014	200638	203	988.4
GLP1R221-083	212185	215	986.9
GLP1R221-043	195703	201	973.6
GLP1R221-082	195548	202	968.1
GLP1R221-018	160183	167	959.2
GLP1R221-001	200655	213	942.0
GLP1R221-066	222608.5	240	927.5
GLP1R221-065	272533	298	914.5
GLP1R221-051	212862.5	234	909.7
GLP1R221-003	203683.5	226	901.3
GLP1R221-019	197108	224	879.9
GLP1R221-088	197424	225.5	875.5
GLP1R221-020	175621	205	856.7
GLP1R221-021	163480.5	192	851.5
GLP1R221-077	197424	236	836.5
GLP1R221-069	191848	230	834.1
GLP1R221-002	181529	219	828.9
GLP1R221-040	208274	251.5	828.1
GLP1R221-027	197258.5	241	818.5
GLP1R221-094	203152	253	803.0
GLP1R221-042	214005.5	268	798.5
GLP1R221-022	199293	252	790.8
GLP1R221-012	217522	283	768.6
GLP1R221-031	168691	221	763.3
GLP1R221-079	195512.5	257	760.7

GLP1R221-059	194935.5	257	758.5
GLP1R221-086	173390.5	229.5	755.5
GLP1R221-076	235931.5	316	746.6
GLP1R221-016	162165.5	220.5	735.4
GLP1R221-054	163917	224	731.8
GLP1R221-036	191269	264	724.5
GLP1R221-072	218347	303	720.6
GLP1R221-038	178492	248	719.7
GLP1R221-092	232027	326	711.7
GLP1R221-034	223303.5	314	711.2
GLP1R221-058	168846	240	703.5
GLP1R221-057	185403	268.5	690.5
GLP1R221-090	183560	268	684.9
GLP1R221-063	184038	274	671.7
GLP1R221-029	197088	305	646.2
GLP1R221-013	171640	266	645.3
GLP1R221-030	160279	251	638.6
GLP1R221-011	175641	283	620.6
GLP1R221-060	178266.5	290	614.7
GLP1R221-039	132161.5	219	603.5
GLP1R221-015	176341.5	293	601.8
GLP1R221-091	174624	295	591.9
GLP1R221-074	173151	295.5	586.0
GLP1R221-035	184526	315	585.8
GLP1R221-041	101875	174	585.5
GLP1R221-028	158490.5	271.5	583.8
GLP1R221-046	137324.5	236	581.9
GLP1R221-052	205979	370	556.7
GLP1R221-073	102371	205	499.4
GLP1R221-053	146049.5	301.5	484.4
GLP1R221-056	197814	409	483.7
GLP1R221-005	105542	226.5	466.0
GLP1R221-087	178772	389	459.6
GLP1R221-089	148048	325	455.5
GLP1R221-071	138673	313	443.0
GLP1R221-025	100871	233	432.9
GLP1R221-032	172291	399	431.8
GLP1R221-055	137657	329	418.4
GLP1R221-010	107233	285	376.3
GLP1R221-078	108233.5	301.5	359.0
GLP1R221-024	79574	225	353.7
GLP1R221-050	65939	204	323.2
GLP1R221-008	74751.5	239	312.8

GLP1R221-007	94850	358	264.9
GLP1R221-062	59544	279	213.4
GLP1R221-093	94190	444	212.1
GLP1R221-068	56581	298	189.9
GLP1R221-067	54810	300	182.7
GLP1R221-085	201695	1352.5	149.1
GLP1R221-064	42803	308	139.0
GLP1R221-023	155330	1174	132.3
GLP1R221-080	196473	1547	127.0
GLP1R221-061	47559	482	98.7
GLP1R221-070	21104.5	224	94.2
GLP1R221-006	17593.5	286	61.5
GLP1R221-045	603.5	174	3.5
GLP1R221-004	519	164	3.2
GLP1R221-047	397	167	2.4
GLP1R221-048	214	142.5	1.5
Stained Control	145	142	1.0

Table 6D.

Sample	Median RL1-H of Expressing Singlets	Median RL1-H of Parent Singlets	MFI Ratio
GLP1R222-005	203990	173	1179.1
GLP1R222-058	217592	186	1169.8
GLP1R222-004	201104	189	1064.0
GLP1R222-035	180903	172	1051.8
GLP1R222-069	193190	187	1033.1
GLP1R222-001	195159	193	1011.2
GLP1R222-077	207327.5	208	996.8
GLP1R222-072	196881.5	198.5	991.8
GLP1R222-062	207390	209.5	989.9
GLP1R222-073	225325	229	984.0
GLP1R222-009	173411	176.5	982.5
GLP1R222-064	207016	218	949.6
GLP1R222-056	217636.5	230	946.2
GLP1R222-089	196242	213	921.3
GLP1R222-055	190727	209	912.6
GLP1R222-046	204177	225.5	905.4
GLP1R222-008	210228	234	898.4
GLP1R222-078	176537.5	198	891.6
GLP1R222-092	212558	240.5	883.8
GLP1R222-007	211051	239	883.1
GLP1R222-010	171471	195	879.3

GLP1R222-081	221047	260	850.2
GLP1R222-006	191343	227	842.9
GLP1R222-066	189419	227	834.4
GLP1R222-079	170284	206	826.6
GLP1R222-042	214181	261	820.6
GLP1R222-036	172934	214.5	806.2
GLP1R222-014	237480	299	794.2
GLP1R222-087	200143	252	794.2
GLP1R222-086	181615.5	230	789.6
GLP1R222-033	181334	230	788.4
GLP1R222-074	205325	261	786.7
GLP1R222-070	166040	212	783.2
GLP1R222-002	192431	246	782.2
GLP1R222-023	241120.5	310	777.8
GLP1R222-012	225014	290.5	774.6
GLP1R222-016	243028	314	774.0
GLP1R222-063	214679.5	278	772.2
GLP1R222-011	185538	242	766.7
GLP1R222-028	182568	242	754.4
GLP1R222-085	177368	239	742.1
GLP1R01-3	223916.5	302.5	740.2
GLP1R222-045	179811	246	730.9
GLP1R222-054	153121	211	725.7
GLP1R222-083	195648.5	274.5	712.7
GLP1R222-082	223995	315	711.1
GLP1R222-084	172287	247	697.5
GLP1R222-076	186158	269	692.0
GLP1R222-029	204757	300	682.5
GLP1R222-060	113206.5	167	677.9
GLP1R222-038	158998.5	236	673.7
GLP1R222-026	154255.5	229	673.6
GLP1R222-071	193867	288	673.1
GLP1R222-053	131845	196	672.7
GLP1R222-051	149756.5	224	668.6
GLP1R222-093	152427	232	657.0
GLP1R222-075	194948.5	297	656.4
GLP1R222-065	184054.5	281	655.0
GLP1R222-032	165221	255	647.9
GLP1R222-059	142048	223	637.0
GLP1R222-021	175543	278	631.4
GLP1R222-025	134869	216	624.4
GLP1R222-024	208523	345	604.4
GLP1R222-022	200898	337	596.1

GLP1R222-027	190430	326.5	583.2
GLP1R222-015	187125	344.5	543.2
GLP1R222-041	182770	344	531.3
GLP1R222-090	226951	432	525.3
GLP1R222-044	107845.5	208	518.5
GLP1R222-040	167413.5	324	516.7
GLP1R222-031	155641	331	470.2
GLP1R222-088	170891	373	458.2
GLP1R222-048	197618	441.5	447.6
GLP1R222-018	126619	290	436.6
GLP1R222-003	65950	155	425.5
GLP1R222-080	96756.5	228	424.4
GLP1R222-057	83288.5	204	408.3
GLP1R222-047	118739	307	386.8
GLP1R222-030	162896	506	321.9
GLP1R222-091	56735.5	192	295.5
GLP1R222-043	70814	406	174.4
GLP1R222-037	58889	388	151.8
GLP1R222-094	23462.5	176	133.3
GLP1R222-068	135253	1167.5	115.8
GLP1R222-019	39294	350	112.3
GLP1R222-067	146186	1452	100.7
GLP1R222-020	112537	1189	94.6
GLP1R222-049	178616.5	2138.5	83.5
GLP1R222-052	377875	27565.5	13.7
Stained Control	127	121	1.0

Table 6E.

Sample	GLP1 R221-009	GLP1 R221-017	GLP1 R221-033	GLP1 R221-034	GLP1 R221-065	GLP1 R221-066	GLP1 R221-075	GLP1 R221-076	GLP1 R221-084	GLP1 R221-092	GLP1 R01-3
EC_{50} [nM] CHO GLP1R	12.46	27.65	9.041	ND	ND	57.39	ND	ND	4.091	13.29	11.51
B_{max} CHO GLP1R	215146	249646	167203	932518	797529	171812	213495	799149	286814	144511	179967
EC_{50} [nM] CHO Parent	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B_{max} CHO Parent	267.4	228.7	146	279.8	261.9	112.1	234	183.2	266.6	291.2	268

Table 6F.

Sample	GLP1R222-012	GLP1R222-014	GLP1R222-016	GLP1R222-023	GLP1R222-052	GLP1R222-056	GLP1R222-073	GLP1R222-081	GLP1R222-082	GLP1R222-090	GLP1R01-3
EC_{50} [nM] CHO GLP1R	23.14	34.29	7.709	18.35	17.36	77.43	13.07	22.51	11.49	ND	15.4
B_{max} CHO GLP1R	233768	213081	129918	220325	228012	292619	150681	193955	134940	107876	152782
EC_{50} [nM] CHO Parent	ND	ND	ND	89.37	ND	ND	ND	ND	ND	ND	ND
B_{max} CHO Parent	340.6	336.4	218.5	237.9	47529	237.5	228.4	243.4	305	413.4	265.3

Table 6G.

[IgG] nM	GLP1R221-009	GLP1R221-017	GLP1R221-033	GLP1R221-034	GLP1R221-065	GLP1R221-066	GLP1R221-075	GLP1R221-076	GLP1R221-084	GLP1R221-092	GLP1R01-3
100.00	1635.4	1844.6	1596.5	1015.0	1157.8	1056.4	834.9	1499.3	910.9	960.9	1193.7
33.33	1322.9	1303.9	1211.3	593.5	799.1	698.8	507.9	597.8	666.7	1019.4	1531.0
11.11	1058.6	707.5	1012.5	332.2	368.9	229.7	416.1	372.2	412.4	447.3	689.3
3.70	448.3	424.8	385.6	209.0	280.0	171.2	242.0	293.6	344.2	297.4	425.2
1.23	176.6	181.4	175.6	87.7	140.1	91.4	119.1	121.3	153.3	141.2	166.6
0.41	95.2	94.7	89.7	48.9	80.0	46.5	54.7	51.8	63.5	54.9	77.4
0.14	37.7	36.2	39.3	19.7	31.0	20.4	23.8	22.3	24.6	19.6	28.6
0.05	16.8	14.8	17.4	8.8	14.9	9.6	9.3	8.8	9.4	8.7	12.3

Table 6H.

[IgG] nM	GLP1R222-012	GLP1R222-014	GLP1R222-016	GLP1R222-023	GLP1R222-052	GLP1R222-056	GLP1R222-073	GLP1R222-081	GLP1R222-082	GLP1R222-090	GLP1R01-3
100.00	1281.5	952.5	1049.1	1804.8	8.0	1522.2	1264.2	1404.0	845.8	746.6	1047.7
33.33	916.5	913.2	1412.1	1277.6	19.8	815.1	1057.9	1181.5	1027.4	526.8	1040.9
11.11	626.0	432.9	743.0	699.7	57.9	421.2	680.4	528.8	567.7	336.3	567.3
3.70	300.5	190.8	335.9	300.6	37.6	193.8	296.5	244.0	233.4	165.8	265.1
1.23	144.0	85.2	154.9	140.3	43.8	79.0	115.5	99.2	125.3	70.6	124.6
0.41	67.4	45.3	75.9	55.8	28.7	32.8	55.6	50.4	53.5	31.6	66.6
0.14	26.1	17.3	28.1	26.4	14.5	13.2	20.5	16.5	15.8	8.8	22.9
0.05	12.3	7.2	14.2	11.4	7.3	6.4	9.2	7.9	8.1	4.4	10.1

[00281] The GLP1R-221 and GLP1R-222 variants were assayed in competition assays. Data is seen in **Figs. 25A-25B**. The variants were also assayed in a cAMP assay. Briefly, cells were pre-incubated with anti-GLP1R antibody at 100 nM followed by agonist stimulation 3X titration from 12.5 nM. Data is seen in **Fig. 26** with improved variants highlighted in green.

[00282] **Example 6: Sequences**

Table 7. Sequences of GLP1 embedded in CDRH3

SEQ ID NO	Sequence
1	CAKHMSMQEGAVTGEGQAAKEFIAWLVKGRVRADLVGDAFDVW
2	CARDGRGSLPRPKGGPQTVGEGQAAKEFIAWLVKGGLTYDSSEDSGGAFDIW
3	CAKHMSMQDYLVIGEGQAAKEFIAWLVKGGPARADLVGDAFDVW
4	CAKHMSMQEGAVTGEGQDAKEFIAWLVKGRVRADLVGDAFDVW
5	WAKHMSMQEGAVTGEGQAAKEFIAWLVKGRVRADLVGDAFDVW
6	CARDGRGSLPRPKGGPQTVGEGQAAKEFIAWLVKGRVRADLVGDAFDVW
7	CARANQHFYEQEGTFTSDVSSYLEGQAAKEFIAWLVKGGIRGYHYYGMDVW
8	CARANQHFTELHGEGQAAKEFIAWLVKGRGQIDIGYHYYGMDVW
9	CARANQHFLGAGVSSYLEGQAAKEFIAWLVKGDTTGYHYYGMDVW
10	CARANQHFLDKGTFTSDVSSYLEGQAAKEFIAWLVKGIYPGYHYYGMDVW
11	CARANQHFGTLSAGEGQAAKEFIAWLVKGGSQYDSSEDSGGAFDIW
12	CARANQHFGLHAQGEGQAAKEFIAWLVKGSGTYGYHYYGMDVW
13	CARANQHFGGKGEGQAAKEFIAWLVKGGGSGAGYHYYGMDVW
14	CAKQMSMQEGAVTGEGQAAKEFIAWLVKGRVRADLVGDAFDVW
15	CAKHMSMQEGAVTGEGQAAKEFIAWLVKGGPARADLVGDAFDVW
16	CAKHMSMQEGAVTGEGQAAKEFIAWLVKGGLTYDSSEDSGGAFDIW
17	CAKHMSMQDYLVIGEGQAAKEFIAWLVKGRVRADLVGDAFDVW

Table 8. GLP1R Variants CDRH3 Sequences

Variant	SEQ ID NO.	Sequence
GLP1R-1	18	CARANQHFVDLYGWHGVPKGYHYYGMDVW
GLP1R-2	19	CARDMYYDFETVVEGIQWYEALKAGKLGEVVPADDAFDIW
GLP1R-3	20	CAKHMSMQEGAVTG**EGQAAKEFIAWLVKGR**VRADLVGDAFDVW
GLP1R-8	21	CARDGRGSLPRPKGGPQTVG**EGQAAKEFIAWLVKG**GLTYDSSEDSGGAFDIW
GLP1R-10	22	CARANQHFFVPGSLKVWLKGVAPESSSEYDSSEDSGGAFDIW
GLP1R-25	23	CARANQHFLSHAG**AARDFINWL**IQTKITGLGSGYHYYGMDVW
GLP1R-26	24	CAKHMSMQEGVLQGQIPSTIDWEGLLHLIRADLVGDAFDVW
GLP1R-30	25	CARDMYYDFLKIGDNL**AARDFINWL**IQTKITDGTDTEVVPADDAFDIW
GLP1R-50	26	CARDGRGSLPRPKGGPKFVPGKHETYGHKTGYRLRPGYHYYGMDVW

GLP1R-56	27	CARANQHFFSGAEG**EGQAAKEFIAWLVKG**IIPGYHYYGMDVW
GLP1R-58	28	CARANQHFGLHAQG**EGQAAKEFIAWLVKG**SGTYGYHYYGMDVW
GLP1R-60	29	CAKHMSMQDYLVIG**EGQAAKEFIAWLVKG**GPARADLVGDAFDVW
GLP1R-70	30	CARDGRGSLPRPKGGPPSSG**RDFINWLIQTKIT**DGFRYDSSEDSGGAFDIW
GLP1R-71	31	CARDLRELECEEWTRHGGKKHHGKRQSNRAHQGKHETYGHKTGSLVPSRGPCVD PRGVAGSFDVW
GLP1R-72	32	CARDMYYDFHPEGTFTSDVSSYL**EGQAAKEFIAWLVKG**SLIYEVVPADDAFDIW
GLP1R-80	33	CARANQHFGPVAGGATPSEEPGSQLTRAELGWDAPPGQESLADELLQLGTEHGYH YYGMDVW
GLP1R-83	34	CAKHMSMQEGAVTG**EGQAAKEFIAWLVKG**RVRADLVGDAFDVW
GLP1R-93	35	CARANQHFLSHAG**AARDFINWLIQTKIT**GLGSGYHYYGMDVW
GLP1R-98	36	CARDGRGSLPRPKGGPHSGRLGSGYKSYDSSEDSGGAFDIW
GLP1R-238	37	CARANQHFSQAGRAARVPGPSSSLGPRGYHYYGMDVW
GLP1R-239	38	CAKHMSMQSQG**LDNLAARDFINWLIQTKITD**GFELSRADLVGDAFDVW
GLP1R-240	39	CARDMYYDFFGL**GTFTSDVSSYLEGQAAKEFIAWLVKG**VSPEVVPADDAFDIW
GLP1R-241	40	CAKHMSMQGSVAG**GTFTSDVSSYLEGQAAKEFIAWLVKG**GPSFIRADLVGDAFD VW
GLP1R-242	41	CAKHMSMQADT**GTFTSDVSSYLEGQAAKEFIAWLVKG**EFSSRADLVGDAFDVW
GLP1R-243	42	CARANQHFFGKG**DNLAARDFINWLIQTKITD**GSNPGYHYYGMDVW
GLP1R-244	43	CARANQHFAATGAG**EGQAAKEFIAWLVKGR**VEIGYHYYGMDVW

* **bold** corresponds to GLP1 or GLP2 motif

Table 9. Variable Heavy Chain Sequences

Variant	SEQ ID NO.	Variable Heavy Chain Sequence
GLP1R-238	44	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGSFSSHAISW VRQAPGQGLEWMGGIIPIFGAPNYAQKFQGRVTITADESTSTAYMELSSLRSEDTA VYYCARANQHFSQAGRAARVPGPSSSLGPRGYHYYGMDVWGQGTLVTVSSASAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPV AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-239	45	MEWSWVFLFFLSVTTGVHSQVQLVESGGGVVQPGRSLRLSCAASGFDFSNYGMH WVRQAPGKGLEWVADISYEGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCAKHMSMQSQGLDNLAARDFINWLIQTKITDGFELSRADLVGDAFDVW GQGTLVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAP IEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
GLP1R-240	46	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFNNYGIS WVRQAPGQGLEWMGGIIPVFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARDMYYDFFGLGTFTSDVSSYLEGQAAKEFIAWLVKGVSPEVVPADDA FDIWGQGTLVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS

		WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVD KTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
GLP1R-241	47	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSDYAIS WVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITADESTSTAYMELSSLRSEDT AVYYCAKHMSMQGSVAGGTFTSDVSSYLEGQAAKEFIAWLVKGGPSFIRADLVG DAFDVWGQGTLVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTK VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKV SNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPG
GLP1R-242	48	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYEISW VRQAPGQGLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTA VYYCAKHMSMQADTGTFTSDVSSYLEGQAAKEFIAWLVKGEFSSRADLVGDAFD VWGQGTLVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTV ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
GLP1R-243	49	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSTYGIN WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDT AVYYCARANQHFFGKGDNLAARDFINWLIQTKITDGSNPGYHYYGMDVWGQGT LVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCV ECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-244	50	MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTA VYYCARANQHFAATGAGEGQAAKEFIAWLVKGRVEIGYHYYGMDVWGQGTLVT VSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECP PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-59-2	51	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVAVISYD AGNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDMYYDFETVV EGIQWYEALKAGKLGEVVPADDAFDIWGQGTLVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSN FGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GLP1R-59-241	52	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSDYAISWVRQAPGQGLEWMGGIIPIF GTTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAKHMSMQGSVAGG TFTSDVSSYLEGQAAKEFIAWLVKGGPSFIRADLVGDAFDVWGQGTLVTVSSASA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS

		DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-59-243	53	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSTYGINWVRQAPGQGLEWMGGIIPIF GTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARANQHFFGKGDNL AARDFINWLIQTKITDGSNPGYHYYGMDVWGQGTLVTVSSASASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-3	54	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSFISYDE SNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRV VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GLP1R-43-8	55	MEWSWVFLFFLSVTTGVHSEVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGW FRQAPGKEREGVAAINNFGTTKYADSAKGRFTISADNAKNTVYLQMNSLKPEDTA VYYCAAVRWGPHNDDRYDWGQGTQVTVSSGGGGSEPKSSDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GLP1R-10	56	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAPGKGLEWVAVISYE GSDKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARANQHFFVPGSL KVWLKGVAPESSSEYDSSEDSGGAFDIWGQGTLVTVSS
GLP1R-26	57	QVQLVQSGAEVKKPGSSVKVSCKASGGTRSNYAINWVRQAPGQGLEWMGGIIPIL GTADYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAKHMSMQEGVLQG QIPSTIDWEGLLHLIRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-065	58	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYAMHWVRQAPGKGLEWVAVISY DRSNEYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGDGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-075	59	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYPMHWVRQAPGKGLEWVAVISYD ETNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAAKEFIAWLVKGIVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-017	60	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYGVHWVRQAPGKGLEWVAFISYD ESNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEYQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-033	61	QVQLVESGGGVVQPGRSLRLSCAASGFSFSNYAMHWVRQAPGKGLEWVAVISHD RSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAAKDFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-076	62	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYPMHWVRQAPGKGLEWVAVISYD ETNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAAKEFIAWLVKGIVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-092	63	QVQLVESGGGVVQPGRSLRLSCAASGFIFNNYGMHWVRQAPGKGLEWVAFISYG GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEGQAVKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-034	64	QVQLVESGGGVVQPGRSLRLSCAASGFPFSNYGMHWVRQAPGKGLEWVAVISHD RSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAVKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-066	65	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYAMHWVRQAPGKGLEWVAVISY DRSNEYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEGQAIKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-084	66	QVQLVESGGGVVQPGRSLRLSCAASGFAFSNYGMHWVRQAPGKGLEWVAVISSD ENNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEMQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-221-009	67	QVQLVESGGGVVQPGRSLRLSCAASGFIFSNYGMHWVRQAPGKGLEWVAVISDE GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV

		TGAGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-052	68	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYPMHWVRQAPGKGLEWVAVISYD ESNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GGGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-016	69	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYAMHWVRQAPGKGLEWVAVISDE GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEYQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-023	70	QVQLVESGGGVVQPGRSLRLSCAASGFSFSDYGMHWVRQAPGKGLEWVAFISYD ANNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEWQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-014	71	QVQLVESGGGVVQPGRSLRLSCAASGFAFSNYGMHWVRQAPGKGLEWVSFISYD ESNKYYADSVKGRFTISRDNSKNTLYLQMNNLRAEDTAVYYCAKHMSMQEGAV TGEWQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-090	72	QVQLVESGGGVVQPGRSLRLSCAASGFSFSDYGIHWVRQAPGKGLEWVALISYEG SNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEKQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-073	73	QVQLVESGGGVVQPGRSLRLSCAASGFTFRDYGMHWVRQAPGKGLEWVAFIRYD EINKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GEGQAAKEFIAWLVGGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-012	74	QVQLVESGGGVVQPGRSLRLSCAASGFTFNNYGMHWVRQAPGKGLEWVAVISDE GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGVGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-082	75	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYSMHWVRQAPGKGLEWVALISYD ATNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEFQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-081	76	QVQLVESGGGVVQPGRSLRLSCAASGFTFDNYALHWVRQAPGKGLEWVALISYD AGNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV TGEGQAAKEFIAWLVKGFVRADLVGDAFDVWGQGTLVTVSS
GLP1R-222-056	77	QVQLVESGGGVVQPGRSLRLSCAASGFPFSSYAMHWVRQAPGKGLEWVAVISYD RSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT GYGQAAKEFIAWLVKGFVRADLVGDAFDVWGQGTLVTVSS

Table 10. Variable Light Chain Sequences

Variant	SEQ ID NO.	Variable Light Chain Sequence
GLP1R-238	78	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSTSNIANNYVSW YQQLPGTAPKLLIYANNRRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGAW DVRLDVGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLS
GLP1R-239	79	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSTSNIEKNYVSW YQQLPGTAPKLLIYGNDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW ENRLSAVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS
GLP1R-240	80	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSSIGNNYVSW YQQLPGTAPKLLIYANNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCATW SSSPRGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS
GLP1R-241	81	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGISSNIGNNYVSW YQQLPGTAPKLLIYDDDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW DNILSAAVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVT VAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS
GLP1R-242	82	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSNIENNDVSW YQQLPGTAPKLLIYGNDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW DNTLSAGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS

GLP1R-243	83	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSRSNIGKNYVSW YQQLPGTAPKLLIYENNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCSSYT TSNTQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS
GLP1R-244	84	MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNVVSW YQQLPGTAPKLLIYDNDKRRSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGSW DTSLSVWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS
GLP1R-59-243	85	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRGGGGGSGGGGSGGGGSQSVLTQPPS VSAAPGQKVTISCSGSRSNIGKNYVSWYQQLPGTAPKLLIYENNERPSGIPDRFSGS KSGTSATLGITGLQTGDEADYYCSSYTTSNTQVFGGGTKLTVLGQPKAAPSVTLFP PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
GLP1R-59-241	86	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRGGGGGSGGGGSGGGGSQSVLTQPPS VSAAPGQKVTISCSGISSNIGNNYVSWYQQLPGTAPKLLIYDDDQRPSGIPDRFSGS KSGTSATLGITGLQTGDEADYYCGTWDNILSAAVFGGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
GLP1R-59-2	87	HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGGGGGGSGGGGSGGGGSQSALTQPAS VSGSPGQSITISCTGTSNDIGTYNYVSWYQQHPGKAPKLMIYDVSGRPSGVSNRFS GSKSGNTASLTISGLQAEDEADYYCSSYTTSSTEVFGGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
GLP1R-59-2A	88	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRGGGGGSGGGGSGGGGSQSALTQPAS VSGSPGQSITISCTGTSNDIGTYNYVSWYQQHPGKAPKLMIYDVSGRPSGVSNRFS GSKSGNTASLTISGLQAEDEADYYCSSYTTSSTEVFGGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
GLP1R-3	89	QSVLTQPPSVSAAPGQKVTISCSGSSSNIADNYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDNYLGAGVFGGGTKLTVLGQ PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTP SKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
GLP1R-10	90	EIVMTQSPATLSVSPGERATLSCRASHSVSSDLAWYQQKPGQAPRLLIYSASSRAT GIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPPASTFGGGTKVEIK
GLP1R-26	91	EIVMTQSPATLSVSPGERATLSCSASQSVSTKLAWYQQKPGQAPRLLIYGASTRAK GIPARFSGSGSGTEFTLTIZSLQSEDFAVYYCQHYHNWPLTFGGGTKVEIK
GLP1R-221-065	92	QSVLTQPPSVSAAPGQKVTISCSGTTSNIANNFVSWYQQLPGTAPKLLIYDHNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSAGAFGGGTKLTVL
GLP1R-221-075	93	QSVLTQPPSVSAAPGQKVTISCSGSGSNIGNNDVSWYQQLPGTAPKLLIYDNDKRP AGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSNYVFGGGTKLTVL
GLP1R-221-017	94	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNTYVSWYQQLPGTAPKLLIYDDYKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCATWDATLNTGVFGGGTKLTVL
GLP1R-221-033	95	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNEYVSWYQQLPGTAPKLLIYDNNKRV SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCATWDTSLNVGVFGGGTKLTVL
GLP1R-221-076	96	QSVLTQPPSVSAAPGQKVTISCSGTSSNIGNNDVSWYQQLPGTAPKLLIYENNKRH SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCLTWDHSLTAYVFGGGTKLTVL
GLP1R-221-092	97	QSVLTQPPSVSAAPGQKVTISCSGTTSNIANNFVSWYQQLPGTAPKLLIYDNNKRPP GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGMFGGGTKLTVL
GLP1R-221-034	98	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNPVSWYQQLPGTAPKLLIYENDNRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCATWDRGLSTGVFGGGTKLTVL
GLP1R-221-066	99	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYLSWYQQLPGTAPKLLIYENNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGIWDRSLSAWVFGGGTKLTVL
GLP1R-221-084	100	QSVLTQPPSVSAAPGQKVTISCSGSSSNIADNYVSWYQQLPGTAPKLLIYENNRRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDVSLSVGMFGGGTKLTVL
GLP1R-221-009	101	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNQYVSWYQQLPGTAPKLLIYDDHKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGEFGGGTKLTVL
GLP1R-222-052	102	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGKRSVSWYQQLPGTAPKLLIYDNNKRAS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCVTWDRSLSAGVFGGGTKLTVL

GLP1R-222-016	103	QSVLTQPPSVSAAPGQKVTISCSGSSSNIENNDVSWYQQLPGTAPKLLIYDFNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGMFGGGTKLTVL
GLP1R-222-023	104	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNDVSWYQQLPGTAPKLLIYENTKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDAGLSTGVFGGGTKLTVL
GLP1R-222-014	105	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNHDVSWYQQLPGTAPKLLIYDNNKRH SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSAGVFGGGTKLTVL
GLP1R-222-090	106	QSVLTQPPSVSAAPGQKVTISCSGSSSNIADNYVSWYQQLPGTAPKLLIYDNNKRA SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCATWDNRLSAGVFGGGTKLTVL
GLP1R-222-073	107	QSVLTQPPSVSAAPGQKVTISCSGSGSNIGNNDVSWYQQLPGTAPKLLIYDNNKRA SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDRGPNTGVFGGGTKLTVL
GLP1R-222-012	108	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNDVSWYQQLPGTAPKLLIYDDDKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGEFGGGTKLTVL
GLP1R-222-082	109	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGSKYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDISPSAWVFGGGTKLTVL
GLP1R-222-081	110	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGSDYVSWYQQLPGTAPKLLIYDNNKRSS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDESLRSWVFGGGTKLTVL
GLP1R-222-056	111	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGSNYISWYQQLPGTAPKLLIYDNDKRPA GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGEFGGGTKLTVL

Table 11. GLP1R Sequences

GLP1R Variant	SEQ ID NO	Sequence
GLP1R-40-01	112	EVQLVESGGGLVQPGGSLRLSCAASGFTCGDYTMGWFRQAPGKEREFLAAITSG GATTYDDNRKSRFTISADNSKNTAYLQMNSLKPEDTAVYYCWAALDGYGGRW GQGTLVTVSS
GLP1R-40-02	113	EVQLVESGGGLVQPGGSLRLSCAASGRTFRINRMGWFRQAPGKEREWVSTICSR GDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAATLDGYSGSWG QGTLVTVSS
GLP1R-40-03	114	EVQLVESGGGLVQPGGSLRLSCAASGRDFRVKNMGWFRQAPGKEREFVARITW NGGSAYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAARILSRNWG QGTLVTVSS
GLP1R-40-04	115	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMGWFRQAPGKEREFVAAISSGG RTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYEGSWGQ GTLVTVSS
GLP1R-40-05	116	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYAMGWFRQAPGKEREFVAAISSGG RTRYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCSAALDGYNGIWGQ GTLVTVSS
GLP1R-40-06	117	EVQLVESGGGLVQPGGSLRLSCAASGHTSDTYIMGWFRQAPGKEREFVSLINWSS GKTIYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKGDYRGGYYYP QTSQWGQGTLVTVSS
GLP1R-40-07	118	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYPMGWFRQAPGKEREFVATIPSGG STYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYNGSWGQ GTLVTVSS
GLP1R-40-08	119	EVQLVESGGGLVQPGGSLRLSCAASGFTFGEFTMGWFRQAPGKERERVATITSGG STNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVVDDYSGSWGQ GTLVTVSS
GLP1R-40-09	120	EVQLVESGGGLVQPGGSLRLSCAASGFTDGIDAMGWFRQAPGKEREVVAGIAW GDGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASYNVYYNN WGQGTLVTVSS
GLP1R-40-10	121	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSGVMGWFRQAPGKEREFVAAINRS GSTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTKRTGIFTTAR MVDWGQGTLVTVSS
GLP1R-40-11	122	EVQLVESGGGLVQPGGSLRLSCAASGVTLDDYAMGWFRQAPGKEREFVAAINRS GSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYTDYDEALE ETRGSYDWGQGTLVTVSS
GLP1R-40-12	123	EVQLVESGGGLVQPGGSLRLSCAASGLTFGIYAMGWFRQAPGKEREFVATISRSG ASTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYNDYDRGH DWGQGTLVTVSS

GLP1R-40-13	124	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSDGMGWFRQAPGKERELVAAINRS GSTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTARPGIFTTAPV EDWGQGTLVTVSS
GLP1R-40-14	125	EVQLVESGGGLVQPGGSLRLSCAASGFTCGNYTMGWFRQAPGKERESVASITSG GRTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAATLDGYTGSWG QGTLVTVSS
GLP1R-40-15	126	EVQLVESGGGLVQPGGSLRLSCAASGFTFNYYPMGWFRQAPGKEREWVATISRG GGTYYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCSAALDGYSGIWG QGTLVTVSS
GLP1R-40-16	127	EVQLVESGGGLVQPGGSLRLSCAASGIIGSFRTMGWFRQAPGKEREFVGFITGSG GTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAARRYGNLYNT NNYDWGQGTLVTVSS
GLP1R-40-17	128	EVQLVESGGGLVQPGGSLRLSCAASGITFRFKAMGWFRQAPGKEREFVAAISWR GGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAATLGEPLVKY TWGQGTLVTVSS
GLP1R-40-18	129	EVQLVESGGGLVQPGGSLRLSCAASGSFFSINAMGWFRQAPGKEREFVAGISSKG GSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHRIVVGGTSV GDWRWGQGTLVTVSS
GLP1R-40-19	130	EVQLVESGGGLVQPGGSLRLSCAASGSRFSGRFNILNMGWFRQAPGKEREFVAAI SRSGDTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASLRNSGS NVEGRWGQGTLVTVSS
GLP1R-40-20	131	EVQLVESGGGLVQPGGSLRLSCAASGGTSNSYRMGWFRQAPGKEREFVAVISWT GGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVALDGYSGSW GQGTLVTVSS
GLP1R-40-21	132	EVQLVESGGGLVQPGGSLRLSCAASGFNIGTYTMGWFRQAPGKEREFVAAIGSN GLANYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCSAALDGYSGTWG QGTLVTVSS
GLP1R-40-22	133	EVQLVESGGGLVQPGGSLRLSCAASGRTFSVYAMGWFRQAPGKEREFVAGIHSD GSTLYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYMGTWG QGTLVTVSS
GLP1R-40-23	134	EVQLVESGGGLVQPGGSLRLSCAASGNIKSIDVMGWFRQAPGKERELVAAVRWS GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVVYYGDWEG SEPVQHEYDWGQGTLVTVSS
GLP1R-40-24	135	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMGWFRQAPGKEREFVAAIYCS DGSTQYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAEALDGYWGQG TLVTVSS
GLP1R-40-25	136	EVQLVESGGGLVQPGGSLRLSCAASGYTFRAYAMGWFRQAPGKEREMVAAMR WSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGSLYDD YDGLPIKYDWGQGTLVTVSS
GLP1R-40-26	137	EVQLVESGGGLVQPGGSLRLSCAASGLTFSSYAMGWFRQAPGKERECVTAIFSDG GTYYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYNGYWG QGTLVTVSS
GLP1R-40-27	138	EVQLVESGGGLVQPGGSLRLSCAASGIHFAISTMGWFRQAPGKEREIVTAINWSG ARTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAKFVNTDSTWS RSEMYTWGQGTLVTVSS
GLP1R-40-28	139	EVQLVESGGGLVQPGGSLRLSCAASGLTFTSYAMGWFRQAPGKEREGVAVIDSD GTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYLDGYSGSWG QGTLVTVSS
GLP1R-40-29	140	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSLPMGWFRQAPGKERELVAIRWSG GSTVYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAYEEGVYRW GQGTLVTVSS
GLP1R-40-30	141	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSGVMGWFRQAPGKEREFVAAINRS GSTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTKRTGIFTTWG QGTLVTVSS
GLP1R-40-31	142	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMGWFRQAPGKERELVAAISSGG STSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAMDGYSGSWGQ GTLVTVSS
GLP1R-40-32	143	EVQLVESGGGLVQPGGSLRLSCAASGFTDGIDAMGWFRQAPGKEREYVAAISGS GSITNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANGIESYGWGN RHFNWGQGTLVTVSS

GLP1R-40-33	144	EVQLVESGGGLVQPGGSLRLSCAASGFTDGIDAMGWFRQAPGKEREFVAAIRWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAIFDVTDYERADWGQGTLVTVSS
GLP1R-40-34	145	EVQLVESGGGLVQPGGSLRLSCAASGFAFSGYAMGWFRQAPGKEREFVAAISWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAFVTTNSDYDLGRDWGQGTLVTVSS
GLP1R-40-35	146	EVQLVESGGGLVQPGGSLRLSCAASGIPASIRTMGWFRQAPGKEREGVSWISSSDGSIYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCVAALDGYSGSWGQGTLVTVSS
GLP1R-40-36	147	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSLPMGWFRQAPGKERELVAIRWSGGSTVYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAYEEGVYRWDWGQGTLVTVSS
GLP1R-40-37	148	EVQLVESGGGLVQPGGSLRLSCAASGFNSGSYTMGWFRQAPGKEREGVSWISTTDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGIWGQGTLVTVSS
GLP1R-40-38	149	EVQLVESGGGLVQPGGSLRLSCAASGFTFSVYAMGWFRQAPGKEREFVTAIDSESRTLYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAALLDGYLGTWGQGTLVTVSS
GLP1R-40-39	150	EVQLVESGGGLVQPGGSLRLSCAASGSVFKINVMGWFRQAPGKEREFLGSILWSDDSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANLKQGSYGYRFNDWGQGTLVTVSS
GLP1R-40-40	151	EVQLVESGGGLVQPGGSLRLSCAASGTIVNIHVMGWFRQAPGKERELVAAITSGGSTSYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASAIGSGALRHFEYDWGQGTLVTVSS
GLP1R-40-41	152	EVQLVESGGGLVQPGGSLRLSCAASGRSLGTYHMGWFRQAPGKEREGVSWISSSDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVLDGYSGSWGQGTLVTVSS
GLP1R-40-42	153	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDTGMGWFRQAPGKEREFVAAIRWSGKETWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEDPSMYYTLEEYEYDWGQGTLVTVSS
GLP1R-40-43	154	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYVMGWFRQAPGKERECVAAISSSDGRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGNWGQGTLVTVSS
GLP1R-40-44	155	EVQLVESGGGLVQPGGSLRLSCAASGSIFRVNVMGWFRQAPGKEREFIATIFSGGDTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRWDWGQGTLVTVSS
GLP1R-40-45	156	EVQLVESGGGLVQPGGSLRLSCAASGFTCGDYTMGWFRQAPGKEREIVASITSGGRKNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDDYSGSWGQGTLVTVSS
GLP1R-40-46	157	EVQLVESGGGLVQPGGSLRLSCAASGHSFGNFPMGWFRQAPGKEREVIAAIDWSGGSTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAKGIGVYGWGQGTLVTVSS
GLP1R-40-47	158	EVQLVESGGGLVQPGGSLRLSCAASGSSFRFRAMGWFRQAPGKEREFVAAINRGGKISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYIRPDTYLSRDYRKYDWGQGTLVTVSS
GLP1R-40-48	159	EVQLVESGGGLVQPGGSLRLSCAASGFTWGDYTMGWFRQAPGKEREGVAAIDSDGRTRYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGSWGQGTLVTVSS
GLP1R-40-49	160	EVQLVESGGGLVQPGGSLRLSCAASGNILSLNTMGWFRQAPGKEREFVAGISWSGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSDYDLGNDWGQGTLVTVSS
GLP1R-40-50	161	EVQLVESGGGLVQPGGSLRLSCAASGITFRRYDMGWFRQAPGKEREGVAYISSSDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDDYSGGWGQGTLVTVSS
GLP1R-40-51	162	EVQLVESGGGLVQPGGSLRLSCAASGLTLSNYAMGWFRQAPGKEREFVAAISRSGSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEMSGISGWDWGQGTLVTVSS
GLP1R-40-52	163	EVQLVESGGGLVQPGGSLRLSCAASGYTTSINTMGWFRQAPGKEREVVAAISRTGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASAIGSGALRRFEYDWGQGTLVTVSS

GLP1R-40-53	164	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIDAMGWFRQAPGKEREFVAAIKPDGSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASASDYGLGLELFHDEYNWGQGTLVTVSS
GLP1R-40-54	165	EVQLVESGGGLVQPGGSLRLSCAASGSIFSLNAMGWFRQAPGKERELVAGISSKGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFRGIMRPDWGQGTLVTVSS
GLP1R-40-55	166	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMGWFRQAPGKEREAVAAIASMGGLTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYIGSWGQGTLVTVSS
GLP1R-40-56	167	EVQLVESGGGLVQPGGSLRLSCAASGFTFGAFTMGWFRQAPGKERERVAAITCSGSTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCSAALDGYNGSWGQGTLVTVSS
GLP1R-40-57	168	EVQLVESGGGLVQPGGSLRLSCAASGIPSTIRAMGWFRQAPGKERESVGRIYWRDDNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYSGSWGQGTLVTVSS
GLP1R-40-58	169	EVQLVESGGGLVQPGGSLRLSCAASGFTDGIDAMGWFRQAPGKEREVVAGIAWGDGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASYNVYYNNYYYPISRDEYDWGQGTLVTVSS
GLP1R-43-1	170	EVQLVESGGGLVQAGGSLRLSCAASGRTIVPYTMGWFRQAPGKEREVVASISWSGKSTYYADSVRGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAQRRWSQDWGQGTQVTVSS
GLP1R-43-2	171	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSGGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPTGRGERDYWGQGTQVTVSS
GLP1R-43-3	172	EVQLVESGGGLVQAGGSLRLSCAASGFTFSNYAMGWFRQAPGKEREFVATITWSGSSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRLYREYGYWGQGTQVTVSS
GLP1R-43-4	173	EVQLVESGGGLVQAGGSLRLSCAASGSIFHINPMGWFRQAPGKERefVAAINIFGTTNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVDGGPLWDDGYDWGQGTQVTVSS
GLP1R-43-5	174	EVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGWFRQAPGKEREGVASINIFGTTKYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCSAVGWGPHNDDRYDWGQGTQVTVSS
GLP1R-43-6	175	EVQLVESGGGLVQAGGSLRLSCAASGTTFSIYAMEWFRQAPGKERELVATISRSGGTTYYADSVGGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAASWYYRDDYWGQGTQVTVSS
GLP1R-43-7	176	EVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGWFRQAPGKEREGVAAINNFGTTKYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCSAVRWGPHNDDRYDWGQGTQVTVSS
GLP1R-43-8	177	EVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGWFRQAPGKEREGVAAINNFGTTKYADSAKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRWGPHNDDRYDWGQGTQVTVSS
GLP1R-43-9	178	EVQLVESGGGLVQAGGSLRLSCAASGFILYGYAMGWFRQAPGKEREGVSSISPSDASTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVLNTYSDSWGQGTQVTVSS
GLP1R-43-10	179	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREGVTAISTSDGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAARDGYSGSWGQGTQVTVSS
GLP1R-43-11	180	EVQLVESGGGLVQAGGSLRLSCAASGYTITNSYRMGWFRQAPGKEREFVAGITMSGFNTRYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAANRGLAGPAWGQGTQVTVSS
GLP1R-43-12	181	EVQLVESGGGLVQAGGSLRLSCAASGFTFDDNAMGWFRQAPGKEREFVSGISTSGSTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAAAGGYDYWGQGTQVTVSS
GLP1R-43-13	182	EVQLVESGGGLVQAGGSLRLSCAASGRTFSYYHMGWFRQAPGKEREGVSWISSYYSSTYYADSESGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVLDGYSCSWGQGTQVTVSS
GLP1R-43-14	183	EVQLVESGGGLVQAGGSLRLSCAASGSPFRLYTMGWFRQAPGKEREVVAHIYSYGSINYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALWGHSGDWGQGTQVTVSS

GLP1R-43-15	184	EVQLVESGGGLVQAGGSLRLSCAASGSTFDTYGMGWFRQAPGKEREFVASITWS GSSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAANRIHWSGFYY WGQGTQVTVSS
GLP1R-43-16	185	EVQLVESGGGLVQAGGSLRLSCAASGRTSSPYTMGWFRQAPGKEREFVSAISWS GGSTVYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCALIRRAPYSRLE TWGQGTQVTVSS
GLP1R-43-17	186	EVQLVESGGGLVQAGGSLRLSCAASGSIFPINAMGWFRQAPGKEREGVAAITNFG TTKYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRWGPRNDDHY DWGQGTQVTVSS
GLP1R-43-18	187	EVQLVESGGGLVQAGGSLRLSCAASGRTFDTYAMGWFRQAPGKEREFVAAITW GGGRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRLYRDY DYWGQGTQVTVSS
GLP1R-43-19	188	EVQLVESGGGLVQAGGSLRLSCAASGRRFSAYGMGWFRQAPGKEREFVAAVSW DGRNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCASTDDYGVDW GQGTQVTVSS
GLP1R-43-20	189	EVQLVESGGGLVQAGGSLRLSCAASGSTFDNYAMGWFRQAPGKEREFVSAISGD GGTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRLYRNRD YWGQGTQVTVSS
GLP1R-43-21	190	EVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGWFRQAPGKEREGVSWITSFD ASTYYADSVRGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALDGYSGSWG QGTQVTVSS
GLP1R-43-22	191	EVQLVESGGGLVQAGGSLRLSCAASGRTFSNYAMGWFRQAPGKEREFVSTISTG GSSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPTGRGRRD YWGQGTQVTVSS
GLP1R-43-23	192	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPVVPNTKD YWGQGTQVTVSS
GLP1R-43-24	193	EVQLVESGGGLVQAGGSLRLSCAASGNVFMIKDMGWFRQAPGKEREWVTAISW NGGSTDYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAIVTYSDYDL GNDWGQGTQVTVSS
GLP1R-43-25	194	EVQLVESGGGLVQAGGSLRLSCAASGFPFSIWPMGWFRQAPGKEREFIATIFSGG DTDYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAIAYEEGVYRWD WGQGTQVTVSS
GLP1R-43-26	195	EVQLVESGGGLVQAGGSLRLSCAASGRGFSRYAMGWFRQAPGKEREFVAAIRW SGKETWYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCALGPVRRSRLE WGQGTQVTVSS
GLP1R-43-27	196	EVQLVESGGGLVQAGGSLRLSCAASGRTSDIYGMGWFRQAPGKEREFVARIYWS SGNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAAYRFSDYSRP AGYDWGQGTQVTVSS
GLP1R-43-28	197	EVQLVESGGGLVQAGGSLRLSCAASGNDFSFNSMGWFRQAPGKEREFLASVSWG FGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCARAYGNPTWGQ GTQVTVSS
GLP1R-43-29	198	EVQLVESGGGLVQAGGSLRLSCAASGRTFTDYPMGWFRQAPGKERELESFVPIN GTSTYYADSDSGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALDGYSCSW GQGTQVTVSS
GLP1R-43-30	199	EVQLVESGGGLVQAGGSLRLSCAASGRTFSIYAMGWFRQAPGKEREFVATISRGG STTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAGPRSGKDYWG QGTQVTVSS
GLP1R-43-31	200	EVQLVESGGGLVQAGGSLRLSCAASGFIFQLYVMGWFRQAPGKEREGVTYINNI DGSTYYAYSVRGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRDGYSGSW GQGTQVTVSS
GLP1R-43-32	201	EVQLVESGGGLVQAGGSLRLSCAASGSTFSSYAMEWFRQAPGKERELVATISRSG GRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAANWYYRYDY WGQGTQVTVSS
GLP1R-43-33	202	EVQLVESGGGLVQAGGSLRLSCAASGFPFRINAMGWFRQAPGKERELVTAISSSG SSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAASGYYATYYGE RDYWGQGTQVTVSS
GLP1R-43-34	203	EVQLVESGGGLVQAGGSLRLSCAASGFTLSSYTMGWFRQAPGKEREFVSAISRGG GNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPSYAEYDYW GQGTQVTVSS

GLP1R-43-35	204	EVQLVESGGGLVQAGGSLRLSCAASGRTFSIYGMGWFRQAPGKEREGVAAINGG GDSTNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAASASPYSGRN YWGQGTQVTVSS
GLP1R-43-36	205	EVQLVESGGGLVQAGGSLRLSCAASGLtfSTTVMGWFRQAPGKEREGDGYISITD GSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCSAALDGYSGSWG QGTQVTVSS
GLP1R-43-37	206	EVQLVESGGGLVQAGGSLRLSCAASGRTLENYRMGWFRQAPGKEREFVAAVSW SSGNAYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAANWKMLLG VENDWGQGTQVTVSS
GLP1R-43-38	207	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPTVYGERD YWGQGTQVTVSS
GLP1R-43-39	208	EVQLVESGGGLVQAGGSLRLSCAASGSILSISPMGWFRQAPGKERELVAINFSWG TTDYADSvKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAIAYEQGVYRWD WGQGTQVTVSS
GLP1R-43-40	209	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAERYRYSGYY ARDSWGQGTQVTVSS
GLP1R-43-41	210	EVQLVESGGGLVQAGGSLRLSCAASGFTLSDYAMGWFRQAPGKEREFVSAISRD GTTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPTSQYATD YWGQGTQVTVSS
GLP1R-43-42	211	EVQLVESGGGLVQAGGSLRLSCAASGRDLDYYVMGWFRQAPGKERELVAIKFS GGTTDYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCADIAYEEGVYR WDWGQGTQVTVSS
GLP1R-43-43	212	EVQLVESGGGLVQAGGSLRLSCAASGSIFTFNAMGWFRQAPGKEREFVAGITRSA VSTSYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAFRGIMRPDWG QGTQVTVSS
GLP1R-43-44	213	EVQLVESGGGLVQAGGSLRLSCAASGRTFDSYAMGWFRQAPGKEREFVAAITSS GGNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPARYGARD YWGQGTQVTVSS
GLP1R-43-45	214	EVQLVESGGGLVQAGGSLRLSCAASGRTFNNDHMGWFRQAPGKEREFVAVIEIG GATNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCATWDGRQVWGQ GTQVTVSS
GLP1R-43-46	215	EVQLVESGGGLVQAGGSLRLSCAASGGTFRKLAMGWFRQAPGKERELVAAIRW SGGITWYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAATLAKGGGR WGQGTQVTVSS
GLP1R-43-47	216	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRAPSDRD YWGQGTQVTVSS
GLP1R-43-48	217	EVQLVESGGGLVQAGGSLRLSCAASGRTFRIYAMGWFRQAPGKERELVSSISWN SGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAAAYSYTQGTT YESWGQGTQVTVSS
GLP1R-43-49	218	EVQLVESGGGLVQAGGSLRLSCAASGRTFTSYRMGWFRQAPGKEREWMGTIDY SGRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAAMDGYSGSW GQGTQVTVSS
GLP1R-43-50	219	EVQLVESGGGLVQAGGSLRLSCAASGRTFSIYAMGWFRQAPGKEREFVAAINWN GDTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRYSDYDY WGQGTQVTVSS
GLP1R-43-51	220	EVQLVESGGGLVQAGGSLRLSCAASGRFFSTRVMGWFRQAPGKERELVAIKFSG GTTDYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAIAHEEGVYRW DWGQGTQVTVSS
GLP1R-43-52	221	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPSVYGTRD YWGQGTQVTVSS
GLP1R-43-53	222	EVQLVESGGGLVQAGGSLRLSCAASGSTFSIDVMGWFRQAPGKEREGVSYISMS DGRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAELDGYSGSW GQGTQVTVSS
GLP1R-43-54	223	EVQLVESGGGLVQAGGSLRLSCAASGLSFSGYTMGWFRQAPGKEREVVAAISRT GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCALIQRRAPYSRL ETWGQGTQVTVSS

GLP1R-43-55	224	EVQLVESGGGLVQAGGSLRLSCAASGSTLSIYGMGWFRQAPGKEREGVAAISWS DGSTSYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVADIGLASDF DYWGQGTQVTVSS
GLP1R-43-56	225	EVQLVESGGGLVQAGGSLRLSCAASGSTFSNYAMGWFRQAPGKEREFVATITRSS GNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPFKPYSYDY WGQGTQVTVSS
GLP1R-43-57	226	EVQLVESGGGLVQAGGSLRLSCAASGSTFSIYTMGWFRQAPGKEREFVAAISGSS DSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCATVPKTRYTRDY WGQGTQVTVSS
GLP1R-43-58	227	EVQLVESGGGLVQAGGSLRLSCAASGNTFSSYAMGWFRQAPGKEREFVAIISRSG GRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAAPYNETNSWG QGTQVTVSS
GLP1R-43-59	228	EVQLVESGGGLVQAGGSLRLSCAASGSTFSTYAMGWFRQAPGKEREFVASISRSG GRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAARYNERNSWG QGTQVTVSS
GLP1R-43-60	229	EVQLVESGGGLVQAGGSLRLSCAASGGTLNNNPMAMGWFRQAPGKEREFVVAI YWSNGKTPYADSVKRRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALDGYS GAWGQGTQVTVSS
GLP1R-43-61	230	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPRAPSERDY WGQGTQVTVSS
GLP1R-43-62	231	EVQLVESGGGLVQAGGSLRLSCAASGRTFNNNDMGWFRQAPGKEREFVAVIKL GGATTYDDYSEGRFTISADNAKNTVYLQMNSLKPEDTAVYYCATWDARHVWG QGTQVTVSS
GLP1R-43-63	232	EVQLVESGGGLVQAGGSLRLSCAASGRAFSYYNMGWFRQAPGKEREGVSWISSS DGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVLDGCSGSW GQGTQVTVSS
GLP1R-43-64	233	EVQLVESGGGLVQAGGSLRLSCAASGSTFSTYAMGWFRQAPGKEREFVAAINRS GASTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALLGGRGGC GKGYWGQGTQVTVSS
GLP1R-43-65	234	EVQLVESGGGLVQAGGSLRLSCAASGSILDTYAMGWFRQAPGKERELVSGINTS GDTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVLAGYEYWG QGTQVTVSS
GLP1R-43-66	235	EVQLVESGGGLVQAGGSLRLSCAASGSTLSINAMGWFRQAPGKEREFVAHMSHD GTTNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCARLPNYRWGQGT QVTVSS
GLP1R-43-67	236	EVQLVESGGGLVQAGGSLRLSCAASGSIFRLNAMGWFRQAPGKEREGVAAINNF DTTKYADSSKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRWGPRSDDR WGQGTQVTVSS
GLP1R-43-68	237	EVQLVESGGGLVQAGGSLRLSCAASGLTNPPFDNFPMGWFRQAPGKEREFVAVIS WTGGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCPAVYPRYYG DDDRPPVDWGQGTQVTVSS
GLP1R-43-69	238	EVQLVESGGGLVQAGGSLRLSCAASGPTFSKAVMGWFRQAPGKEREFVAAMNW SGRSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAATPAGRGGY WGQGTQVTVSS
GLP1R-43-70	239	EVQLVESGGGLVQAGGSLRLSCAASGSIFSDYAMGWFRQAPGKEREFVATINWG GGRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPKTRYARD YWGQGTQVTVSS
GLP1R-43-71	240	EVQLVESGGGLVQAGGSLRLSCAASGFILSDYAMGWFRQAPGKEREFVAAISSSE ASTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRFWAGYDSW GQGTQVTVSS
GLP1R-43-72	241	EVQLVESGGGLVQAGGSLRLSCAASGYTDYKYDMGWFRQAPGKEREFVAAISW GGGLTVYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVATVTDYT GTYSDGWGQGTQVTVSS
GLP1R-43-73	242	EVQLVESGGGLVQAGGSLRLSCAASGRTFSNYAMGWFRQAPGKEREFVATINW GGGNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPKTRYAY DYWGQGTQVTVSS
GLP1R-43-74	243	EVQLVESGGGLVQAGGSLRLSCAASGRTFSRYYMGWFRQAPGKERELVAVILRG GSTNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAARRYGNLYNT NNYDWGQGTQVTVSS

GLP1R-43-75	244	EVQLVESGGGLVQAGGSLRLSCAASGSILSSYVMGWFRQAPGKEREFVSAISRSG TSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPKTRYDRDY WGQGTQVTVSS
GLP1R-43-76	245	EVQLVESGGGLVQAGGSLRLSCAASGFTLDNYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPKTRYSYD YWGQGTQVTVSS
GLP1R-43-77	246	EVQLVESGGGLVQAGGSLRLSCAASGNTYSYKVMGWFRQAPGKEREFVGIIIRN GDTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAASPKYMTAYE RSYDWGQGTQVTVSS
GLP1R-43-78	247	EVQLVESGGGLVQAGGSLRLSCAASGSIFRNYAMGWFRQAPGKEREFVATITTSG GNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPKTRYRRDY WGQGTQVTVSS
GLP1R-43-79	248	EVQLVESGGGLVQAGGSLRLSCAASGFTFGTTTMGWFRQAPGKEREVVAAITGS GRSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAASAIGSGALRR FEYDWGQGTQVTVSS
GLP1R-43-80	249	EVQLVESGGGLVQAGGSLRLSCAASGGTFSAYAMGWFRQAPGKEREGVAAIRW DGGYTRYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAATTPTTSYLP RSERQYEWGQGTQVTVSS
GLP1R-43-81	250	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWS GGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVPSVYGERD YWGQGTQVTVSS
GLP1R-43-82	251	EVQLVESGGGLVQAGGSLRLSCAASGSFFSINAMGWFRQAPGKEREFVAGISQSG GSTAYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAHRIVVGGTSVG DWRWGQGTQVTVSS
GLP1R-43-83	252	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYRMGWFRQAPGKEREMVASITSR KIPKYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAVWSGRDWGQGT QVTVSS
GLP1R-43-84	253	EVQLVESGGGLVQAGGSLRLSCAASGFTFRRYVMGWFRQAPGKEREFVAAISRD GDRTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCASTRLAGRWYR DSEYKWGQGTQVTVSS
GLP1R-43-85	254	EVQLVESGGGLVQAGGSLRLSCAASGRTFSDNAMGWFRQAPGKEREFVATISRG GSRTSYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAGPRSGRDYW GQGTQVTVSS
GLP1R-43-86	255	EVQLVESGGGLVQAGGSLRLSCAASGFTFRSYAMGWFRQAPGKEREFVATITRN GDNTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCATVGTRYNYW GQGTQVTVSS
GLP1R-43-87	256	EVQLVESGGGLVQAGGSLRLSCAASGSTFSDYVMGWFRQAPGKERELISGITWN GDTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAVVRLGGYDY WGQGTQVTVSS
GLP1R-43-88	257	EVQLVESGGGLVQAGGSLRLSCAASGGIISNYHMGWFRQAPGKEREFVATITRSG GSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAMAGRGRWGQG TQVTVSS
GLP1R-43-89	258	EVQLVESGGGLVQAGGSLRLSCAASGFSFDDDYVMGWFRQAPGKERELVSAIG WSGASTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAYYTDYDE ALEETRGSYDWGQGTQVTVSS
GLP1R-43-90	259	EVQLVESGGGLVQAGGSLRLSCAASGSTFPIYAMGWFRQAPGKEREWVSGISSR DDTTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCSAHRIVFRGTSV GDWRWGQGTQVTVSS
GLP1R-43-91	260	EVQLVESGGGLVQAGGSLRLSCAASGRAFSYYNMGWFRQAPGKEREGVSWISSS DGSTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVLDGYSGSW GQGTQVTVSS
GLP1R-43-92	261	EVQLVESGGGLVQAGGSLRLSCAASGSTFSIDVMGWFRQAPGKERELVAATGRR GGPTYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAARTSYSGTYD YGVDWGQGTQVTVSS
GLP1R-43-93	262	EVQLVESGGGLVQAGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAAINWS GSITYYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAVGRSGRDYWG QGTQVTVSS
GLP1R-43-94	263	EVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGWFRQAPGKEREGVAAINNF GTTKYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAVRWGPRNDDR YDWGQGTQVTVSS

GLP1R-43-95	264	EVQLVESGGGLVQAGGSLRLSCAASGGTLNNNPMAMGWFRQAPGKEREFVVAIYWSNGKTQYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCAAALDGYSGSWGQGTQVTVSS
GLP1R-43-96	265	EVQLVESGGGLVQAGGSLRLSCAASGRTFNNDHMGWFRQAPGKEREFVAVIEIGGATNYADSVKGRFTISADNAKNTVYLQMNSLKPEDTAVYYCASWDGRQVWGQGTQVTVSS
GLP1R-41-01	266	EVQLVESGGGLVQPGGSLRLSCAASGRTFAMGWMGWFRQAPGKEREFVARVSWDGRNAYYANSRFGRFTISADNSKNTAYLQMNSLKPEDTAVYYCPRYVSPARDHGCWGQGTLVTVSS
GLP1R-41-02	267	EVQLVESGGGLVQPGGSLRLSCAASGLTISTYIMGWFRQAPGKEREFVAVVNWNGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYTDYDEALEETRGSYDWGQGTLVTVSS
GLP1R-41-03	268	EVQLVESGGGLVQPGGSLRLSCAASGTLFKINAMGWFRQAPGKERELVAAINRGGKITHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASLRNSGSNVEGRWGQGTLVTVSS
GLP1R-41-04	269	EVQLVESGGGLVQPGGSLRLSCAASGVTLDLYAMGWFRQAPGKEREFVAAISPSAVTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYDYYSDYPLPDANEYEWGQGTLVTVSS
GLP1R-41-05	270	EVQLVESGGGLVQPGGSLRLSCAASGRTFSDYIMGWFRQAPGKEREFVAVINRSGSTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVQAYSNSSDYYSQEGAYDWGQGTLVTVSS
GLP1R-41-06	271	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYVMGWFRQAPGKEREGVSYISSSDGRTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYNGSWGQGTLVTVSS
GLP1R-41-07	272	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRFGMGWFRQAPGKEREGVAAIGSDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASGRDRYARDLSEYEYVWGQGTLVTVSS
GLP1R-41-08	273	EVQLVESGGGLVQPGGSLRLSCAASGFTFRFNAMGWFRQAPGKEREFVAAINWRGSHPYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAATLGEPLVKYTWGQGTLVTVSS
GLP1R-41-09	274	EVQLVESGGGLVQPGGSLRLSCAASGGTFGVYHMGWFRQAPGKEREFLASVTWGFGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAATTTRSYDDTYRNSWVYNWGQGTLVTVSS
GLP1R-41-10	275	EVQLVESGGGLVQPGGSLRLSCAASGFSFDDYAMGWFRQAPGKERELVAAIRWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYGSGSDYLPMDWGQGTLVTVSS
GLP1R-41-11	276	EVQLVESGGGLVQPGGSLRLSCAASGPTFTIYAMGWFRQAPGKEREFVGAISMSGEDTIYADSEKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVQAYTSNTNYYNQEGAYDWGQGTLVTVSS
GLP1R-41-12	277	EVQLVESGGGLVQPGGSLRLSCAASGPTFSNYYVGWFRQAPGKEREFVAAILCSGGITCYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYIGTWGQGTLVTVSS
GLP1R-41-13	278	EVQLVESGGGLVQPGGSLRLSCAASGGTFSSIGMGWFRQAPGKEREGVAAIGSDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAASDRYARVLTEYEYVWGQGTLVTVSS
GLP1R-41-14	279	EVQLVESGGGLVQPGGSLRLSCAASGVTFNNYGMGWFRQAPGKERELVAAIRWSGSATFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADDGARGSWGQGTLVTVSS
GLP1R-41-15	280	EVQLVESGGGLVQPGGSLRLSCAASGRTFTMDGMGWFRQAPGKEREGVAAIGSDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGSNIGGSRWRYDWGQGTLVTVSS
GLP1R-41-16	281	EVQLVESGGGLVQPGGSLRLSCAASGGIFRFNAMGWFRQAPGKERELVAAISPAALTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYLPSPYYSSYYDSTKYEWGQGTLVTVSS
GLP1R-41-17	282	EVQLVESGGGLVQPGGSLRLSCAASGSGFSPNVMGWFRQAPGKEREVVAAISWNGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASAIGSGALRRFEYDWGQGTLVTVSS
GLP1R-41-18	283	EVQLVESGGGLVQPGGSLRLSCAASGFTFGFYAMGWFRQAPGKERELVAAISWSDASTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRRSYVDYYNVSEYDWGQGTLVTVSS

GLP1R-41-19	284	EVQLVESGGGLVQPGGSLRLSCAASGFTFSIYPMGWFRQAPGKERECVSTIWSRGDTYYADNVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSATWGQGTLVTVSS
GLP1R-41-20	285	EVQLVESGGGLVQPGGSLRLSCAASGFTFDYYAMGWFRQAPGKERELVAAISWSNDITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRRSYVDYYSVSEYDWGQGTLVTVSS
GLP1R-41-21	286	EVQLVESGGGLVQPGGSLRLSCAASGGTFSTYTMGWFRQAPGKEREFVAGIYNDGTASYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFDGYTGNDWGQGTLVTVSS
GLP1R-41-22	287	EVQLVESGGGLVQPGGSLRLSCAASGVTLDLYAMGWFRQAPGKEREWVARMYLDGDYPYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYSGSWGQGTLVTVSS
GLP1R-41-23	288	EVQLVESGGGLVQPGGSLRLSCAASGRTISRYIMGWFRQAPGKERELVAAINRSGKSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASTRFAGRWYRDSEYKWGQGTLVTVSS
GLP1R-41-24	289	EVQLVESGGGLVQPGGSLRLSCAASGRTLSVYAMGWFRQAPGKEREFVAAVRWSGGITWYVDSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFDGYSGSDWGQGTLVTVSS
GLP1R-41-25	290	EVQLVESGGGLVQPGGSLRLSCAASGSIFSITEMGWFRQAPGKERELVAAIAVGGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHDVDDDESPYYSGGYYRALYDWGQGTLVTVSS
GLP1R-41-26	291	EVQLVESGGGLVQPGGSLRLSCAASGSIYSLDAMGWFRQAPGKERELVAAISPAALTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASMSLRPLDPASYSPDIQPYDWGQGTLVTVSS
GLP1R-41-27	292	EVQLVESGGGLVQPGGSLRLSCAASGFTCGDYTMGWFRQAPGKERESVAAIDSDGRTHYADSVISRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGDWGQGTLVTVSS
GLP1R-41-28	293	EVQLVESGGGLVQPGGSLRLSCAASGRTLSfYAMGWFRQAPGKEREFVAAINRGGRISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRRYGSPPHDGSSYEWGQGTLVTVSS
GLP1R-41-29	294	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYAMGWFRQAPGKEREFVAGISWTGGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVNVGFEWGQGTLVTVSS
GLP1R-41-30	295	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMGWFRQAPGKEREGVAAIGSDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAATLRATITNFDEYVWGQGTLVTVSS
GLP1R-41-31	296	EVQLVESGGGLVQPGGSLRLSCAASGRTFNRYPMGWFRQAPGKEREFVAHMSHDGTTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAPGTRYYGSNQVNYNWGQGTLVTVSS
GLP1R-41-32	297	EVQLVESGGGLVQPGGSLRLSCAASGSIFSFNAMGWFRQAPGKEREFVAGITRRGLSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAKGIGVYGWGQGTLVTVSS
GLP1R-41-33	298	EVQLVESGGGLVQPGGSLRLSCAASGGSISSINAMGWFRQAPGKERELVAGIITSGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGSAYVAGVRRRNAYHWGQGTLVTVSS
GLP1R-41-34	299	EVQLVESGGGLVQPGGSLRLSCAASGGTFSADVMGWFRQAPGKEREFVAAISTGSITIYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATYGYDSGLYFITDSNDYEWGQGTLVTVSS
GLP1R-41-35	300	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDAAMGWFRQAPGKEREFVAAMRWRGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGTLYDDYDGLPIKYDWGQGTLVTVSS
GLP1R-41-36	301	EVQLVESGGGLVQPGGSLRLSCAASGDIFNINAMGWFRQAPGKEREPVAAISPAALTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAATPIERLGLDAYEYDWGQGTLVTVSS
GLP1R-41-37	302	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYNMGWFRQAPGKEREFVAAINWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEPPDSSWYLDGSPEFFKWGQGTLVTVSS
GLP1R-41-38	303	EVQLVESGGGLVQPGGSLRLSCAASGSISVFDAMGWFRQAPGKERELVAGISGSGGDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASPKYSTHSIFDASPYNWGQGTLVTVSS

GLP1R-41-39	304	EVQLVESGGGLVQPGGSLRLSCAASGFTSDDYAMGWFRQAPGKEREFVAALRW SSSNIDYTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDLSGHG DVSEYEYDWGQGTLVTVSS
GLP1R-41-40	305	EVQLVESGGGLVQPGGSLRLSCAASGFTFSPNVMGWFRQAPGKEREFVAAITSSG ETTWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEPYGSGSSLMS EYDWGQGTLVTVSS
GLP1R-41-41	306	EVQLVESGGGLVQPGGSLRLSCAASGRNLRMYRMGWFRQAPGKEREFVAAINW SGDNTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANWKMLLGV ENDWGQGTLVTVSS
GLP1R-41-42	307	EVQLVESGGGLVQPGGSLRLSCAASGDTFNCYAMGWFRQAPGKEREFVAVINW SGDNTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYTDYDEA LEETRGRYDWGQGTLVTVSS
GLP1R-41-43	308	EVQLVESGGGLVQPGGSLRLSCAASGSISTINVMGWFRQAPGKEREFVAAISPSA VTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDLSGRGDVSEY EYDWGQGTLVTVSS
GLP1R-41-44	309	EVQLVESGGGLVQPGGSLRLSCAASGRTLSKYRMGWFRQAPGKEREFVAAIRWS GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAIPHGIAGRITWG QGTLVTVSS
GLP1R-41-45	310	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYAMGWFRQAPGKERELVAGIDQS GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADDYLGGDNW YLGPYDWGQGTLVTVSS
GLP1R-41-46	311	EVQLVESGGGLVQPGGSLRLSCAASGFTIDDYAMGWFRQAPGKEREFVAAVSGT GTIAYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYIDYDEALE ETRGSYDWGQGTLVTVSS
GLP1R-41-47	312	EVQLVESGGGLVQPGGSLRLSCAASGRTFNNYVMGWFRQAPGKERELVAGITSG RDITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADGVLATTLNW DWGQGTLVTVSS
GLP1R-41-48	313	EVQLVESGGGLVQPGGSLRLSCAASGSGISFNAMGWFRQAPGKERELVAAISRSG DTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADLTTWADGPY RWGQGTLVTVSS
GLP1R-41-49	314	EVQLVESGGGLVQPGGSLRLSCAASGRTFSfYAMGWFRQAPGKEREFVAAINRG GKISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVRRYGNPPHD GSSYEWGQGTLVTVSS
GLP1R-41-50	315	EVQLVESGGGLVQPGGSLRLSCAASGRTFSfYGMGWFRQAPGKERELVAIKFSGG TTDYADSvkGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRWGQ GTLVTVSS
GLP1R-41-51	316	EVQLVESGGGLVQPGGSLRLSCAASGGIFRFNAMGWFRQAPGKERELVAGISGSG GDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFRGIMRPDWG QGTLVTVSS
GLP1R-41-52	317	EVQLVESGGGLVQPGGSLRLSCAASGRTFSfYAMGWFRQAPGKEREFVAAINRG GKISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVRRYGSPPHD GSSYEWGQGTLVTVSS
GLP1R-41-53	318	EVQLVESGGGLVQPGGSLRLSCAASGSDFSLNAMGWFRQAPGKEREFVAAISWS GGSTLYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASNESDAYNWG QGTLVTVSS
GLP1R-41-54	319	EVQLVESGGGLVQPGGSLRLSCAASGRTLVNYDMGWFRQAPGKEREFVAAIRW SGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFRGIMLPPW GQGTLVTVSS
GLP1R-41-55	320	EVQLVESGGGLVQPGGSLRLSCAASGRTFEKDAMGWFRQAPGKEREMVAAIRW SGGITCYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYGSLPDDYD GLECEYDWGQGTLVTVSS
GLP1R-41-56	321	EVQLVESGGGLVQPGGSLRLSCAASGSFFKINAMGWFRQAPGKEREFVAGITRSG GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAESLGRWWGQG TLVTVSS
GLP1R-41-57	322	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIDAMGWFRQAPGKEREFVAAIRWS GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASHDSDWGQG TLVTVSS
GLP1R-41-58	323	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIDAMGWFRQAPGKEREFVAAIRWS GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASHDSDYGGT NANLYDWGQGTLVTVSS

GLP1R-41-59	324	EVQLVESGGGLVQPGGSLRLSCAASGRTDRSNVMGWFRQAPGKEREFVAAINRSGSTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTKRTGIFTTARMVDWGQGTLVTVSS
GLP1R-41-60	325	EVQLVESGGGLVQPGGSLRLSCAASGSFFSINVMGWFRQAPGKERELVAATGRRGGPTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHRIVVGGTSVGDWRWGQGTLVTVSS
GLP1R-41-61	326	EVQLVESGGGLVQPGGSLRLSCAASGFTWGDYTMGWFRQAPGKEREGVAAIDSDGRTRYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGNWGQGTLVTVSS
GLP1R-41-62	327	EVQLVESGGGLVQPGGSLRLSCAASGNIFSLNTMGWFRQAPGKEREFVAAINCSGNHPYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSDDDGRDNWGQGTLVTVSS
GLP1R-41-63	328	EVQLVESGGGLVQPGGSLRLSCAASGSIFSINAMGWFRQAPGKEREFVAAVSGSGDDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVQAYSSSSDYYSQEGAYDWGQGTLVTVSS
GLP1R-41-64	329	EVQLVESGGGLVQPGGSLRLSCAASGFTFPAYVMGWFRQAPGKERELLAVITRDGSTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVNGRWRIWSSRNPWGQGTLVTVSS
GLP1R-41-65	330	EVQLVESGGGLVQPGGSLRLSCAASGFSFDDDYVMGWFRQAPGKERELVAVIGWGGKETWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEDPSMGYYTLEEYEYDWGQGTLVTVSS
GLP1R-41-66	331	EVQLVESGGGLVQPGGSLRLSCAASGPTFDTYVMGWFRQAPGKEREFVAAISMSGDDTAYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDLRGRGDVSEYEYDWGQGTLVTVSS
GLP1R-41-67	332	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIDAMGWFRQAPGKEREFVGAITWGGGNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTDGDYDGWGQGTLVTVSS
GLP1R-41-68	333	EVQLVESGGGLVQPGGSLRLSCAASGNTFSINVMGWFRQAPGKEREFVAAINWNGGSTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSDYDLDNDWGQGTLVTVSS
GLP1R-41-69	334	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTHWMGWFRQAPGKEREVVAVIYTSDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANEYGLGSSIYAYKWGQGTLVTVSS
GLP1R-41-70	335	EVQLVESGGGLVQPGGSLRLSCAASGRTFSISAMGWFRQAPGKEREFVAAISRSGGTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDEDYALGPNEYDWGQGTLVTVSS
GLP1R-41-71	336	EVQLVESGGGLVQPGGSLRLSCAASGSTFRINAMGWFRQAPGKERELVAAISPAALTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAEPYGSGSLYDDYDGLPIKYDWGQGTLVTVSS
GLP1R-41-72	337	EVQLVESGGGLVQPGGSLRLSCAASGFTDGIDAMGWFRQAPGKEREFVAAISWSNDITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALSEVWRGSENLREGYDWGQGTLVTVSS
GLP1R-41-73	338	EVQLVESGGGLVQPGGSLRLSCAASGLPVDYYAMGWFRQAPGKERELVAAISGSGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQTEDSASIFGYGMDWGQGTLVTVSS
GLP1R-41-74	339	EVQLVESGGGLVQPGGSLRLSCAASGRTLSTVNMGWFRQAPGKEREFVGAISRSGETTWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVDCPDYYSDYECPLEWGQGTLVTVSS
GLP1R-41-75	340	EVQLVESGGGLVQPGGSLRLSCAASGFSFDDYAMGWFRQAPGKERELVAAVRWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGDTGGAAYGWGQGTLVTVSS
GLP1R-41-76	341	EVQLVESGGGLVQPGGSLRLSCAASGSTLSINAMGWFRQAPGKEREGVSWISSSDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGRWGQGTLVTVSS
GLP1R-41-77	342	EVQLVESGGGLVQPGGSLRLSCAASGSSVSIDAMGWFRQAPGKEREFVAGISRSGDTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASYNVYYNNYYYPISRDEYDWGQGTLVTVSS
GLP1R-41-78	343	EVQLVESGGGLVQPGGSLRLSCAASGSIFRVNVMGWFRQAPGKERELVAVTWSGGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAYEEGVYRWDWGQGTLVTVSS

GLP1R-41-79	344	EVQLVESGGGLVQPGGSLRLSCAASGRTFSfYAMGWFRQAPGKEREFVAVVNWS GRRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASSRMGVDDP ETYGWGQGTLVTVSS
GLP1R-41-80	345	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDAAMGWFRQAPGKEREFVAAVRW RGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGSLYDDY DGLPIKYDWGQGTLVTVSS
GLP1R-41-81	346	EVQLVESGGGLVQPGGSLRLSCAASGSIFRINAMGWFRQAPGKERELVASISRFG RTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANGIESWGQGTLV TVSS
GLP1R-41-82	347	EVQLVESGGGLVQPGGSLRLSCAASGFTWGDYTMGWFRQAPGKEREFVASITSG GRMWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGSW GQGTLVTVSS
GLP1R-41-83	348	EVQLVESGGGLVQPGGSLRLSCAASGFRFSSYGMGWFRQAPGKEREGVAAIGSD GSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASWDGRQVWGQG TLVTVSS
GLP1R-41-84	349	EVQLVESGGGLVQPGGSLRLSCAASGRTFDNYNMGWFRQAPGKEREFVAAISW NGVTIYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGSLYDDW GQGTLVTVSS
GLP1R-41-85	350	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYSMGWFRQAPGKEREFVAAISSGG LKAYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDDYSGSWGQ GTLVTVSS
GLP1R-41-86	351	EVQLVESGGGLVQPGGSLRLSCAASGYTFRAYVMGWFRQAPGKERELLAVITRD GSTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVNGRWRSWSSR NPWGQGTLVTVSS
GLP1R-41-87	352	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYAMGWFRQAPGKEREFVAAISRGS NSTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYTDYDLWG QGTLVTVSS
GLP1R-41-88	353	EVQLVESGGGLVQPGGSLRLSCAASGRTISSYAMGWFRQAPGKERELVAAISKSS ISTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALGPVRRSRLEWG QGTLVTVSS
GLP1R-41-89	354	EVQLVESGGGLVQPGGSLRLSCAASGPTFDTYVMGWFRQAPGKEREFVAAISWT GDSSSDGDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAIFDV TDYERADWGQGTLVTVSS
GLP1R-41-90	355	EVQLVESGGGLVQPGGSLRLSCAASGFTLGNYAMGWFRQAPGKERELVSAITWS DGSSYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASTRFAGRWGQ GTLVTVSS
GLP1R-41-91	356	EVQLVESGGGLVQPGGSLRLSCAASGNIDRLYAMGWFRQAPGKEREPVAAISPA AVTAGMTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYGSGSY YYTDDELDWGQGTLVTVSS
GLP1R-41-92	357	EVQLVESGGGLVQPGGSLRLSCAASGRTFGRRAMGWFRQAPGKERELVAAIRWS GKETWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGNGGRTYGH SRARYEWGQGTLVTVSS
GLP1R-41-93	358	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIGAMGWFRQAPGKEREYVGSITWR GGNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGVTGGAAYG WGQGTLVTVSS
GLP1R-41-94	359	EVQLVESGGGLVQPGGSLRLSCAASGLTFSTYWMGWFRQAPGKEREVVAVIYTS DGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATIDGSWREWG QGTLVTVSS
GLP1R-41-95	360	EVQLVESGGGLVQPGGSLRLSCAASGFGIDfyAMGWFRQAPGKEREFVAAISGSG DDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASASDYGLGLEL FHDEYNWGQGTLVTVSS
GLP1R-41-96	361	EVQLVESGGGLVQPGGSLRLSCAASGNILSLNTMGWFRQAPGKEREFVASVTWG FGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSDYDLG NDWGQGTLVTVSS
GLP1R-41-97	362	EVQLVESGGGLVQPGGSLRLSCAASGSIYSLDAMGWFRQAPGKEREFVAAISPAA LTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAGSSRIYIYSDSLSE RSYDWGQGTLVTVSS
GLP1R-41-98	363	EVQLVESGGGLVQPGGSLRLSCAASGRTFSfYGMGWFRQAPGKERELVAIKFSGG TTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRWD WGQGTLVTVSS

GLP1R-41-99	364	EVQLVESGGGLVQPGGSLRLSCAASGRTFSKYAMGWFRQAPGKEREFVAAIRWSGGTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGGWGTGRYNWGQGTLVTVSS
GLP1R-44-01	365	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIYAMDWFRQAPGKEREFVAAISSDDSTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCTAVLPAYDDWGQGTLVTVSS
GLP1R-44-02	366	EVQLVESGGGLVQPGGSLRLSCAASGFNSGSYTMGWFRQAPGKEREGVSYISSSDGRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGLNGAAAAWGQGTLVTVSS
GLP1R-44-03	367	EVQLVESGGGLVQPGGSLRLSCAASGRTFSNGPMGWFRQAPGKEREFVAHISTGGATNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASWDGRQGWGQGTLVTVSS
GLP1R-44-04	368	EVQLVESGGGLVQPGGSLRLSCAASGRALSSYSMGWFRQAPGKEREFVALITRSGGTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRHSYVDWGQGTLVTVSS
GLP1R-44-05	369	EVQLVESGGGLVQPGGSLRLSCAASGSIGSINAMGWFRQAPGKEREFVAAISWSGGATNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASVAYSDYDLGNDWGQGTLVTVSS
GLP1R-44-06	370	EVQLVESGGGLVQPGGSLRLSCAASGLSFDDYAMGWFRQAPGKEREFVAAISGRSGNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALIQRRAPYSRLETWGQGTLVTVSS
GLP1R-44-07	371	EVQLVESGGGLVQPGGSLRLSCAASGFTFSIYAMGWFRQAPGKEREGVAAISWSGGTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAAGWVAEYGYWGQGTLVTVSS
GLP1R-44-08	372	EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVATISSNGNTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADLRVLRLRRYEYNYWGQGTLVTVSS
GLP1R-44-09	373	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSNAMGWFRQAPGKEREGVAAISTSGGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAERDGYGYWGQGTLVTVSS
GLP1R-44-10	374	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYAMGWFRQAPGKERELVAGISWNGGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVRAGYDYWGQGTLVTVSS
GLP1R-44-11	375	EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKEREWVATISWSGGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVGRSGRDYWGQGTLVTVSS
GLP1R-44-12	376	EVQLVESGGGLVQPGGSLRLSCAASGRAFESYAMGWFRQAPGKEREFVAAIRWSGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATGGWGTGRYNWGQGTLVTVSS
GLP1R-44-13	377	EVQLVESGGGLVQPGGSLRLSCAASGRIFSDYAMGWFRQAPGKEREFVATINGDGDSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANTYWYYTYDSWGQGTLVTVSS
GLP1R-44-14	378	EVQLVESGGGLVQPGGSLRLSCAASGRIFSDYAMGWFRQAPGKEREFVATINGDGDSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANTYCNYTYDSWGQGTLVTVSS
GLP1R-44-15	379	EVQLVESGGGLVQPGGSLRLSCAASGRTLSRSNMGWFRQAPGKEREFVAAVRWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALGPVRRSRLEWGQGTLVTVSS
GLP1R-44-16	380	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMGWFRQAPGKEREFVAAITWSGGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRAGRDSWGQGTLVTVSS
GLP1R-44-17	381	EVQLVESGGGLVQPGGSLRLSCAASGRTFNSYAMGWFRQAPGKEREFVAGITRSAVSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAFRGIMRPDWGQGTLVTVSS
GLP1R-44-18	382	EVQLVESGGGLVQPGGSLRLSCAASGFTFRNYVMGWFRQAPGKEREFVASITWSGGTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRGSGRDYWGQGTLVTVSS
GLP1R-44-19	383	EVQLVESGGGLVQPGGSLRLSCAASGRALSSNSMGWFRQAPGKEREFVALITRSGGTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALNNRRRYVDWGQGTLVTVSS

GLP1R-44-20	384	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVGRNGRDYWGQGTLVTVSS
GLP1R-44-21	385	EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKEREFVAAISWSGGNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVPTIAYNTGYDYWGQGTLVTVSS
GLP1R-44-22	386	EVQLVESGGGLVQPGGSLRLSCAASGRTFDDYAMGWFRQAPGKERELVSGITWSGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLGYDGYDYWGQGTLVTVSS
GLP1R-44-23	387	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYAMGWFRQAPGKERELVSAISTDDGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALPDDTYLATTYDYWGQGTLVTVSS
GLP1R-44-24	388	EVQLVESGGGLVQPGGSLRLSCAASGSIFSDNVMGWFRQAPGKEREMVAAIRWSGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDLSGRGDVSEYEYDWGQGTLVTVSS
GLP1R-44-25	389	EVQLVESGGGLVQPGGSLRLSCAASGEIASIIAMGWFRQAPGKEREWVSAINSGGDTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADRSRTIWPDWGQGTLVTVSS
GLP1R-44-26	390	EVQLVESGGGLVQPGGSLRLSCAASGRTFSVSTMGWFRQAPGKEREIVAAITWSGSATYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQRRWSQDWGQGTLVTVSS
GLP1R-44-27	391	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKERELVAGITGGGSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTRYGYDYWGQGTLVTVSS
GLP1R-44-28	392	EVQLVESGGGLVQPGGSLRLSCAASGIPFRSRTMGWFRQAPGKEREFVAGITRNSIRTRYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAPRRPYLPIRIRDYIWGQGTLVTVSS
GLP1R-44-29	393	EVQLVESGGGLVQPGGSLRLSCAASGRTIVPYTMGWFRQAPGKEREFVAAISWSGASTIYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAIGGTLYDRRRFEWGQGTLVTVSS
GLP1R-44-30	394	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNNAMGWFRQAPGKEREGVAAINGSGSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAARDDYGYWGQGTLVTVSS
GLP1R-44-31	395	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYGMGWFRQAPGKEREGVAGISWSDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAASDASFDYWGQGTLVTVSS
GLP1R-44-32	396	EVQLVESGGGLVQPGGSLRLSCAASGGTFSDYGMGWFRQAPGKEREGVASISWNDGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAATADYDYWGQGTLVTVSS
GLP1R-44-33	397	EVQLVESGGGLVQPGGSLRLSCAASGSTFSTYAMGWFRQAPGKERELVAAISWSSGTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLVTSDGVSEYNYWGQGTLVTVSS
GLP1R-44-34	398	EVQLVESGGGLVQPGGSLRLSCAASGFLFDSYAMGWFRQAPGKEREPVAAISPAALTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYTDYDEALEETRGSYDWGQGTLVTVSS
GLP1R-44-35	399	EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYAMGWFRQAPGKEREGVAAISWNSGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDARRYGYWGQGTLVTVSS
GLP1R-44-36	400	EVQLVESGGGLVQPGGSLRLSCAASGSTFGNYAMGWFRQAPGKEREFVAAISRSGSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDEDYALGPNEYDWGQGTLVTVSS
GLP1R-44-37	401	EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYAMGWFRQAPGKERELVAGISWGGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGNGYDYWGQGTLVTVSS
GLP1R-44-38	402	EVQLVESGGGLVQPGGSLRLSCAASGFNSGSYTMGWFRQAPGKEREGVSYISSSDGRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGSWGQGTLVTVSS
GLP1R-44-39	403	EVQLVESGGGLVQPGGSLRLSCAASGLTFWTSGMGWFRQAPGKEREYVAAISRSGSLKGYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATVATALIWGQGTLVTVSS

GLP1R-44-40	404	EVQLVESGGGLVQPGGSLRLSCAASGFTFSINAMGWFRQAPGKERELVSGISWGG GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVNEDGFDYWG QGTLVTVSS
GLP1R-44-41	405	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDNAMGWFRQAPGKERELVAAISTS GSNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAELREYGYWG QGTLVTVSS
GLP1R-44-42	406	EVQLVESGGGLVQPGGSLRLSCAASGRTFTSYNMGWFRQAPGKEREFLGSILWS DDSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASWDGRQVWGQ GTLVTVSS
GLP1R-44-43	407	EVQLVESGGGLVQPGGSLRLSCAASGFTFRNYVMGWFRQAPGKEREFVAAINW NGSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRSARNYW GQGTLVTVSS
GLP1R-44-44	408	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISTSG GITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDRIEYSRGGYD YWGQGTLVTVSS
GLP1R-44-45	409	EVQLVESGGGLVQPGGSLRLSCAASGSTFRKYAMGWFRQAPGKEREFVAAISSG GGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRYRERDSW GQGTLVTVSS
GLP1R-44-46	410	EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKEREFVAAISWSG DTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAIDLPDDTYLATE YDYWGQGTLVTVSS
GLP1R-44-47	411	EVQLVESGGGLVQPGGSLRLSCAASGSGFSPNVMGWFRQAPGKERELVAIKFSG GTTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAYEEGVYRW DWGQGTLVTVSS
GLP1R-44-48	412	EVQLVESGGGLVQPGGSLRLSCAASGRTLTNHDMGWFRQAPGKEREGVSYISMS DGRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYSGSW GQGTLVTVSS
GLP1R-44-49	413	EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKEREFVAAISRSG DSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTLDNYGYWG QGTLVTVSS
GLP1R-44-50	414	EVQLVESGGGLVQPGGSLRLSCAASGGTASSYHMGWFRQAPGKEREFVAFIHRS GTSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADSITDRRSVA VAHTSYYWGQGTLVTVSS
GLP1R-44-51	415	EVQLVESGGGLVQPGGSLRLSCAASGLTFSTYAMGWFRQAPGKEREIVAAITWS GGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHGSILLDRIEW GQGTLVTVSS
GLP1R-44-52	416	EVQLVESGGGLVQPGGSLRLSCAASGGTFSIYAMGWFRQAPGKERELVAAISSSG SITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAAALDGPGDMY DYWGQGTLVTVSS
GLP1R-44-53	417	EVQLVESGGGLVQPGGSLRLSCAASGGTFDNYAMGWFRQAPGKERELVSGINSD GGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVPISSPSDRNY WGQGTLVTVSS
GLP1R-44-54	418	EVQLVESGGGLVQPGGSLRLSCAASGRTFSLTAMGWFRQAPGKEREFVAAISPAA LTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASRRAFRLSSDYE WGQGTLVTVSS
GLP1R-44-55	419	EVQLVESGGGLVQPGGSLRLSCAASGRNLRMYRMGWFRQAPGKEREFVAAVN WNGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANWKMLL GVENDWGQGTLVTVSS
GLP1R-44-56	420	EVQLVESGGGLVQPGGSLRLSCAASGFTFDIYAMGWFRQAPGKERELVAGISSSG GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLGTYDYWGQ GTLVTVSS
GLP1R-44-57	421	EVQLVESGGGLVQPGGSLRLSCAASGRTFDIYAMGWFRQAPGKERELVAAINRD DSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGLGNYNY WGQGTLVTVSS
GLP1R-44-58	422	EVQLVESGGGLVQPGGSLRLSCAASGRSFSFNAMGWFRQAPGKERELVAAITKL GFRNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASIEGVSGRWGQ GTLVTVSS
GLP1R-44-59	423	EVQLVESGGGLVQPGGSLRLSCAASGSFFSINAMGWFRQAPGKERELVSASTWN GGYTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHRIVVGGTSV GDWRWGQGTLVTVSS

GLP1R-44-60	424	EVQLVESGGGLVQPGGSLRLSCAASGRTFSDYAMGWFRQAPGKEREFVAGITSSGGYTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVVYYGDWEGSEPVQHEYDWGQGTLVTVSS
GLP1R-44-61	425	EVQLVESGGGLVQPGGSLRLSCAASGSIFSRNAMGWFRQAPGKEREFVAAIRWSGKETWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTKRTGIFTTARMVDWGQGTLVTVSS
GLP1R-44-62	426	EVQLVESGGGLVQPGGSLRLSCAASGGTFDTYAMGWFRQAPGKEREFVAGISGDGTITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDNPYWSGYNYWGQGTLVTVSS
GLP1R-44-63	427	EVQLVESGGGLVQPGGSLRLSCAASGGTFSNYAMGWFRQAPGKERELVSGINSDGGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVSTNDGYDYWGQGTLVTVSS
GLP1R-44-64	428	EVQLVESGGGLVQPGGSLRLSCAASGGIYRVNTMGWFRQAPGKERELVAIKFSGGTTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRWDWGQGTLVTVSS
GLP1R-44-65	429	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMGWFRQAPGKERELVAGISSSGSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVSDGGYDYWGQGTLVTVSS
GLP1R-44-66	430	EVQLVESGGGLVQPGGSLRLSCAASGRTSSIYNMGWFRQAPGKEREFVAAISRSGRSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSDYDLGNDWGQGTLVTVSS
GLP1R-44-67	431	EVQLVESGGGLVQPGGSLRLSCAASGRALSSYSMGWFRQAPGKEREFVALITRSGGTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRRSYVDWGQGTLVTVSS
GLP1R-44-68	432	EVQLVESGGGLVQPGGSLRLSCAASGRALSRYGMVWFRQAPGKEREFVAAINRGGKISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGNGGRNYGHSRARYEWGQGTLVTVSS
GLP1R-44-69	433	EVQLVESGGGLVQPGGSLRLSCAASGFKFNDSYMRWFRQAPGKEREFVVAINWSSGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVNGPIFWGQGTLVTVSS
GLP1R-44-70	434	EVQLVESGGGLVQPGGSLRLSCAASGRTLSDYALGWFRQAPGKERELVSGINTSGDTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVTSSYDYWGQGTLVTVSS
GLP1R-44-71	435	EVQLVESGGGLVQPGGSLRLSCAASGSTFDIYGMGWFRQAPGKEREGVAAITGDGSSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADNDTEYGYWGQGTLVTVSS
GLP1R-44-72	436	EVQLVESGGGLVQPGGSLRLSCAASGGTLDIYAMGWFRQAPGKEREFVAAISWSGSTTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLGYDRDYWGQGTLVTVSS
GLP1R-44-73	437	EVQLVESGGGLVQPGGSLRLSCAASGRPYSYDAMGWFRQAPGKEREIVAAISRTGSSIYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGSLYDDYDGLPIKYDWGQGTLVTVSS
GLP1R-44-74	438	EVQLVESGGGLVQPGGSLRLSCAASGRTFRTYGMGWFRQAPGKEREGVAAISWSGNSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAARLSKRGNRSSRDYWGQGTLVTVSS
GLP1R-44-75	439	EVQLVESGGGLVQPGGSLRLSCAASGSTFDNYAMGWFRQAPGKERELVAGINWSDSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGWGEYDYWGQGTLVTVSS
GLP1R-44-76	440	EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKERELVAGINWSDSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTDYDEYNYWGQGTLVTVSS

Table 12. Variable Heavy Chain CDRs

Variant	SEQ ID NO	CDR1	SEQ ID NO	CDR2	SEQ ID NO	CDR3
GLP1R-3	441	GFTFSSYG	620	ISYDESNK	799	AKHMSMQEGAVTGEGQAAKEFIAWLVKGRVRADLVGDAFDV
GLP1R221-	442	GFTFSDYG	621	ISYDRSNE	800	AKHMSMQEGAVTGDG

065						QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-075	443	GFTFSDYG	622	ISYDETNK	801	AKHMSMQEGAVTGEG QAAKEFIAWLVKGIVR ADLVGDAFDV
GLP1R221-017	444	GFTFSDYG	623	ISYDESNK	802	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-033	445	GFTFSDYG	624	ISHDRSNK	803	AKHMSMQEGAVTGEG QAAKDFIAWLVKGRVR ADLVGDAFDV
GLP1R221-076	446	GFTFSDYG	625	ISYDETNK	804	AKHMSMQEGAVTGEG QAAKEFIAWLVKGIVR ADLVGDAFDV
GLP1R221-092	447	GFTFSDYG	626	ISYGGSNK	805	AKHMSMQEGAVTGEG QAVKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-034	448	GFTFSDYG	627	ISHDRSNK	806	AKHMSMQEGAVTGEG QAVKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-066	449	GFTFSDYG	628	ISYDRSNE	807	AKHMSMQEGAVTGEG QAIKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-084	450	GFTFSDYG	629	ISSDENNK	808	AKHMSMQEGAVTGEM QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-009	451	GFTFSDYG	630	ISDEGSNK	809	AKHMSMQEGAVTGAG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-072	452	GFTFSDYG	631	ISSDENNK	810	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-044	453	GFTFSDYG	632	TSYDESNK	811	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-012	454	GFTFSDYG	633	ISSDASDK	812	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-042	455	GFTFSDYG	634	TSYDESNK	813	AKHMSMQEGAVTGVG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-051	456	GFTFSDYG	635	ISYEGSNK	814	AKHMSMQEGAVTGMG QAAKEFIAWLIKGRVR ADLVGDAFDV
GLP1R221-083	457	GFTFSDYG	636	ISSDASDK	815	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-040	458	GFTFSDYG	637	ISYDESNE	816	AKHMSMQEGAVTGEH QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-052	459	GFTFSDYG	638	ISYDRSNE	817	AKHMSMQEGAVHGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-003	460	GFTFSDYG	639	ISDEGSNK	818	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-094	461	GFTFSDYG	640	ISSDENNK	819	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-	462	GFTFSDYG	641	ISYDASNK	820	AKHMSMQEGAVTGEG

001						QAVKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-014	463	GFTFSDYG	642	ISSDASDK	821	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-085	464	GFTFSDYG	643	ISHDRSNK	822	AKHMSMQEGAVTGLG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-022	465	GFTFSDYG	644	ISYDANN K	823	AKHMSMQEGAVTGEG QAAKEFIAWLIKGRVR ADLVGDAFDV
GLP1R221-056	466	GFTFSDYG	645	ISYEGSNQ	824	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-088	467	GFTFSDYG	646	TSYDESN K	825	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-077	468	GFTFSDYG	647	ISYDATNK	826	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-027	469	GFTFSDYG	648	ISYHGSNK	827	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-019	470	GFTFSDYG	649	ISYDASNK	828	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-029	471	GFTFSDYG	650	ISSDASDK	829	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-043	472	GFTFSDYG	651	TSYDESN K	830	AKHMSMQEGAVTGGG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-082	473	GFTFSDYG	652	ISSDASNK	831	AKHMSMQEGAVTGEG QAVKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-079	474	GFTFSDYG	653	ISYDANN K	832	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-080	475	GFTFSDYG	654	ISHDRSNK	833	AKHMSMQEGAVTGPG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-059	476	GFTFSDYG	655	IRYGGSNK	834	AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-069	477	GFTFSDYG	656	ISYDATNK	835	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-036	478	GFTFSDYG	657	ISDEGSNK	836	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-057	479	GFTFSDYG	658	ISYEGSNQ	837	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-035	480	GFTFSDYG	659	ISDEGSNK	838	AKHMSMQEGAVTGLG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-063	481	GFTFSDYG	660	ISDEGSNK	839	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-	482	GFTFSDYG	661	TSYDESN	840	AKHMSMQEGAVTGEW

090				K		QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-002	483	GFTFSDYG	662	ISSDASHK	841	AKHMSMQEGAVTWEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-087	484	GFTFSDYG	663	ISYDETNK	842	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-038	485	GFTFSDYG	664	ISDEGSNK	843	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-060	486	GFTFSDYG	665	ISYGGSNK	844	AKHMSMQEGAVTNEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-015	487	GFTFSDYG	666	ISSDASHK	845	AKHMSMQEGAVTWEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-020	488	GFTFSDYG	667	ISYDESNK	846	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-011	489	GFTFSDYG	668	ISSDASDK	847	AKHMSMQEGAVTGGG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-091	490	GFTFSDYG	669	ISYGGSNK	848	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-086	491	GFTFSDYG	670	TSYDESNK	849	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-074	492	GFTFSDYG	671	ISHDRSNK	850	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-032	493	GFTFSDYG	672	ISHDRSNK	851	AKHMSMQEGAVTGEG QAAKDFIAWLVKGRVR ADLVGDAFDV
GLP1R221-013	494	GFTFSDYG	673	ISSDASDK	852	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-058	495	GFTFSDYG	674	ISHDRSNK	853	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-031	496	GFTFSDYG	675	ISSDASDK	854	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-054	497	GFTFSDYG	676	ISSDASDK	855	AKHMSMQEGAVTGEG WAAKEFIAWLVKGRV RADLVGDAFDV
GLP1R221-021	498	GFTFSDYG	677	ISYDATNK	856	AKHMSMQEGAVTGEG QFAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-016	499	GFTFSDYG	678	ISSDASHK	857	AKHMSMQEGAVTWEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-030	500	GFTFSDYG	679	ISSDASDK	858	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-018	501	GFTFSDYG	680	ISSDASDK	859	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-	502	GFTFSDYG	681	ISYDAGN	860	AKHMSMQEGAVTGMG

028				K		QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-023	503	GFTFSDYG	682	TSYEESNK	861	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-089	504	GFTFSDYG	683	ISHDRSNK	862	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-053	505	GFTFSDYG	684	ISSDASDK	863	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-071	506	GFTFSDYG	685	ISSDENNK	864	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-055	507	GFTFSDYG	686	ISYGGSNK	865	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-046	508	GFTFSDYG	687	ISSDASNK	866	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-039	509	GFTFSDYG	688	IRYDESNK	867	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-078	510	GFTFSDYG	689	ISSDASNK	868	AKHMSMQEGAVMGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-010	511	GFTFSDYG	690	ISSDASDK	869	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-005	512	GFTFSDYG	691	ISDEGSNK	870	AKHMSMQEGAVTGLG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-073	513	GFTFSDYG	692	ISHDRSNK	871	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-041	514	GFTFSDYG	693	ISYDETNK	872	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-025	515	GFTFSDYG	694	ISYDESNK	873	AKHMSMQEGAVTEEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-007	516	GFTFSDYG	695	ISDEGSNK	874	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-093	517	GFTFSDYG	696	ISYDESNK	875	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-024	518	GFTFSDYG	697	ISYDAGNK	876	AKHMSMQEGAVTGEG QAVKEFIAWLVKGDVR ADLVGDAFDV
GLP1R221-008	519	GFTFSDYG	698	ISDEGSNK	877	AKHMSMQEGAVTGLG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-050	520	GFTFSDYG	699	ISYDENNK	878	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-062	521	GFTFSDYG	700	TSYDESNK	879	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-	522	GFTFSDYG	701	ISYDAGN	880	AKHMSMQEGAVTGFG

068				K		QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-067	523	GFTFSDYG	702	ISNDENNK	881	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-061	524	GFTFSDYG	703	TSYDESNK	882	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-064	525	GFTFSDYG	704	ISDEGSNK	883	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-070	526	GFTFSDYG	705	ISYDATNK	884	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-006	527	GFTFSDYG	706	ISDEGSNK	885	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-045	528	GFTFSDYG	707	ISSDASNK	886	AKHMSMQEGAVTGEG QAAKEFIAWLVFGRVR ADLVGDAFDV
GLP1R221-004	529	GFTFSDYG	708	ISDEGSNK	887	AKHMSMQEGAVTGFG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R221-047	530	GFTFSDYG	709	ISSDASDK	888	AKHMSMQEGAVTGEG QAWKEFIAWLVKGRV RADLVGDAFDV
GLP1R221-048	531	GFTFSDYG	710	ISSDASDK	889	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-052	532	GFTFNNYP	711	ISYDESNK	890	AKHMSMQEGAVTGGG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-016	533	GFTFNNYA	712	ISDEGSNK	891	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-023	534	GFSFSDYG	713	ISYDANNK	892	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-014	535	GFAFSNYG	714	ISYDESNK	893	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-090	536	GFSFSDYG	715	ISYEGSNK	894	AKHMSMQEGAVTGEK QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-073	537	GFTFRDYG	716	IRYDEINK	895	AKHMSMQEGAVTGEG QAAKEFIAWLVGGRVR ADLVGDAFDV
GLP1R-222-012	538	GFTFNNYG	717	ISDEGSNK	896	AKHMSMQEGAVTGVG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-082	539	GFTFSAYS	718	ISYDATNK	897	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-081	540	GFTFDNYA	719	ISYDAGNK	898	AKHMSMQEGAVTGEG QAAKEFIAWLVKGFVR ADLVGDAFDV
GLP1R-222-056	541	GFPFSSYA	720	ISYDRSNK	899	AKHMSMQEGAVTGYG QAAKEFIAWLVKGFVR ADLVGDAFDV
GLP1R-222-	542	GFTFRDY	721	ISFDESNK	900	AKHMSMQEGAVTGEW

058		A				QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-063	543	GFTFNNYP	722	ISHDRSNK	901	AKHMSMQEGAVTGTG QAAKEFIAWLVKGIVR ADLVGDAFDV
GLP1R-222-042	544	GLTFSNYA	723	TSYDESNK	902	AKHMSMQEGAVTREG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-092	545	GFTFGSYA	724	TSYDESNK	903	AKHMSMQEGAVTGEG QAAKEFIAWLVMGRVR ADLVGDAFDV
GLP1R-222-007	546	GFTFSSYG	725	ISSDASDK	904	AKHMSMQEGAVTGEG QAAKEFIAWLVKGWV RADLVGDAFDV
GLP1R-222-008	547	GFNFNNYG	726	ISYDASNK	905	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-024	548	GFTSSSYA	727	ISDEGSNK	906	AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-062	549	GFTFSDYP	728	ISYDESNK	907	AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR NDLVGDAFDV
GLP1R-222-077	550	GFTFGNYG	729	ISYDASNK	908	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-064	551	GFTFNNYA	730	ISYAGSNE	909	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-074	552	GFSFRSYG	731	ISSDASNK	910	AKHMSMQEGAQTGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-029	553	GFSFSNYA	732	TSYDESNK	911	AKHMSMQEGAVTGEG QAAKEFIAWLLKGRVR ADLVGDAFDV
GLP1R-222-046	554	GFAFSSYA	733	ISYDENNK	912	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-005	555	GFTFNNYP	734	IWSDASQK	913	AKHMSMQEGAVTGEG WAAKEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-004	556	GFTFGNYA	735	ISSDASDK	914	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-022	557	GFAFSNYG	736	ISYDASNK	915	AKHMSMQEGAVTGEG QAAKNFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-087	558	GFTFSNYA	737	ISYDASNK	916	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-048	559	GFSFGSYA	738	TSYDESNK	917	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-072	560	GFTFSSYP	739	ISYEGTNK	918	AKHMSMQEGAVTGEG QAAKDFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-089	561	GFSFSNYA	740	ISYDESNE	919	AKHMSMQEGAVTGEG QAAKEFIAWLVKGDVR ADLVGDAFDV
GLP1R-222-	562	GFSFSSYG	741	ISYGGSNK	920	AKHMSMQEGAVTGEW

083						QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-001	563	GFSFSNYA	742	TSYDESNK	921	AKHMSMQEGAVTGEG QAAKEFIAWLLKGRVR ADLVGDAFDV
GLP1R-222-075	564	GFTFSDYG	743	ISYDESNK	922	AKHMSMQEGAVTGEG WAAKEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-071	565	GFTFSDFA	744	ISYEGSNK	923	AKHMSMQEGAVQGEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-069	566	GFTFSDYP	745	ISDEGSNK	924	AKHMSMQEGAVTGEIQ AAKEFIAWLVKGRVRA DLVGDAFDV
GLP1R-222-002	567	GFTFRDYA	746	ISYDATNK	925	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-006	568	GFTFNRYG	747	ISYDASNK	926	AKHMSMQEGAVTGEG QAAWEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-055	569	GFPFSSYG	748	ISYDATNK	927	AKHMSMQEGAVTGEG QAAKSFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-027	570	GFSFGSYA	749	ISYDASNK	928	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-066	571	GFTFSNYD	750	ISYAGSNK	929	AKHMSMQEGAVTGTG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-015	572	GFSFRTYG	751	ISDEGSNK	930	AKHMSMQEGAVTGEG YAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-076	573	GFTFSTYG	752	ISYDANNK	931	AKHMSMQEGAVTGEG QAAVEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-011	574	GFSFSDYA	753	ISSDASNK	932	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-065	575	GFTFSNYA	754	ISYDATNK	933	AKHMSMQEGAVTGEA QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-041	576	GFTFSNYD	755	TSYDESKK	934	AKHMSMQEGAVTGKG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-028	577	GFSFSNYA	756	TSYDESNK	935	AKHMSMQEGAVTGEG QAAYEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-086	578	GFTFSDYP	757	ISYAGSNE	936	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-033	579	GFPFSSYA	758	ISYDANNK	937	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-035	580	GFAFSSYA	759	ISYDESNK	938	AKHMSMQEGAVTGEG WAAKEFIFWLVKGRVR ADLVGDAFDV
GLP1R-222-045	581	GFSFSNYA	760	ISFDESNK	939	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-	582	GFTFSDYP	761	ISYDRSNE	940	AKHMSMQEGAVTGTG

085						QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-049	583	GFSFSNYG	762	ISSDASNK	941	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-078	584	GFSFRNYG	763	ISYDESNK	942	AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR PDLVGDAFDV
GLP1R-222-021	585	GFTFNDYG	764	ISSDASNK	943	AKHMSMQEGAVTGTG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-009	586	GFTFGNYA	765	ISSDASNK	944	AKHMSMQEGAVTGEF QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-036	587	GFTFTNYG	766	ISSDASDK	945	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-084	588	GFSFSNYG	767	ISYGGSNK	946	AKHMSMQEGAVTGEG FAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-010	589	GFTFSDYP	768	ISSDASDK	947	AKHMSMQEGAVTGEG QAAKEFIAWLVKGWV RADLVGDAFDV
GLP1R-222-088	590	GFSFSNYA	769	ISYDASNK	948	AKHMSMQEGAVTGGG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-079	591	GFPFSNYA	770	ISSDASNK	949	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-040	592	GFSFSDYG	771	ISYDANNK	950	AKHMSMQEGAVTGLG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-070	593	GFTFGSYG	772	ISDEGSNK	951	AKHMSMQEGAVTNEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-032	594	GFTFNDYG	773	ISSDENNK	952	AKHMSMQEGAVTGEG QWAKEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-030	595	GFTFRDYG	774	ISSDENNK	953	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-038	596	GFTFGNYG	775	ISSDASHK	954	AKHMSMQEGAVTWEG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-031	597	GFTFSGYA	776	ISSDENNK	955	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-026	598	GFTFSNYA	777	ISDEGSNK	956	AKHMSMQEGAVTGAG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-054	599	GFNFNNYG	778	ISYDESNK	957	AKHMSMQEGAVTGEW QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-093	600	GFTFSDYP	779	ISSDASDK	958	AKHMSMQEGAVTGHG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-051	601	GFTFNNYP	780	ISYGGSDK	959	AKHMSMQEGAVTGEG WAAKEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-	602	GFTFSDYA	781	IPYDESNK	960	AKHMSMQEGAVTGEG

067						QAAKNFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-059	603	GFAFSNYG	782	ISDEGSNK	961	AKHMSMQEGAVTGHG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-025	604	GFTFNRYG	783	ISDEGSNK	962	AKHMSMQEGAVTGVG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-068	605	GFIFSNYA	784	ISYDASNK	963	AKHMSMQEGAVTGEY QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-053	606	GFNFNNYG	785	ISSDASNK	964	AKHMSMQEGAVTGEG QAVKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-018	607	GFTFGSYG	786	ISSDENNK	965	AKHMSMQEGAVTGEG FAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-047	608	GFTFGSYA	787	TSYDESNK	966	AKHMSMQEGAVTGYG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-060	609	GFTFSNYD	788	ISDEGSNK	967	AKHMSMQEGAVTGEG WAAKEFIAWLVKGRV RADLVGDAFDV
GLP1R-222-020	610	GFTFKNYG	789	ISYGGSNK	968	AKHMSMQEGAVTGEG PAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-044	611	GFSFSDYA	790	ISDDGSNK	969	AKHMSMQEGAVTGEG QAAKEFIAWLVKGFVR ADLVGDAFDV
GLP1R-222-080	612	GFSFSDYG	791	ISSDASDK	970	AKHMSMQEGAVTGEG QALKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-057	613	GFTFGSYG	792	ISSDENNK	971	AKHMSMQEGAVTGMG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-043	614	GFTLSNYA	793	IPYDESNK	972	AKHMSMQEGAVTGVG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-003	615	GFTFSNFA	794	ISSDASNK	973	AKHMSMQEGAVTGEG QSAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-037	616	GFTFRNFG	795	ISSDASNK	974	AKHMSMQEGAVTGIG QAAKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-091	617	GFTFGSHG	796	ISSDENNK	975	AKHMSMQEGAVTGEG QAIKEFIAWLVKGRVR ADLVGDAFDV
GLP1R-222-019	618	GFNFNNYG	797	ISDEGSNK	976	AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR PDLVGDAFDV
GLP1R-222-094	619	GFTFGSYG	798	ISYDASNK	977	AKHMSMQEGAVTGWG QAAKEFIAWLVKGRVR ADLVGDAFDV

Table 13. Variable Light Chain CDRs

Variant	SEQ ID NO	CDR1	SEQ ID NO	CDR2	SEQ ID NO	CDR3

GLP1R-3	978	SSNIADNY	1157	DNN	1169	GTWDNYLGAGV
GLP1R221-065	979	TSNIANNF	1158	DHN	1170	GTWDTSLSAGA
GLP1R221-075	980	GSNIGNND	1159	DND	1171	GTWDTSLSNYV
GLP1R221-017	981	SSNIGNTY	1160	DDY	1172	ATWDATLNTGV
GLP1R221-033	982	SSNIGNEY	1161	DNN	1173	ATWDTSLNVGV
GLP1R221-076	983	SSNIGNND	1162	ENN	1174	LTWDHSLTAYV
GLP1R221-092	984	TSNIANNF	1163	DNN	1175	GTWDTSLSVGM
GLP1R221-034	985	SSNIGNNP	1164	END	1176	ATWDRGLSTGV
GLP1R221-066	986	SSNIGNNY	1165	ENN	1177	GIWDRSLSAWV
GLP1R221-084	987	SSNIADNY	1166	ENN	1178	GTWDVSLSVGM
GLP1R221-009	988	SSNIGNQY	1167	DDH	1179	GTWDTSLSVGE
GLP1R221-072	989	SSNIGRNF	1168	DHN	1180	GTWDVTLHTGV
GLP1R221-044	990	SSNIGNND	1169	DNN	1181	GTWDTSLSGGV
GLP1R221-012	991	SSTIGNNY	1170	EDD	1182	ATWDRGLSTGV
GLP1R221-042	992	SSNIGNKY	1171	DDD	1183	GTWDTSLSVGM
GLP1R221-051	993	SSNIGNDY	1172	DNN	1184	GTWDRGPNTGV
GLP1R221-083	994	SSNIGSKD	1173	DDD	1185	GTWDRSLGGWV
GLP1R221-040	995	SSNIGDND	1174	DNN	1186	GTWDRSLNVGV
GLP1R221-052	996	SSNIGSKY	1175	DNN	1187	GTWDRGPNTGV
GLP1R221-003	997	SSNIGNNP	1176	DND	1188	ATWDHSLRVGV
GLP1R221-094	998	SSNIGNKY	1177	DNN	1189	GTWDTALTAGV
GLP1R221-001	999	SSNIGSHY	1178	DTN	1190	ATWDRGLSTGV
GLP1R221-014	1000	SSTIGNNY	1179	DND	1191	ATWDTSLNVGV
GLP1R221-085	1001	TSNIGNNH	1180	DNN	1192	GTWDRSLSSAV
GLP1R221-022	1002	SSNIGSNY	1181	DNN	1193	GTWDTSVSAGV
GLP1R221-056	1003	GSNIGNND	1182	DTN	1194	ATWDRTLSIGV
GLP1R221-088	1004	SSNIGSKY	1183	DNN	1195	GTWDTTLNIGV
GLP1R221-077	1005	SSNIGNND	1184	GDD	1196	ATWDRSLRAGV
GLP1R221-027	1006	SSNIGNDF	1185	DNN	1197	GTWDTSLSTGV
GLP1R221-019	1007	SSNIGNNF	1186	DNN	1198	GTWETSLSAGV
GLP1R221-029	1008	SSNIGNND	1187	EDN	1199	GTWVTSLSAGV
GLP1R221-043	1009	SSNIGNHD	1188	DNN	1200	GTWDRSLSGEV
GLP1R221-082	1010	SSNIGSNF	1189	DDK	1201	ATWDRGLSTGV
GLP1R221-079	1011	SSNIGDND	1190	DND	1202	ATWDRSLSAVV
GLP1R221-080	1012	SSNIGNND	1191	DDD	1203	GTWDKSLSAVV
GLP1R221-059	1013	SSNIGDND	1192	ENN	1204	GTWDTSLSGGV
GLP1R221-069	1014	SSNIGKNF	1193	DNN	1205	GTWDVTLHTGV
GLP1R221-036	1015	SSNIGNEY	1194	ENK	1206	GTWDASLSAGL
GLP1R221-057	1016	SSNIGSKY	1195	DNN	1207	GTWESSLSAGV
GLP1R221-035	1017	SSDIGNKY	1196	ENN	1208	ATWDASLSGGV

GLP1R221-063	1018	SSNIGNNF	1197	ENN	1209	ATWDATLNTGV
GLP1R221-090	1019	SSNIGSNY	1198	DTD	1210	GTWDVSLNTQV
GLP1R221-002	1020	SSNIGNKY	1199	DTN	1211	ATWDATLNTGV
GLP1R221-087	1021	SSNIGKDY	1200	ENV	1212	GTWDASLSGVV
GLP1R221-038	1022	TSNIGNND	1201	DNN	1213	GTWDVTLHTGV
GLP1R221-060	1023	GSNIGNND	1202	ETN	1214	GTWDTGLSAGV
GLP1R221-015	1024	TSNIGNNY	1203	DTN	1215	ATWDATLNTGV
GLP1R221-020	1025	SSNIGRNF	1204	DNN	1216	GTWDTSLSRYV
GLP1R221-011	1026	SSNIGKDY	1205	DNY	1217	GTWDTSLSVGV
GLP1R221-091	1027	SSNIGSND	1206	VND	1218	GAWDRSLSAYV
GLP1R221-086	1028	SSNIGKHY	1207	DVD	1219	ATWDRGLSTGV
GLP1R221-074	1029	SSNIGSNY	1208	DNN	1220	GTWDTRLSVGV
GLP1R221-032	1030	SSNIGNNY	1209	DNN	1221	ATWDRSLRAGV
GLP1R221-013	1031	SSNIGNKY	1210	DDD	1222	ATWDTSLNVGV
GLP1R221-058	1032	SSNIGKYY	1211	DNN	1223	GTWDTSLATGL
GLP1R221-031	1033	SSNIGSNL	1212	DNN	1224	GTWDTSLSAGA
GLP1R221-054	1034	RSNIGNYY	1213	DHN	1225	ATWDRTLSIGV
GLP1R221-021	1035	SSNIGNNF	1214	DNN	1226	GAWDRSLSAGV
GLP1R221-016	1036	SSNIGNKY	1215	DND	1227	ATWDATLNTGV
GLP1R221-030	1037	SSNIENND	1216	ENN	1228	GTWDRSLSAAL
GLP1R221-018	1038	SSNIGSNH	1217	ENT	1229	ATWDATLNTGV
GLP1R221-028	1039	SSTIGNNY	1218	DND	1230	GTWDKSLSAGV
GLP1R221-023	1040	SSNIGSKD	1219	DTN	1231	ATWDRGLSTGV
GLP1R221-089	1041	SSNIGKDF	1220	DND	1232	ATWDTSLSAEV
GLP1R221-053	1042	SSNIGKDY	1221	EDN	1233	ATWDRTLSIGV
GLP1R221-071	1043	SSNIGSNY	1222	DDN	1234	GTWGSSLSAGL
GLP1R221-055	1044	SSNIGSND	1223	DKN	1235	GAWDRSLSAGV
GLP1R221-046	1045	SSNIGNND	1224	DDD	1236	AAWDDYLSAVV
GLP1R221-039	1046	SSNIGNHF	1225	DNN	1237	GTWDRSLNVGV
GLP1R221-078	1047	SSNIGNNP	1226	ENI	1238	ATWDRSLRAGV
GLP1R221-010	1048	SSTIGNNY	1227	DNN	1239	GTWDASLSVWV
GLP1R221-005	1049	SSTIGNNY	1228	ENR	1240	GTWDNYLGAGV
GLP1R221-073	1050	SSNIGSNH	1229	END	1241	GTWDTSLSAYI
GLP1R221-041	1051	SSNIGSKY	1230	NDN	1242	GTWDTSLSVGM
GLP1R221-025	1052	SSNIGKYY	1231	DNY	1243	ATWDRGLSTGV
GLP1R221-007	1053	SSNIGNND	1232	ENT	1244	GTWDANLRAGV
GLP1R221-093	1054	SSNIENNH	1233	END	1245	ATWDTSLSEGV
GLP1R221-024	1055	SSNIGKYY	1234	DTN	1246	ATWDRGLSTGV
GLP1R221-008	1056	SSSIGNNY	1235	ANN	1247	GTWDISLSAAV
GLP1R221-050	1057	SSNIGNNF	1236	DKN	1248	ATWDTRLSAVV

GLP1R221-062	1058	SSNIGNNY	1237	ENN	1249	GTWDASLGAWV
GLP1R221-068	1059	SSNIGSND	1238	NNN	1250	GTWDARLGGAV
GLP1R221-067	1060	SSNIGNNY	1239	ANN	1251	GTWDARLGGAV
GLP1R221-061	1061	SSNIGTNF	1240	DNN	1252	GTWDNRLSGWV
GLP1R221-064	1062	SSNIGKDY	1241	ENT	1253	ATWDATLNTGV
GLP1R221-070	1063	SSNIENNH	1242	QNN	1254	GTWDVSLNTQV
GLP1R221-006	1064	SSNIGNNH	1243	GSN	1255	GTWDTSLNIGV
GLP1R221-045	1065	SSNIGNND	1244	GNN	1256	GTWDTSLSGGI
GLP1R221-004	1066	SSTIGNNY	1245	DND	1257	GTWESSLSAGV
GLP1R221-047	1067	SSNIGNEY	1246	GDD	1258	GTWDTSLSVGM
GLP1R221-048	1068	SSNIGNHD	1247	AND	1259	GTWDTSLSVGE
GLP1R-222-052	1069	SSNIGKRS	1248	DNN	1260	VTWDRSLSAGV
GLP1R-222-016	1070	SSNIENND	1249	DFN	1261	GTWDTSLSVGM
GLP1R-222-023	1071	SSNIGNND	1250	ENT	1262	GTWDAGLSTGV
GLP1R-222-014	1072	SSNIGNHD	1251	DNN	1263	GTWDTSLSAGV
GLP1R-222-090	1073	SSNIADNY	1252	DNN	1264	ATWDNRLSAGV
GLP1R-222-073	1074	GSNIGNND	1253	DNN	1265	GTWDRGPNTGV
GLP1R-222-012	1075	SSNIGNND	1254	DDD	1266	GTWDTSLSVGE
GLP1R-222-082	1076	SSNIGSKY	1255	DNN	1267	GTWDISPSAWV
GLP1R-222-081	1077	SSNIGSDY	1256	DNN	1268	GTWDESLRSWV
GLP1R-222-056	1078	SSNIGSNY	1257	DND	1269	GTWDTSLSVGE
GLP1R-222-058	1079	SSNIGNNP	1258	DNN	1270	ATWDNKLTSGV
GLP1R-222-063	1080	SSNIGNYY	1259	DNN	1271	ATWDTSLNVGV
GLP1R-222-042	1081	SSNIGNND	1260	DDN	1272	GTWDTSLSAYI
GLP1R-222-092	1082	SSNIGSDY	1261	ENN	1273	GTWDRGPNTGV
GLP1R-222-007	1083	SSDIGNKY	1262	ENN	1274	GTWDTSLSAGA
GLP1R-222-008	1084	SSNIGSNH	1263	DNN	1275	GTWDTSLSVGE
GLP1R-222-024	1085	TSNIGSNF	1264	DEN	1276	ATWDATLNTGV
GLP1R-222-062	1086	SSNIENND	1265	DNN	1277	GTWDRSLNVGV
GLP1R-222-077	1087	SSSIGNNY	1266	ENN	1278	GTWDNNLGAGV
GLP1R-222-064	1088	SSNIGSKY	1267	DDN	1279	GTWDTSLSTGV
GLP1R-222-074	1089	SSNIGNND	1268	DNN	1280	GTWDRGPNTGV
GLP1R-222-029	1090	SSNIGNNY	1269	END	1281	GTWDTSLATGL
GLP1R-222-046	1091	TSNIGNNY	1270	ENT	1282	GTWDTTLSAGV
GLP1R-222-005	1092	SSNIGNDY	1271	DNN	1283	GTWDASLSAGL
GLP1R-222-004	1093	SSNIGNDY	1272	ENN	1284	GTWDASLSAGL
GLP1R-222-022	1094	SSNIGNND	1273	DND	1285	GTWDRTLSIGV
GLP1R-222-087	1095	SSNIENND	1274	DNN	1286	GTWDRRLSDVV
GLP1R-222-048	1096	RSNIGNNF	1275	DNN	1287	GTWDRSLSSAV
GLP1R-222-072	1097	SSSIGNNY	1276	DTN	1288	GTWDRSLNVGV

GLP1R-222-089	1098	SSNIGNND	1277	DTN	1289	GTWDISLSARV
GLP1R-222-083	1099	SSNIGSKY	1278	DND	1290	ATWDTSLSAGV
GLP1R-222-001	1100	SSNIGSKY	1279	DNN	1291	GTWDTSLATGL
GLP1R-222-075	1101	SSNIGSKD	1280	DTY	1292	GTWDTSVSAGV
GLP1R-222-071	1102	TSNIGNNY	1281	DDN	1293	GTWDRSLNVGV
GLP1R-222-069	1103	SSNIGSHY	1282	DNN	1294	GTWHSSLSAGV
GLP1R-222-002	1104	SSDIGNKY	1283	DND	1295	GTWDTTLSAGV
GLP1R-222-006	1105	SSNIGNND	1284	DNN	1296	GAWDTSLSAVV
GLP1R-222-055	1106	TSNIGNNY	1285	DNN	1297	GTWDTSLSVGE
GLP1R-222-027	1107	TSNIGNNH	1286	EDN	1298	GTWDTSLATGL
GLP1R-222-066	1108	SSTIGNNY	1287	DNN	1299	ATWDRGLSTGV
GLP1R-222-015	1109	RSNIGNYY	1288	DND	1300	GTWDRSLSVGL
GLP1R-222-076	1110	SSNIGSKY	1289	DTY	1301	GTWDAGLSTGV
GLP1R-222-011	1111	SSNIGSNY	1290	ENN	1302	GTWDTSLSVGE
GLP1R-222-065	1112	SSTIGNNY	1291	DNN	1303	ATWDRTLSIGV
GLP1R-222-041	1113	SSNIGSKD	1292	DDN	1304	GIWDRSLSAWV
GLP1R-222-028	1114	TSNIGNNH	1293	DNN	1305	GTWDTSLATGL
GLP1R-222-086	1115	SSNIGNHF	1294	DTN	1306	GTWDRGPNTGV
GLP1R-222-033	1116	SSNIGKYY	1295	DNN	1307	GTWDVSLSVGM
GLP1R-222-035	1117	SSNIGNND	1296	ENN	1308	GTWDVSLSVGM
GLP1R-222-045	1118	SSNIGNTY	1297	ENR	1309	ATWDTSLSEGV
GLP1R-222-085	1119	SSNIGSDY	1298	ANN	1310	GTWDVTLHAGV
GLP1R-222-049	1120	TSNIGKNF	1299	ENK	1311	ATWDRSLSAGV
GLP1R-222-078	1121	SSNIGKYY	1300	DTN	1312	GTWDNNLGAGV
GLP1R-222-021	1122	SSNIGDND	1301	ENR	1313	GTWDASLSAGL
GLP1R-222-009	1123	SSNIGKNF	1302	DTN	1314	GTWDTSLSVGE
GLP1R-222-036	1124	SSNIGSKY	1303	DNN	1315	ATWDDTLTAGV
GLP1R-222-084	1125	SSNIGSKD	1304	DNN	1316	GIWDTSLSAWV
GLP1R-222-010	1126	SSNIGNKY	1305	DNN	1317	GTWDNRLSAGV
GLP1R-222-088	1127	SSNIGNNF	1306	DND	1318	GTWDTSLRVVV
GLP1R-222-079	1128	SSNIGSND	1307	NNN	1319	GTWESGLSAGV
GLP1R-222-040	1129	SSNIGNQY	1308	DTY	1320	ATWDHSLRVGV
GLP1R-222-070	1130	SSNIGNND	1309	ANN	1321	GTWHSSLSAGV
GLP1R-222-032	1131	SSNIGNNP	1310	END	1322	GTWDTRLSVGV
GLP1R-222-030	1132	SSNIGNNL	1311	DND	1323	GTWDTSLTAGV
GLP1R-222-038	1133	SSNIGNKY	1312	DTN	1324	ATWDATLNTGV
GLP1R-222-031	1134	SSNIGNNY	1313	DDN	1325	GTWDTSLSVGM
GLP1R-222-026	1135	SSNIGSKY	1314	DNN	1326	GTWDRGPNTGV
GLP1R-222-054	1136	SSNIGSKY	1315	DDY	1327	GTWDNRLSGWV
GLP1R-222-093	1137	RSNIGNNF	1316	DNY	1328	ATWDRGLSTGV

GLP1R-222-051	1138	RSNIGNNF	1317	DNN	1329	ATWDRSLSAGV
GLP1R-222-067	1139	RSNIGNNF	1318	DNN	1330	GTWDRRLSAVV
GLP1R-222-059	1140	SSNIGNEY	1319	ENN	1331	GTWDNYLGAVV
GLP1R-222-025	1141	SSNIGNEY	1320	DND	1332	ATWDATLNTGV
GLP1R-222-068	1142	RSNIGNNF	1321	ENN	1333	GSWDRSLSAVV
GLP1R-222-053	1143	SSNIGNND	1322	ASN	1334	ATWDNILSAWV
GLP1R-222-018	1144	SSNIGKNF	1323	ETN	1335	ATWDRGLSTGV
GLP1R-222-047	1145	SSNIGTNF	1157	ADN	1336	GTWDRTLSIGV
GLP1R-222-060	1146	SSNIGNNP	1158	GNN	1337	GTWDASLGAVV
GLP1R-222-020	1147	SSNIGNND	1159	DND	1338	GTWDAGLSTGV
GLP1R-222-044	1148	SSNIGNNH	1160	DFN	1339	ATWDRSLRAGV
GLP1R-222-080	1149	SSNIGNHD	1161	ENK	1340	GTWESGLSAGV
GLP1R-222-057	1150	SSNIGDHY	1162	ENN	1341	ATWDNKLTSGV
GLP1R-222-043	1151	SSNIGNNY	1163	DNN	1342	ATWDRSLRAGV
GLP1R-222-003	1152	SSNIGNHD	1164	ENN	1343	GTWDTSLSAGV
GLP1R-222-037	1153	SSNIGNNP	1165	NNN	1344	ATWDTTLNTGV
GLP1R-222-091	1154	SSNIGSNY	1166	GND	1345	ASWDNRLTAVV
GLP1R-222-019	1155	SSNIGNNY	1167	DNN	1346	ATWDRGLSTGV
GLP1R-222-094	1156	SSNIGNTY	1168	ENK	1347	ATWDTSLSEGV

[00283] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. An antibody or antibody fragment comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347.

2. The antibody or antibody fragment of claim 1, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof.

3. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment thereof is chimeric or humanized.

4. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP assay.

5. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay.

6. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay.

7. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment is an agonist of GLP1R.

8. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment is an antagonist of GLP1R.

9. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R.

10. The antibody or antibody fragment of claim 9, wherein the allosteric modulator of GLP1R is a negative allosteric modulator.

11. The antibody or antibody fragment of claim 1, wherein the VH comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 58-77.

12. The antibody or antibody fragment of claim 1, wherein the VH comprises a sequence of any one of SEQ ID NOs: 58-77.

13. The antibody or antibody fragment of claim 1, wherein the VL comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 92-111.

14. The antibody or antibody fragment of claim 1, wherein the VL comprises a sequence of any one of SEQ ID NOs: 92-111.

15. A method of treating a metabolic disease or disorder comprising administering an antibody or antibody fragment that binds GLP1R comprising a variable domain, heavy chain region (VH) and a variable domain, light chain region (VL), wherein VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977; (d) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (e) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347.

16. The method of claim 15, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof.

17. The method of claim 15, wherein the antibody or antibody fragment thereof is chimeric or humanized.

18. The method of claim 15, wherein the antibody or antibody fragment has an EC50 less than about 25 nanomolar in a cAMP assay.

19. The method of claim 15, wherein the antibody or antibody fragment has an EC50 less than about 20 nanomolar in a cAMP assay.

20. The method of claim 15, wherein the antibody or antibody fragment has an EC50 less than about 10 nanomolar in a cAMP assay.

21. The method of claim 15, wherein the antibody or antibody fragment is an agonist of GLP1R.

22. The method of claim 15, wherein the antibody or antibody fragment is an antagonist of GLP1R.

23. The method of claim 15, wherein the antibody or antibody fragment is an allosteric modulator of GLP1R.

24. The method of claim 23, wherein the allosteric modulator of GLP1R is a negative allosteric modulator.

25. The method of claim 15, wherein the antibody or antibody fragment is an allosteric modulator.

26. The method of claim 15, wherein the antibody or antibody fragment is a negative allosteric modulator.

27. The method of claim 15, wherein the VH comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 58-77.

28. The method of claim 15, wherein the VH comprises a sequence of any one of SEQ ID NOs: 58-77.

29. The method of claim 15, wherein the VL comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 92-111.

30. The method of claim 15, wherein the VL comprises a sequence of any one of SEQ ID NOs: 92-111.

31. The method of claim 15, wherein the metabolic disease or disorder is Type II diabetes or obesity.

32. A nucleic acid composition comprising:

a) a first nucleic acid encoding a variable domain, heavy chain region (VH) comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein (i) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 441-619; (ii) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 620-798; (iii) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 799-977;

b) a second nucleic acid encoding a variable domain, light chain region (VL) comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (i) an amino acid

sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 978-1156; (ii) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 1157-1168; and (iii) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1169-1347.

33. A nucleic acid composition comprising: a) a first nucleic acid encoding a variable domain, heavy chain region (VH) comprising an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 58-77; b) a second nucleic acid encoding a variable domain, light chain region (VL) comprising at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 92-111; and an excipient.

34. The nucleic acid composition of claim 33, wherein the VH comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 58-77.

35. The nucleic acid composition of claim 33, wherein the VL comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 92-111.

36. The nucleic acid composition of claim 33, wherein the VH comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 58-77, and wherein the VL comprises an amino acid sequence as set forth in any one of SEQ ID NOs: 92-111.

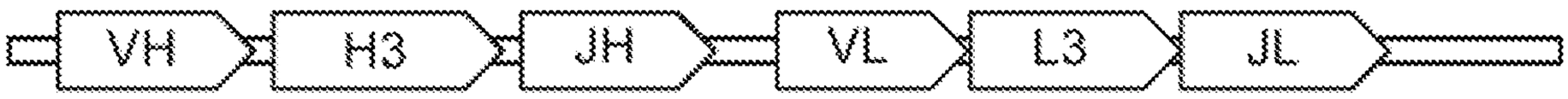


FIG. 1A

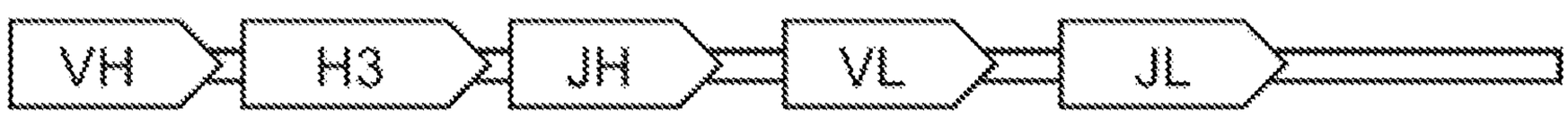


FIG. 1B

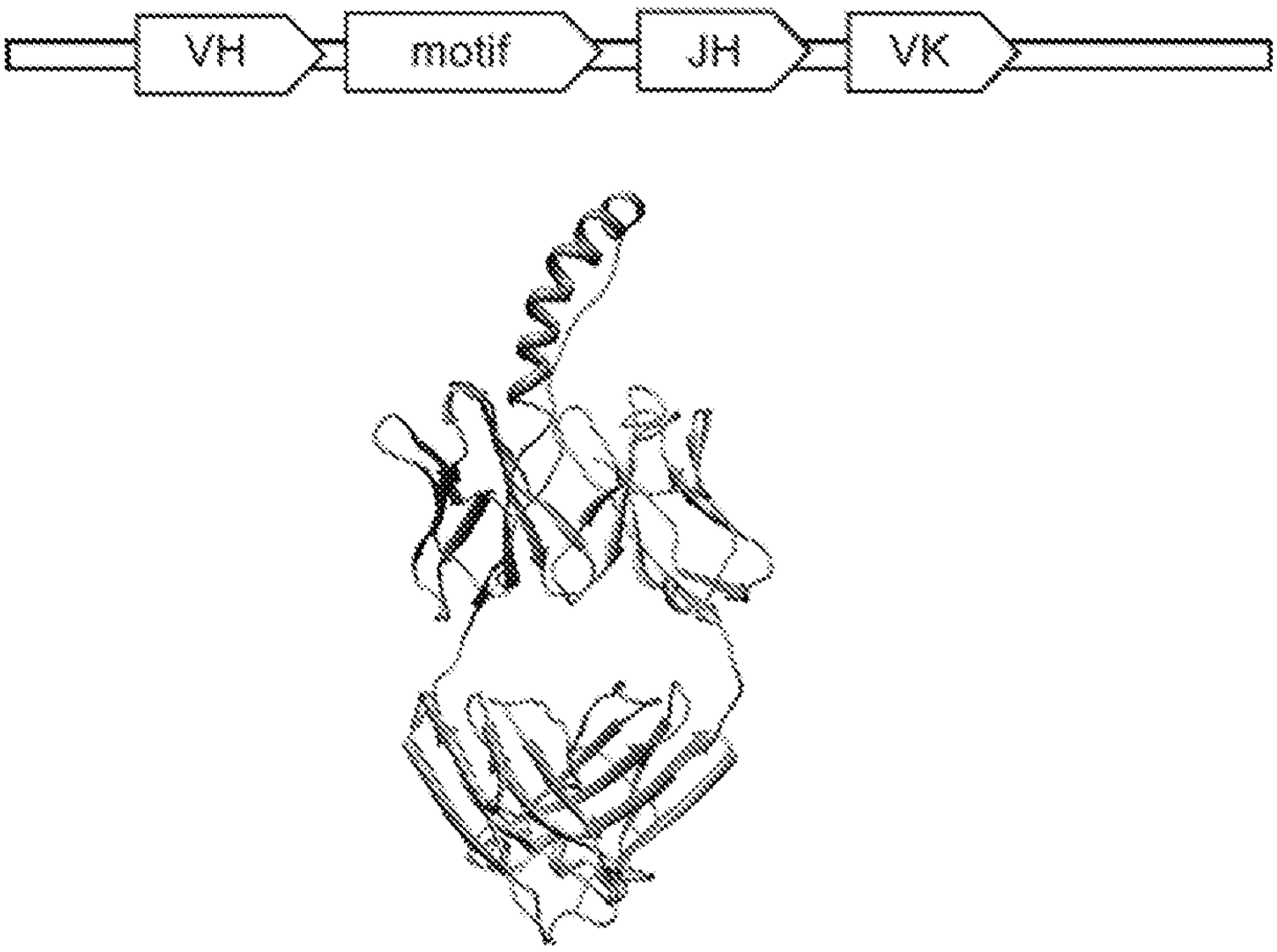


FIG. 2

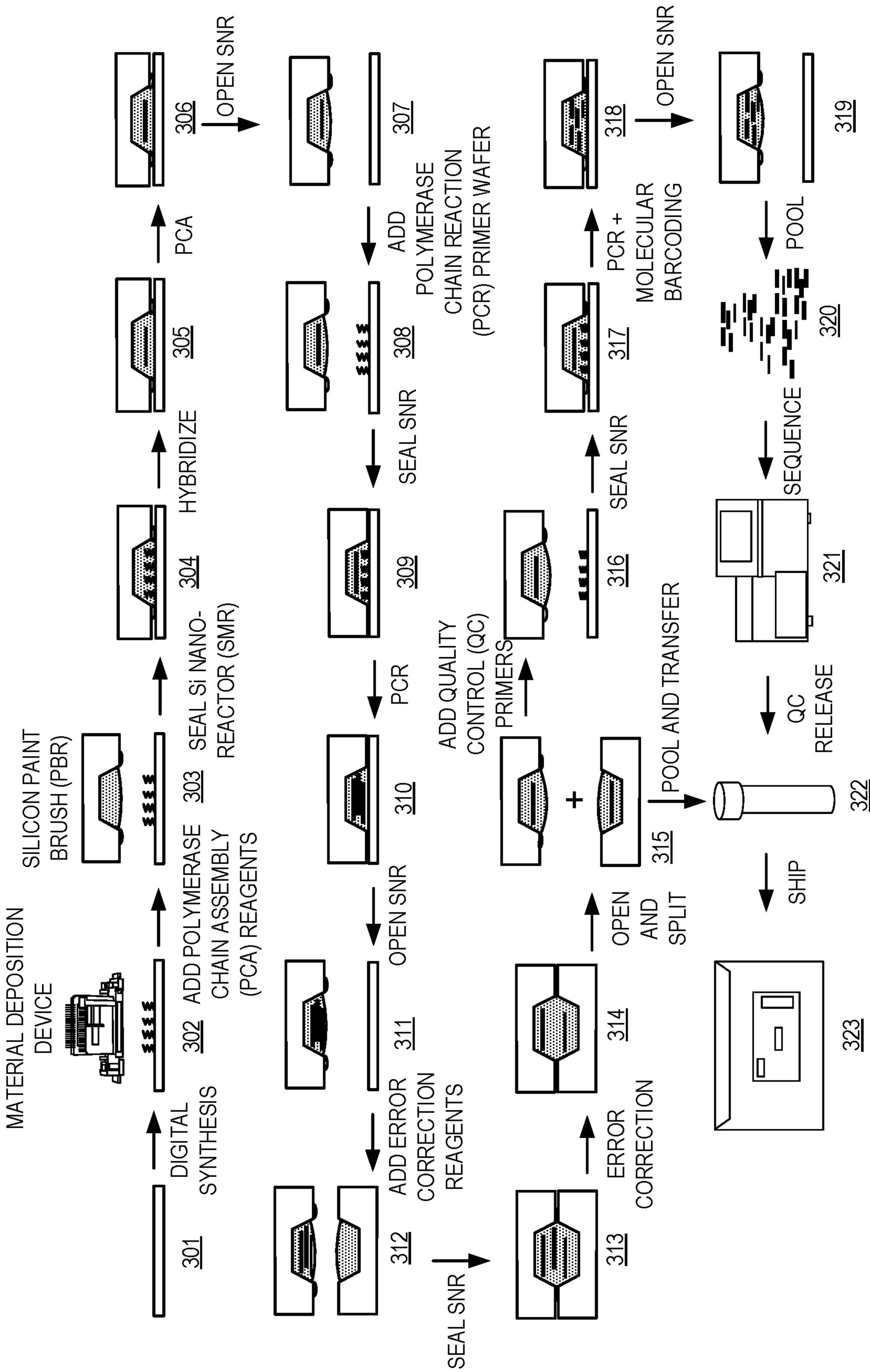

MATERIAL DEPOSITION DEVICE
SILICON PAINT BRUSH (PBR)
DIGITAL SYNTHESIS
302
ADD POLYMERASE CHAIN ASSEMBLY (PCA) REAGENTS
303
SEAL Si NANO-REACTOR (SMR)
304
HYBRIDIZE
305
PCA
306
OPEN SNR
307
ADD POLYMERASE CHAIN REACTION (PCR) PRIMER WAFER
308
SEAL SNR
309
PCR
310
OPEN SNR
311
ADD ERROR CORRECTION REAGENTS
312
SEAL SNR
313
ERROR CORRECTION
314
OPEN AND SPLIT
315
ADD QUALITY CONTROL (QC) PRIMERS
316
SEAL SNR
317
PCR + MOLECULAR BARCODING
318
OPEN SNR
319
POOL
320
SEQUENCE
321
POOL AND TRANSFER
322
QC RELEASE
323
SHIP

FIG. 3

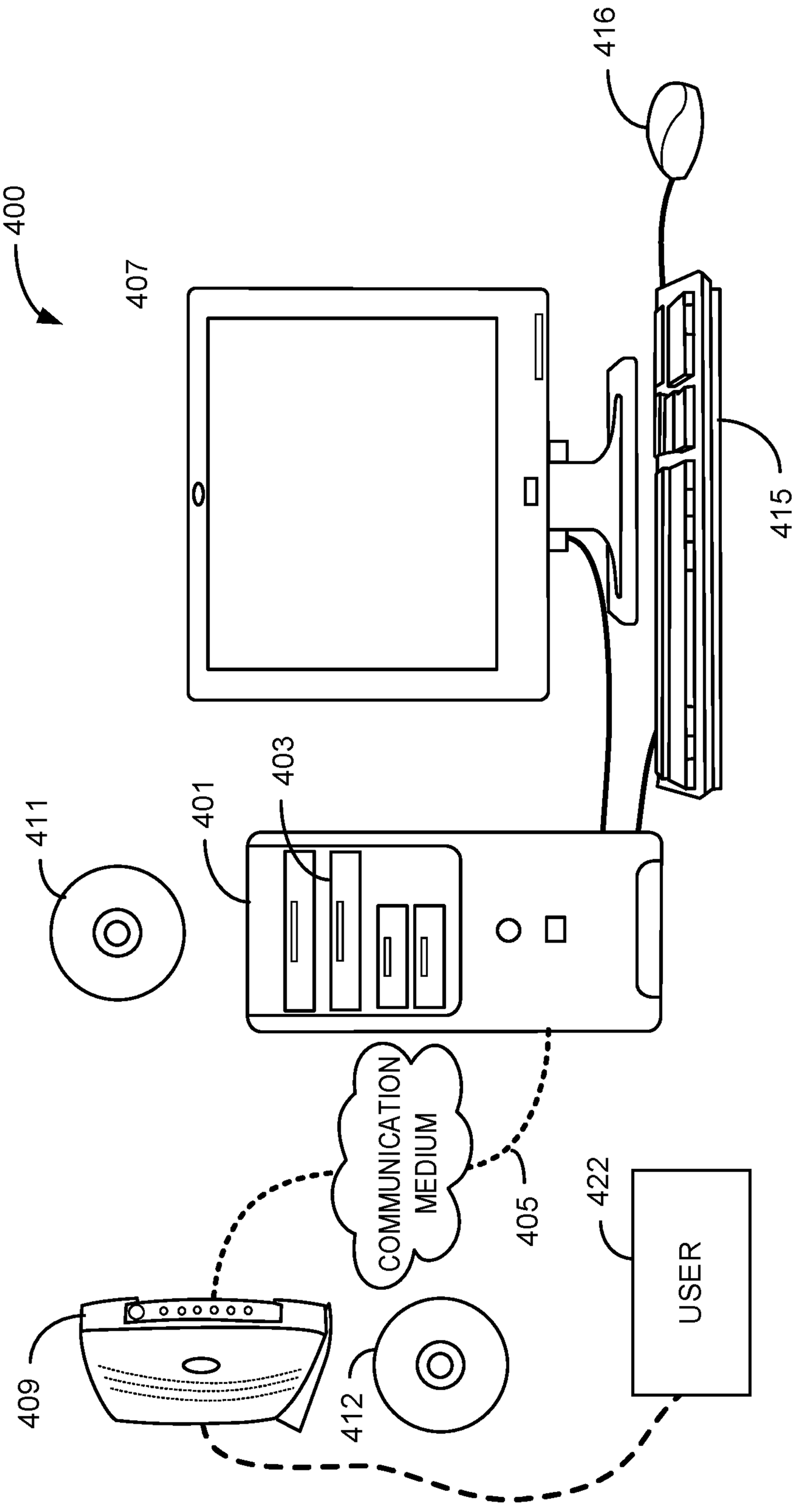

400
407
416
415
411
401
403
409
412
COMMUNICATION MEDIUM
405
422
USER

FIG. 4

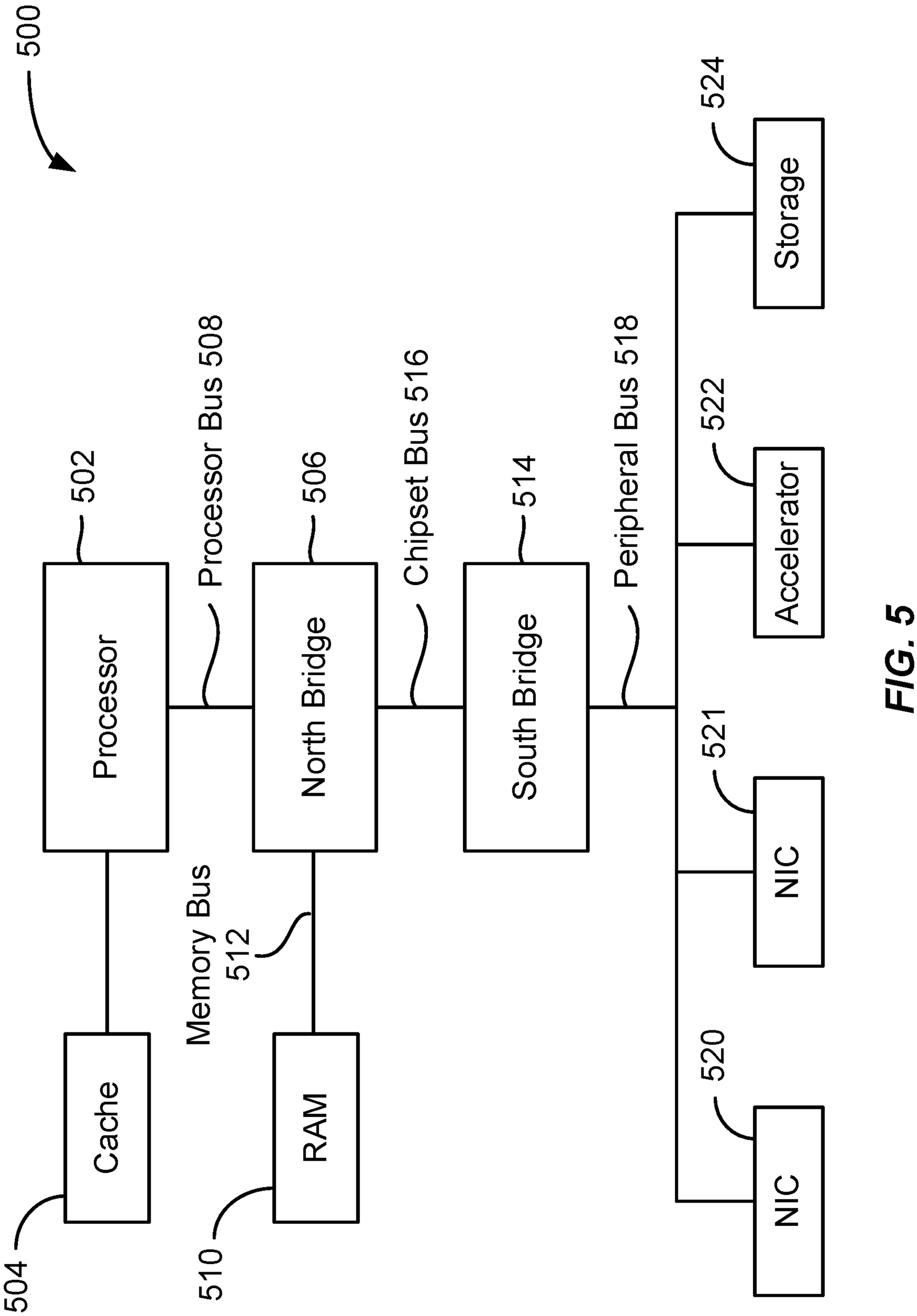

500
502
Processor
Processor Bus 508
506
North Bridge
Chipset Bus 516
514
South Bridge
Peripheral Bus 518
522
Accelerator
524
Storage
521
NIC
520
NIC
Memory Bus
512
504
Cache
510
RAM

FIG. 5

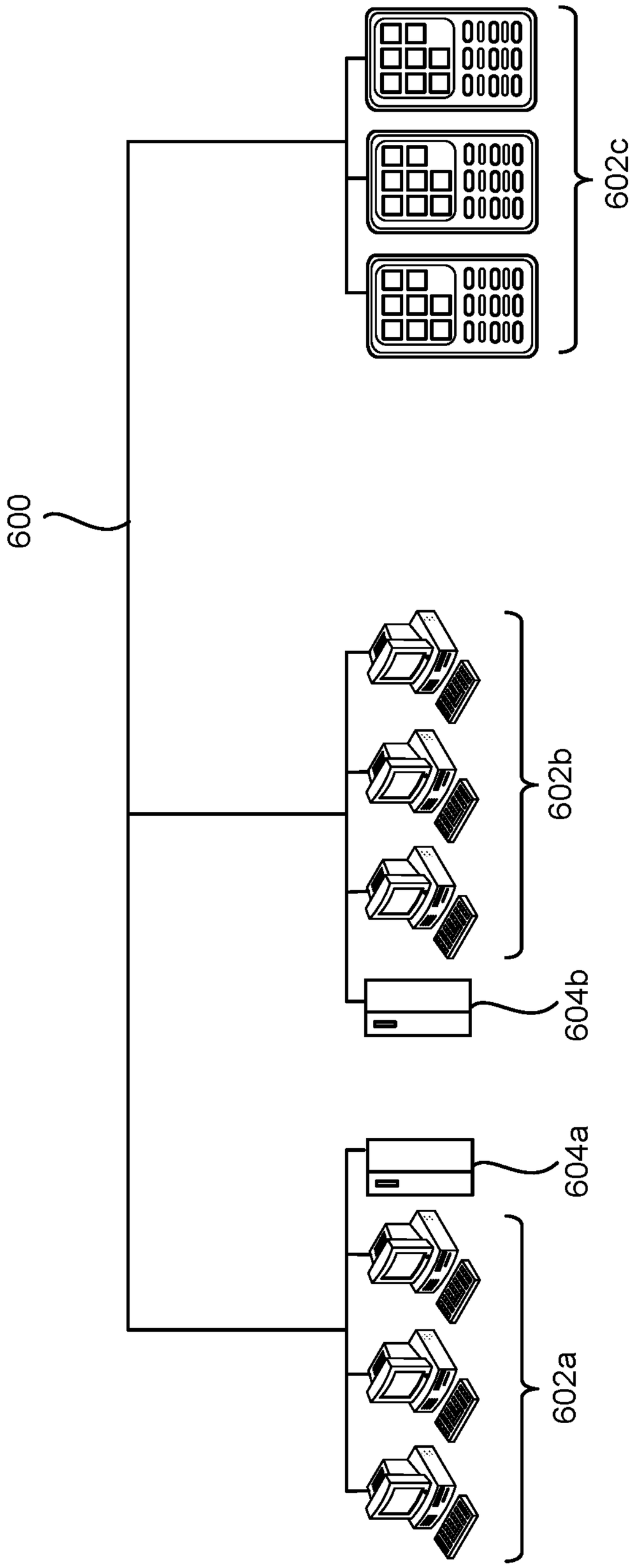


FIG. 6

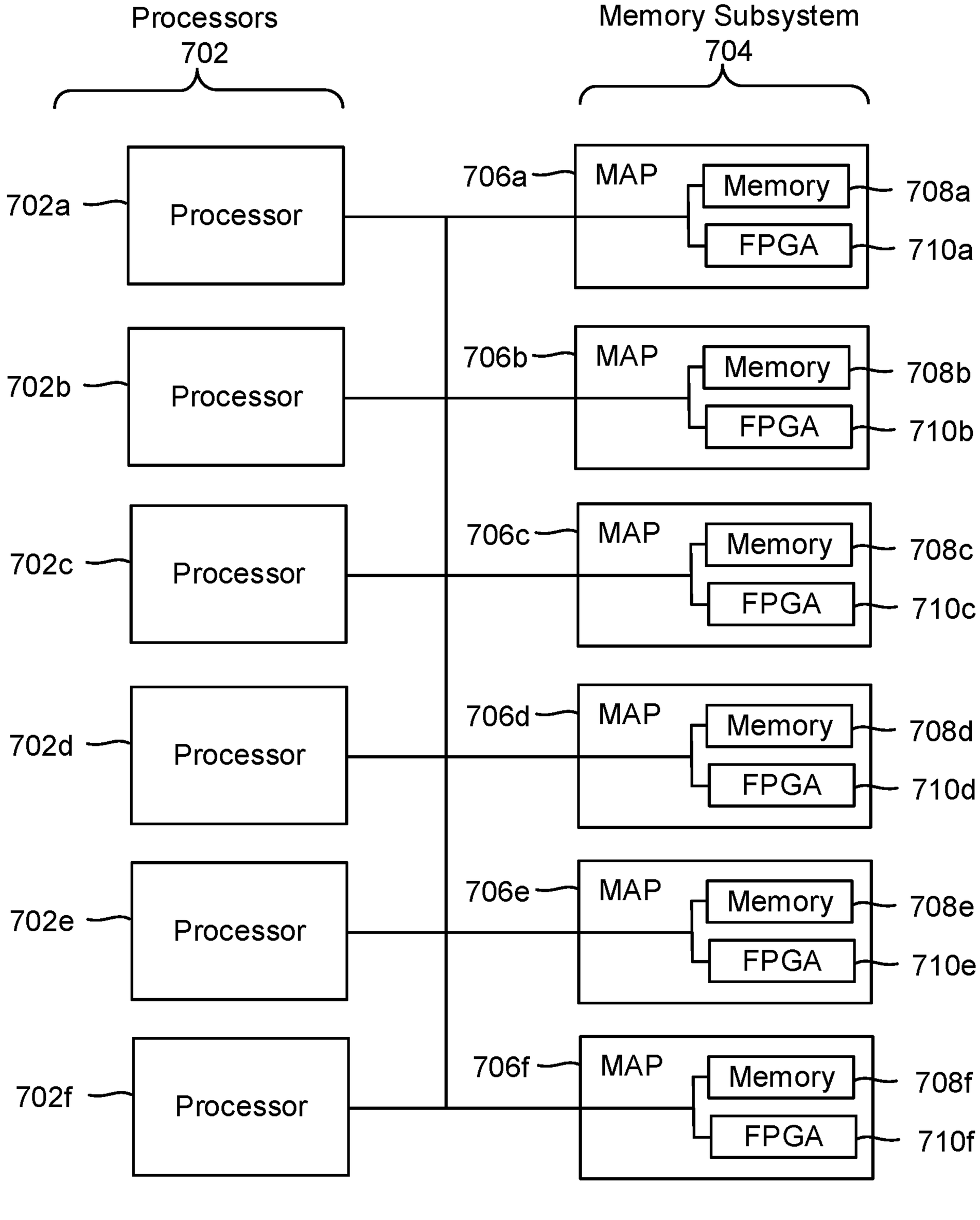

Processors
702
Memory Subsystem
704
702a
Processor
706a
MAP
Memory
708a
FPGA
710a
702b
Processor
706b
MAP
Memory
708b
FPGA
710b
702c
Processor
706c
MAP
Memory
708c
FPGA
710c
702d
Processor
706d
MAP
Memory
708d
FPGA
710d
702e
Processor
706e
MAP
Memory
708e
FPGA
710e
702f
Processor
706f
MAP
Memory
708f
FPGA
710f

FIG. 7



FIG. 8A



FIG. 8B

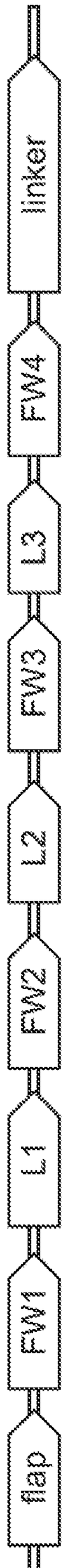
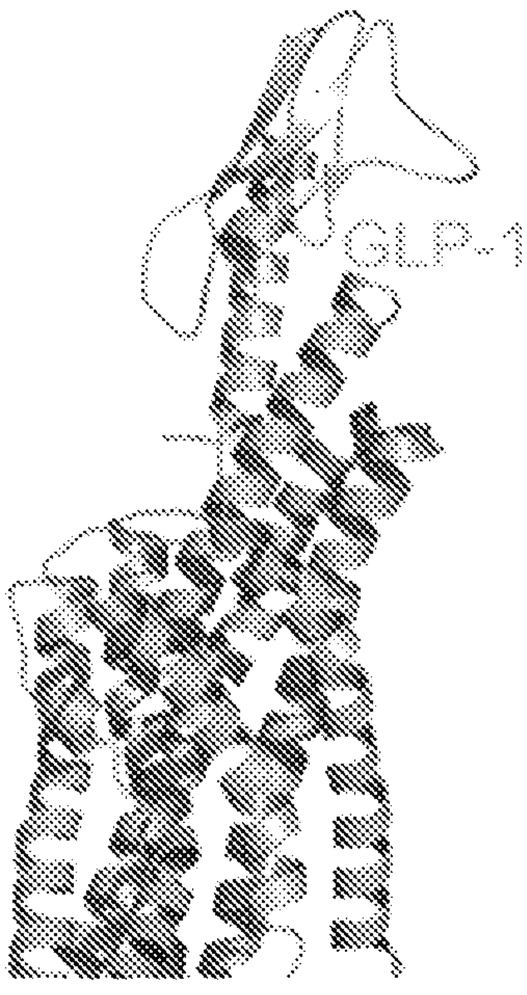


FIG. 8C



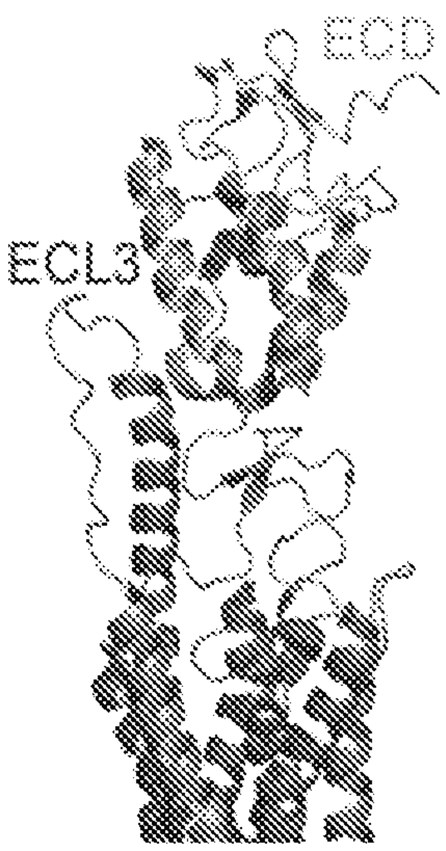
Helical Peptide

FIG. 9A



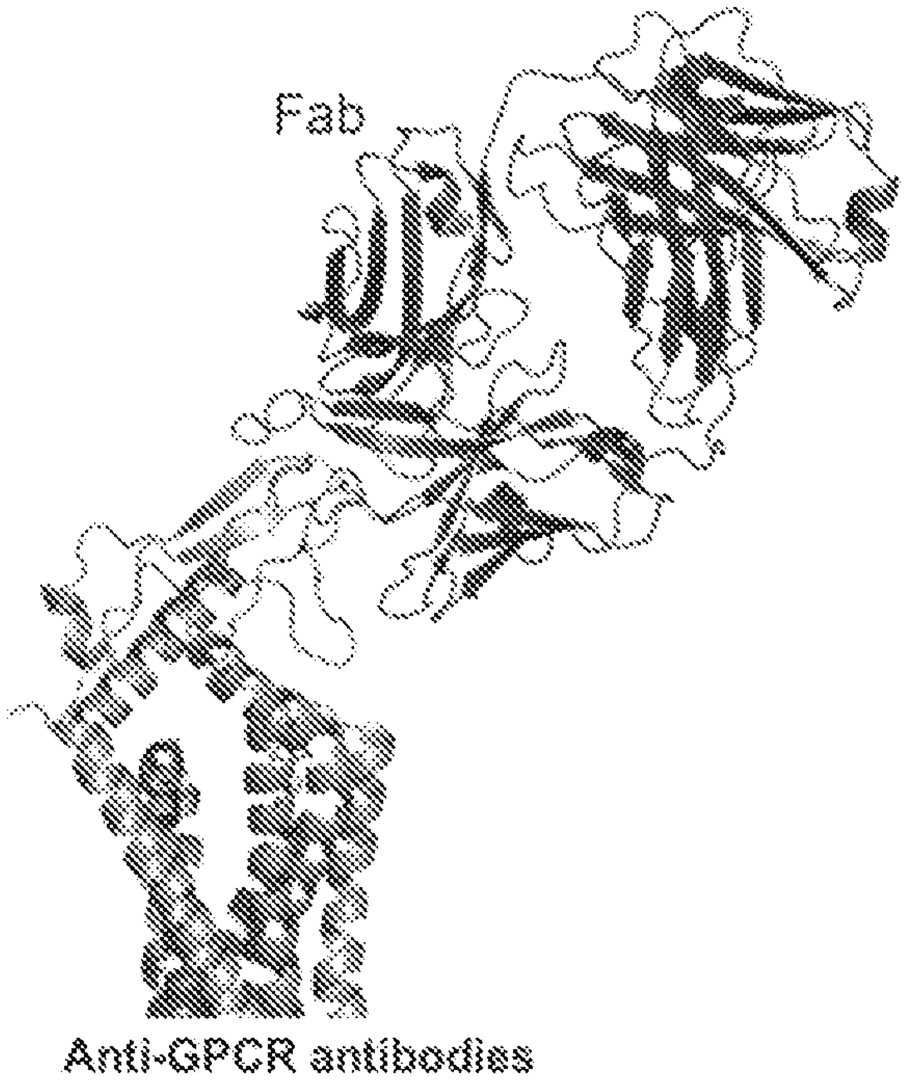
Looped Peptide

FIG. 9B



ECL and ECD

FIG. 9C



Anti-GPCR antibodies

FIG. 9D

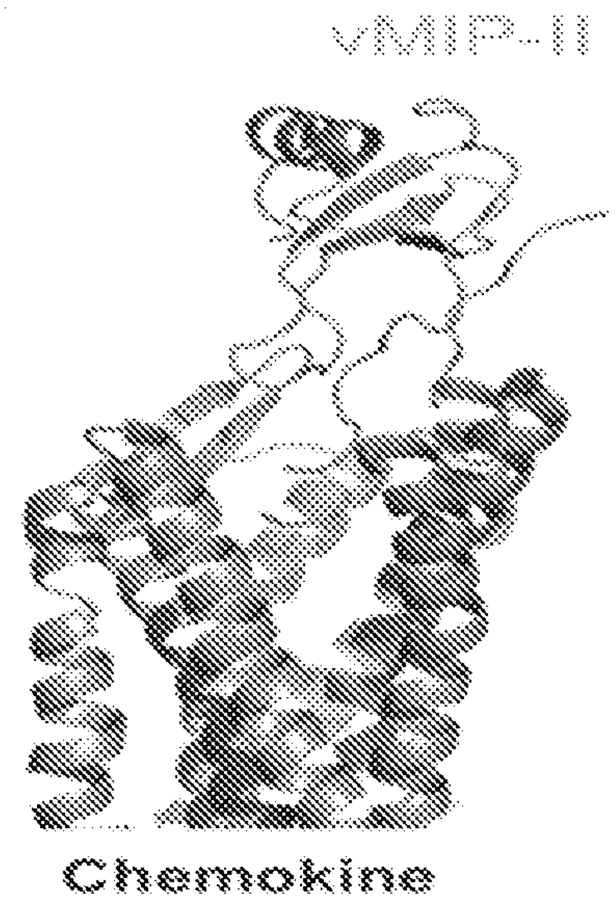


FIG. 9E

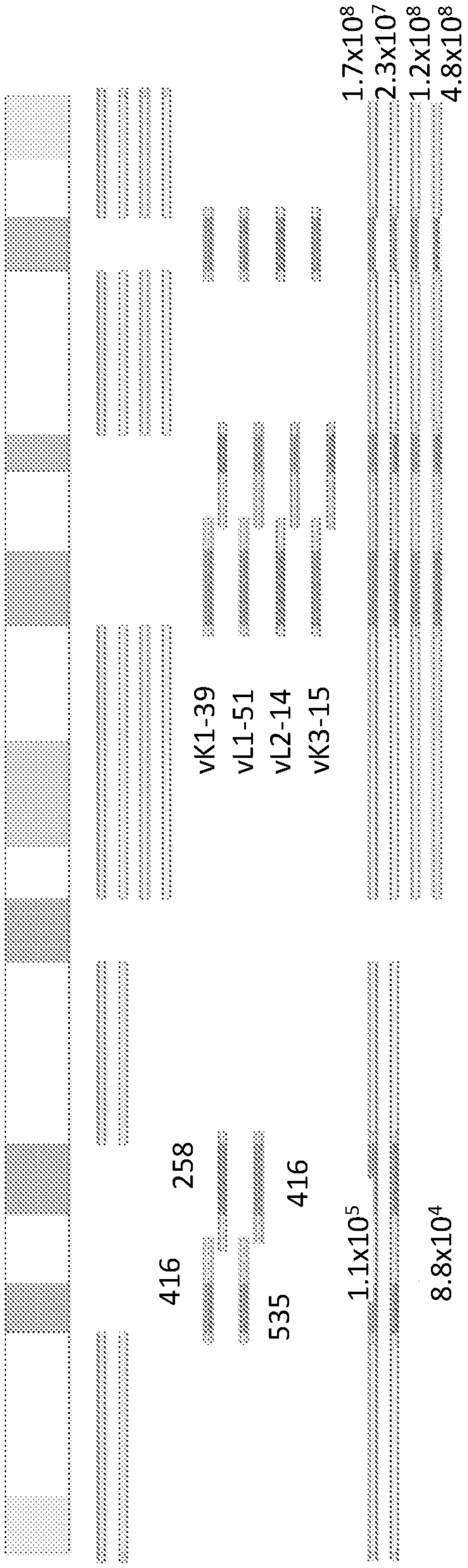

HCDR1
HCDR2
HCDR3
LCDR1
LCDR2
LCDR3
vK1-39
vL1-51
vL2-14
vK3-15
vH1-69
vH3-30
416
258
535
416
1.1x10^5
8.8x10^4
2x10^5
7.9x10^8
1.7x10^8
2.3x10^7
1.2x10^8
4.8x10^8
3819
3637
3819
3481
3819
3637
3559
3637
3637
3637
155,927

FIG. 10

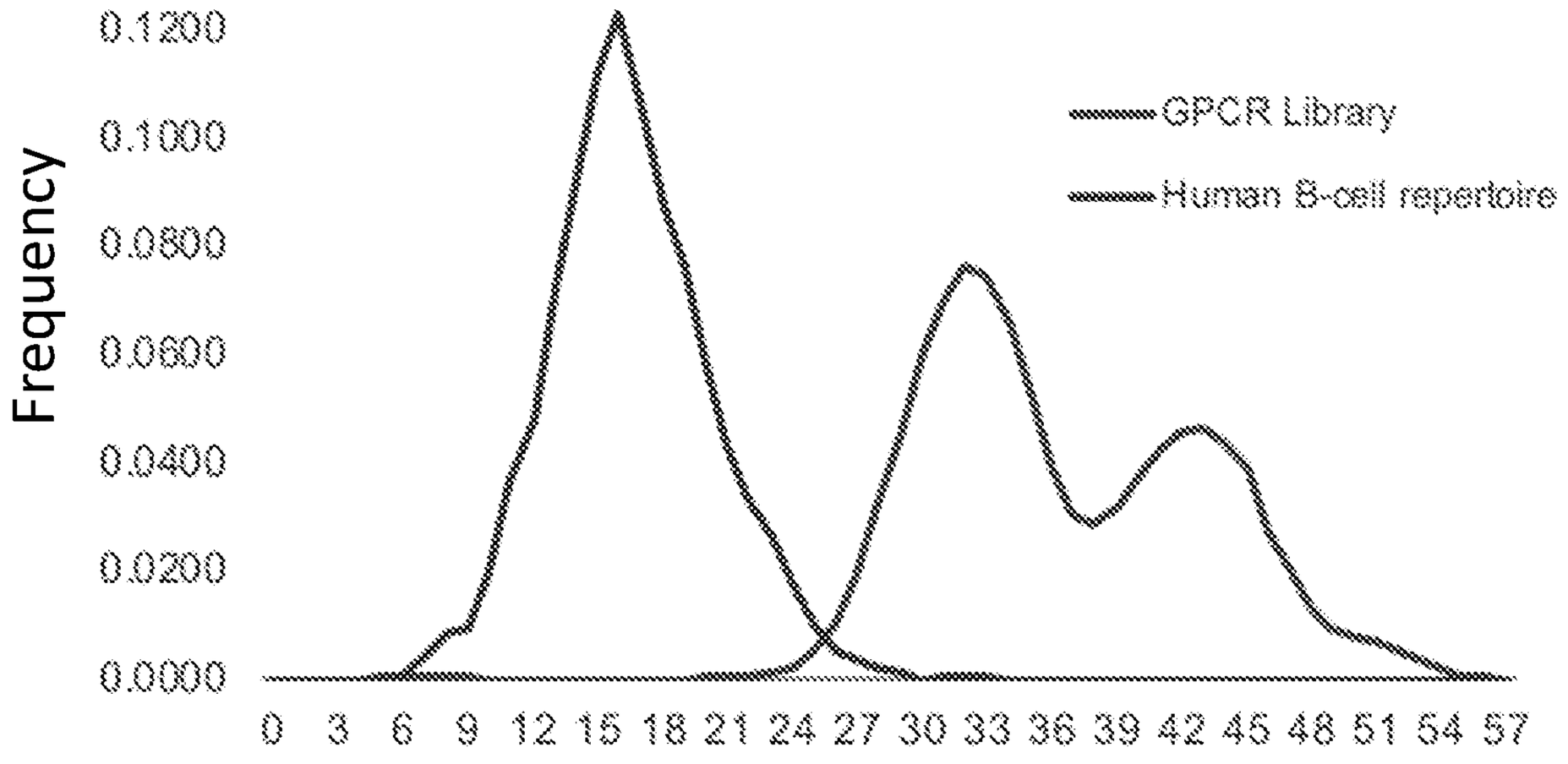


FIG. 11

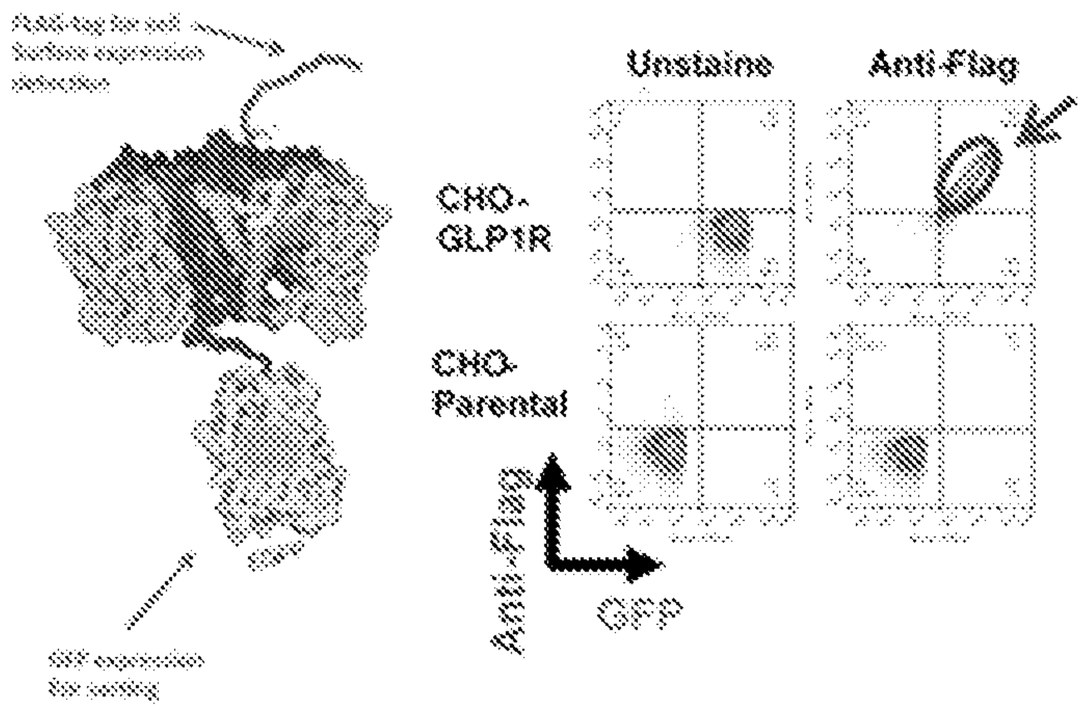


FIG. 12A

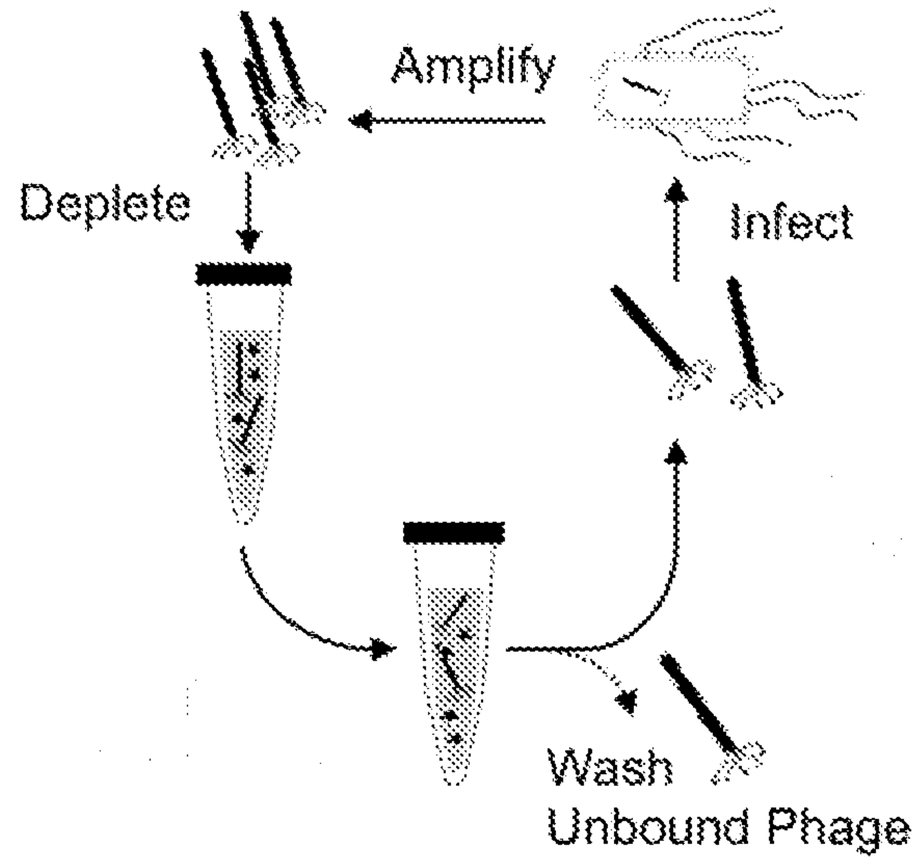


FIG. 12B

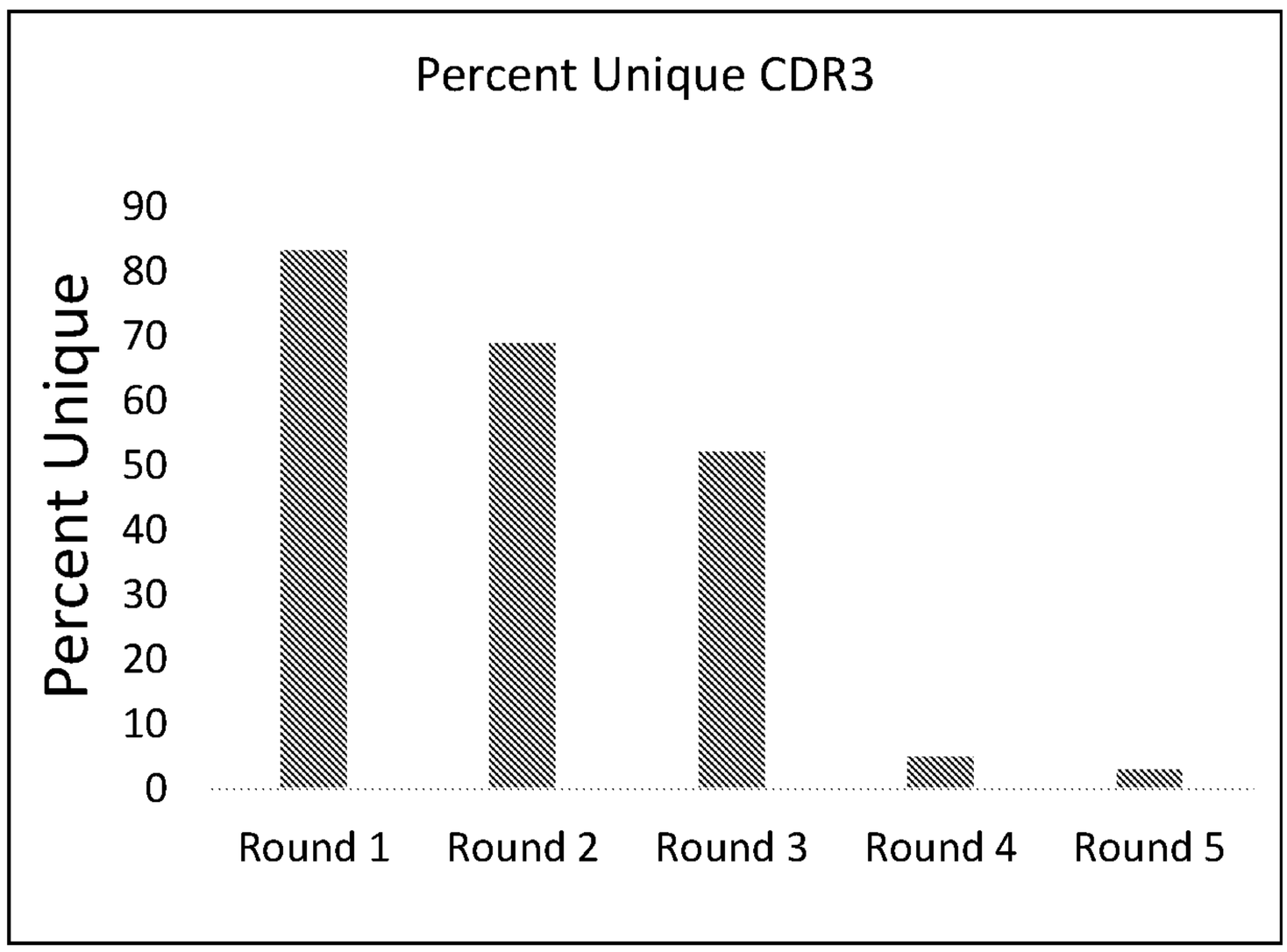


FIG. 13

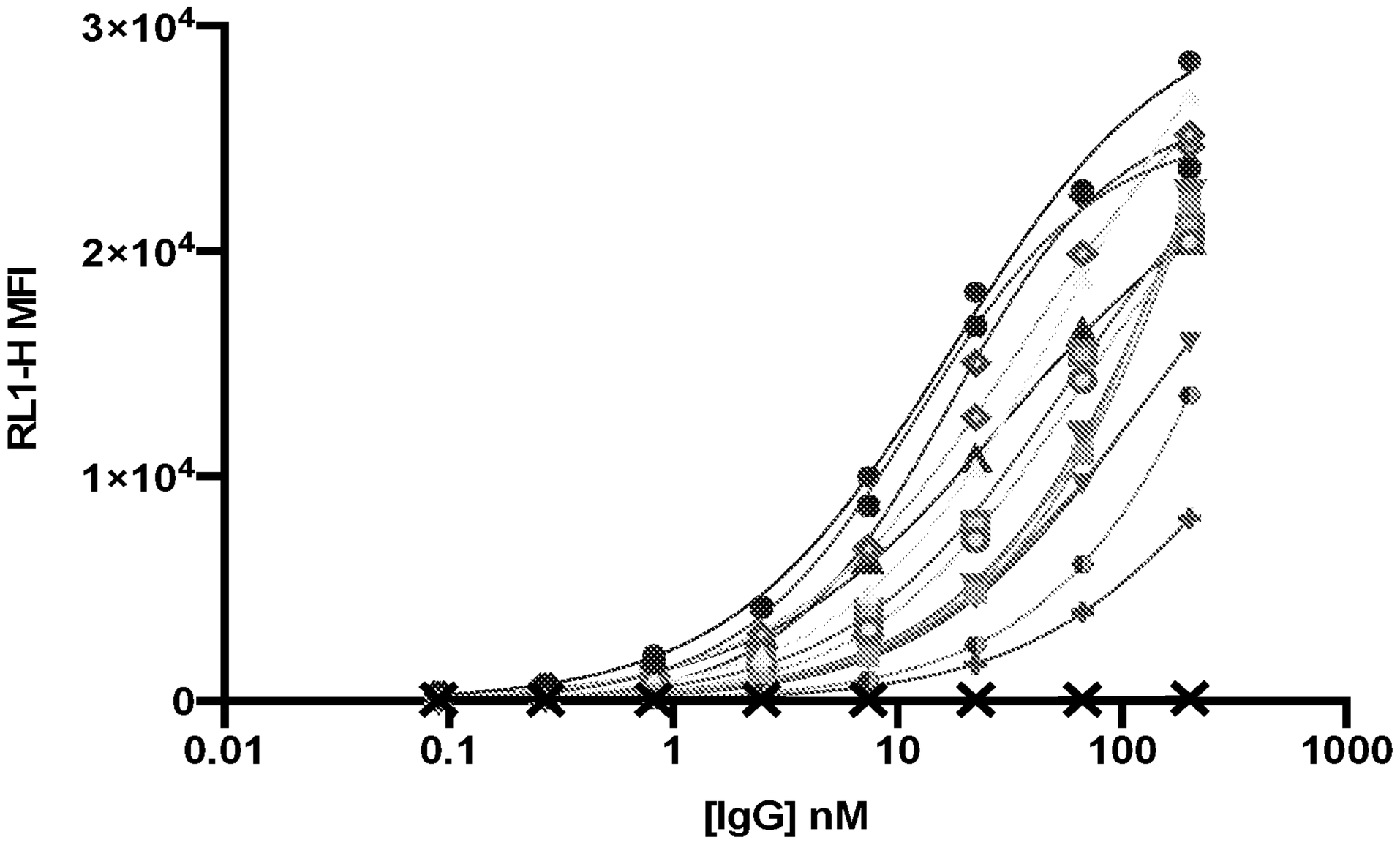
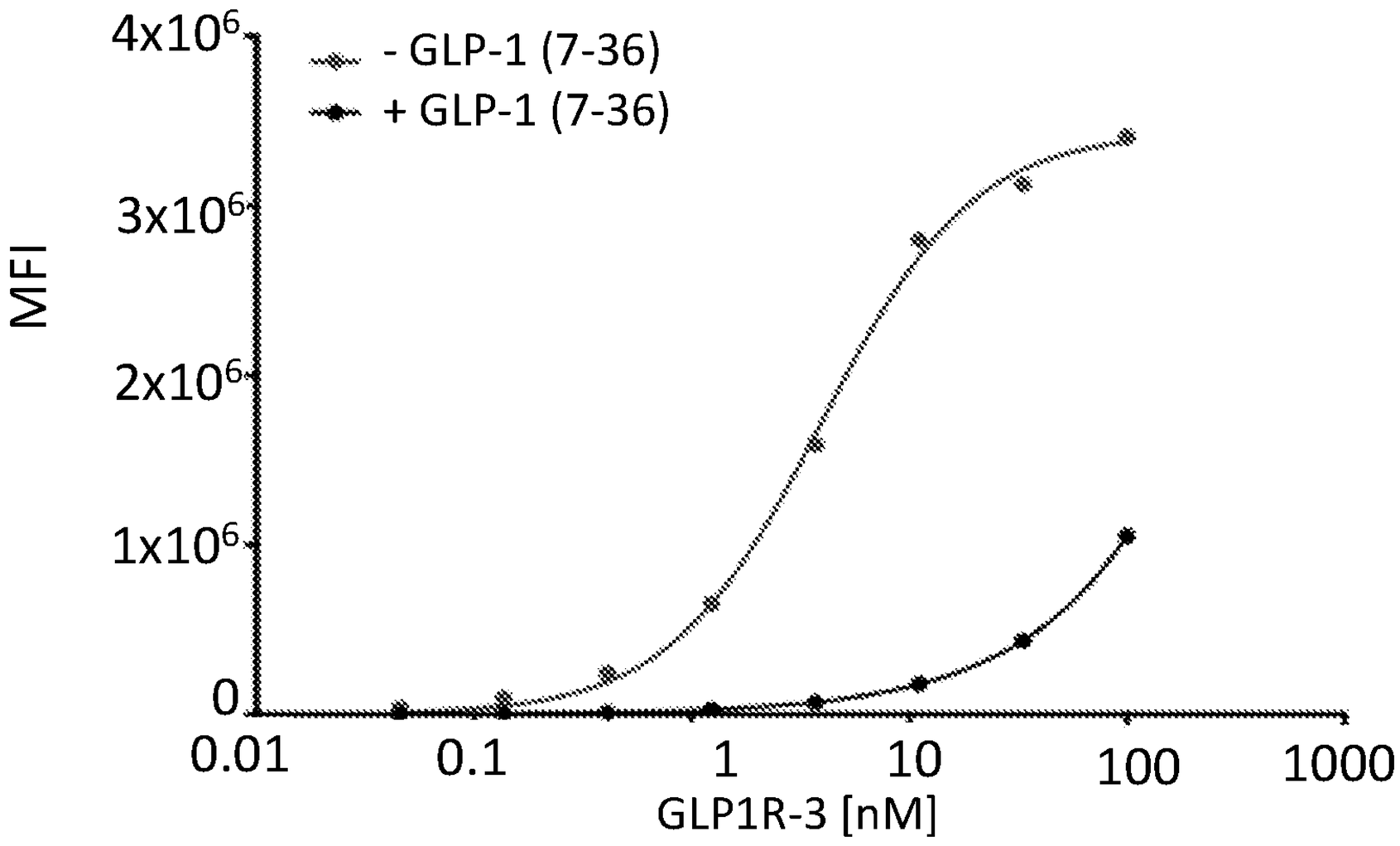


FIG. 14

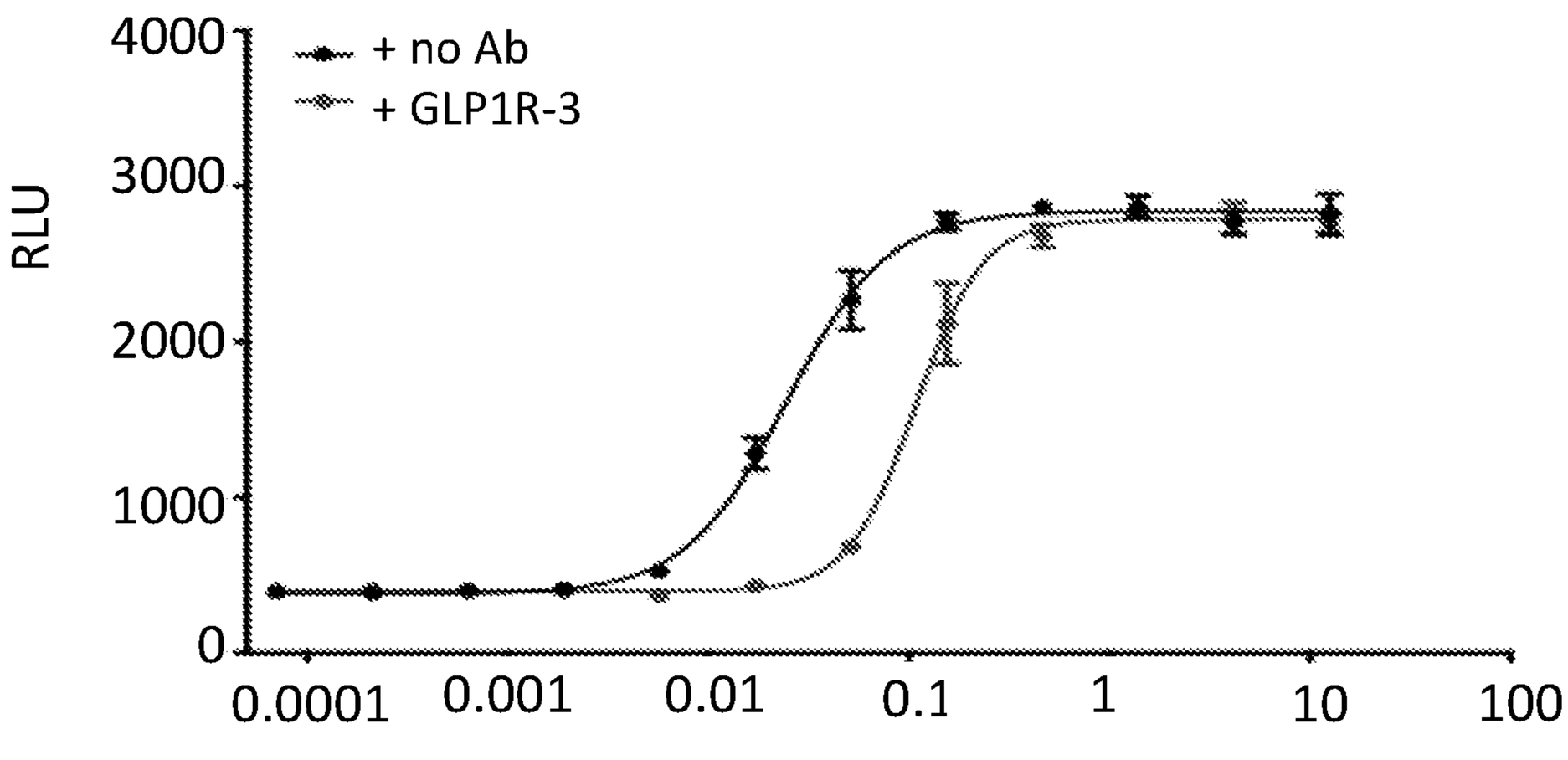
	HCDR3
Glucagon-like peptide 1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
GLP1R-3	CAKHMSMQEGAVTGEGQAAKEFIAWLVKGRVRADLVGDAFDVW
GLP1R-8	CARDGRGSLPRPKGGPQTVGEGQAAKEFIAWLVKGGLTYDSSEDSGGAFDIW
GLP1R-56	CARANQHFFSGAEGEGQAAKEFIAWLVKGIIPGYHYYGMDVW
GLP1R-58	CARANQHFGLHAQGEGQAAKEFIAWLVKGSGIYGYHYYGMDVW
GLP1R-60	CAKHMSMQDYLVIGEGQAAKEFIAWLVKGGPARADLVGDAFDVW
GLP1R-72	CARDMYYDFHPEGTFTSDVSSYLEGQAAKEFIAWLVKGSLIYEVVPADDAFDIW
Glucagon-like peptide 2	HADGSFSDEMNTILDNLAARDFINWLIQTKITD
GLP1R-25	CARANQHFLSHAGAARDFINWLIQTKITGLGSGYHYYGMDVW
GLP1R-30	CARDMYYDFLKIGDNLAARDFINWLIQTKITDGTDTEVVPADDAFDIW
GLP1R-70	CARDGRGSLPRPKGGPPSSGRDFINWLIQTKITDGFRYDSSEDSGGAFDIW
GLP1R-98	CARDMYYDFGYFTGMNTILDNLAARDFINWLIQTKITDRGGGSGGSGGSGGSGGSGGSGEVVPADDAFDIW
GLP1R-2	CARDMYYDFETVVEGIQWYEALKAGKLGEVVPADDAFDIW
GLP1R-10	CARANQHFFVFGSLKVWLKGVAPESSSEYDSSEDSGGAFDIW
GLP1R-26	CAKHMSMQEGVLQGQIPSTIDWEGLLHLIRADLVGDAFDVW

FIG. 15



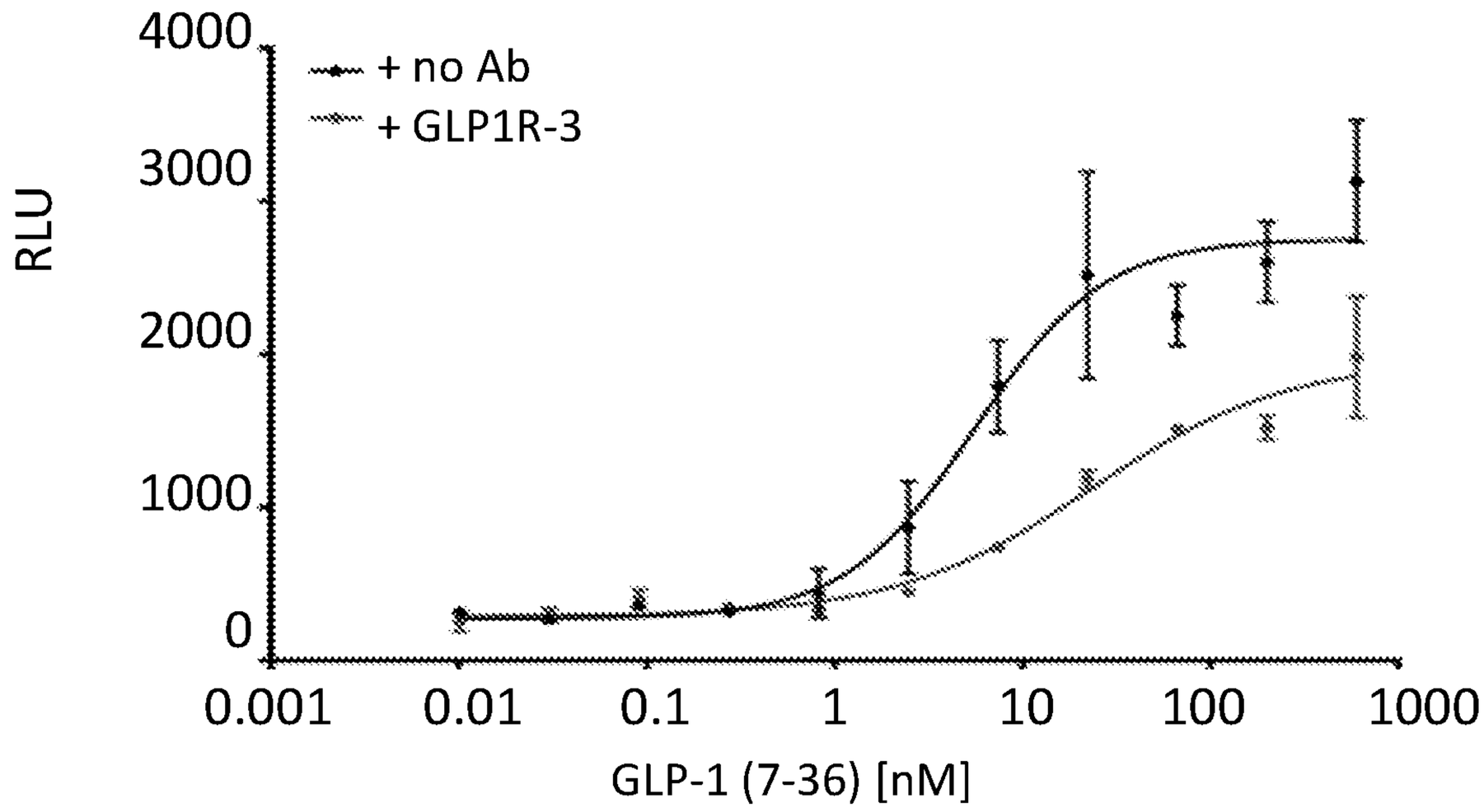
	- GLP-1 (7-36)	+ GLP-1 (7-36)
EC_{50}	3.94	ND

FIG. 16A



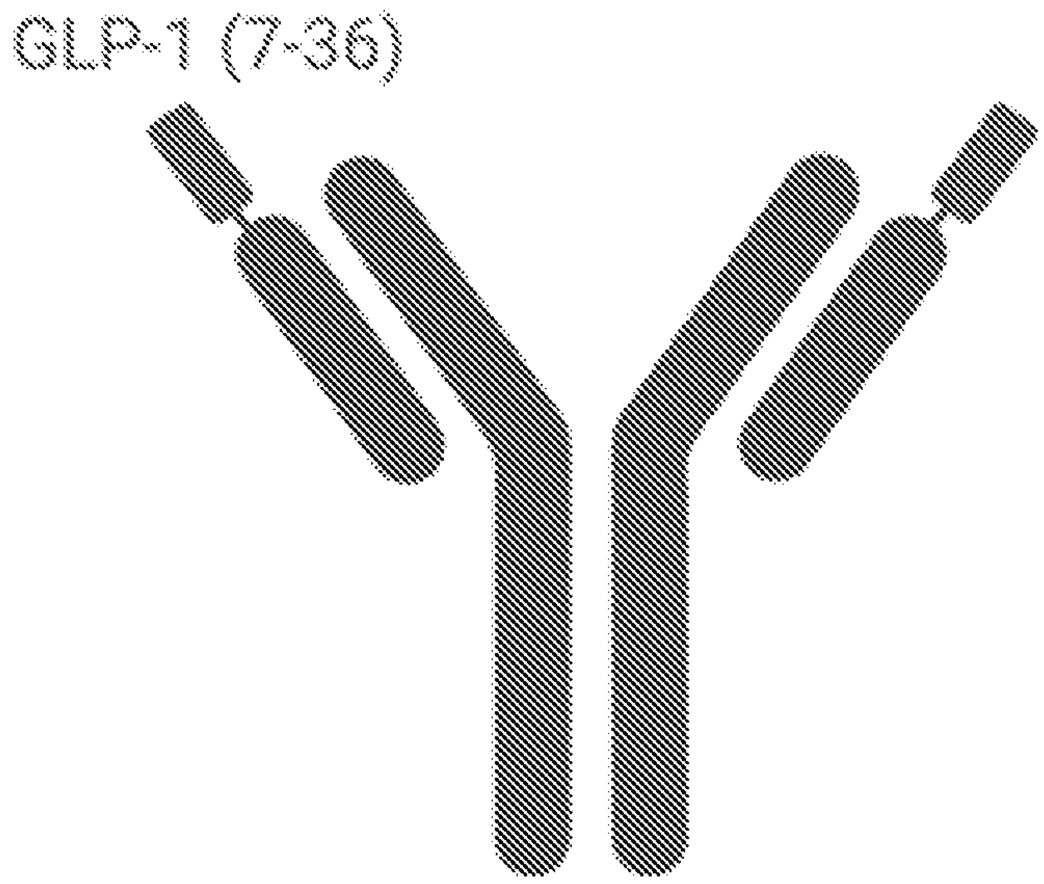
	+ no Ab	+ GLP1R-3
EC_{50}	0.0235	0.11

FIG. 16B



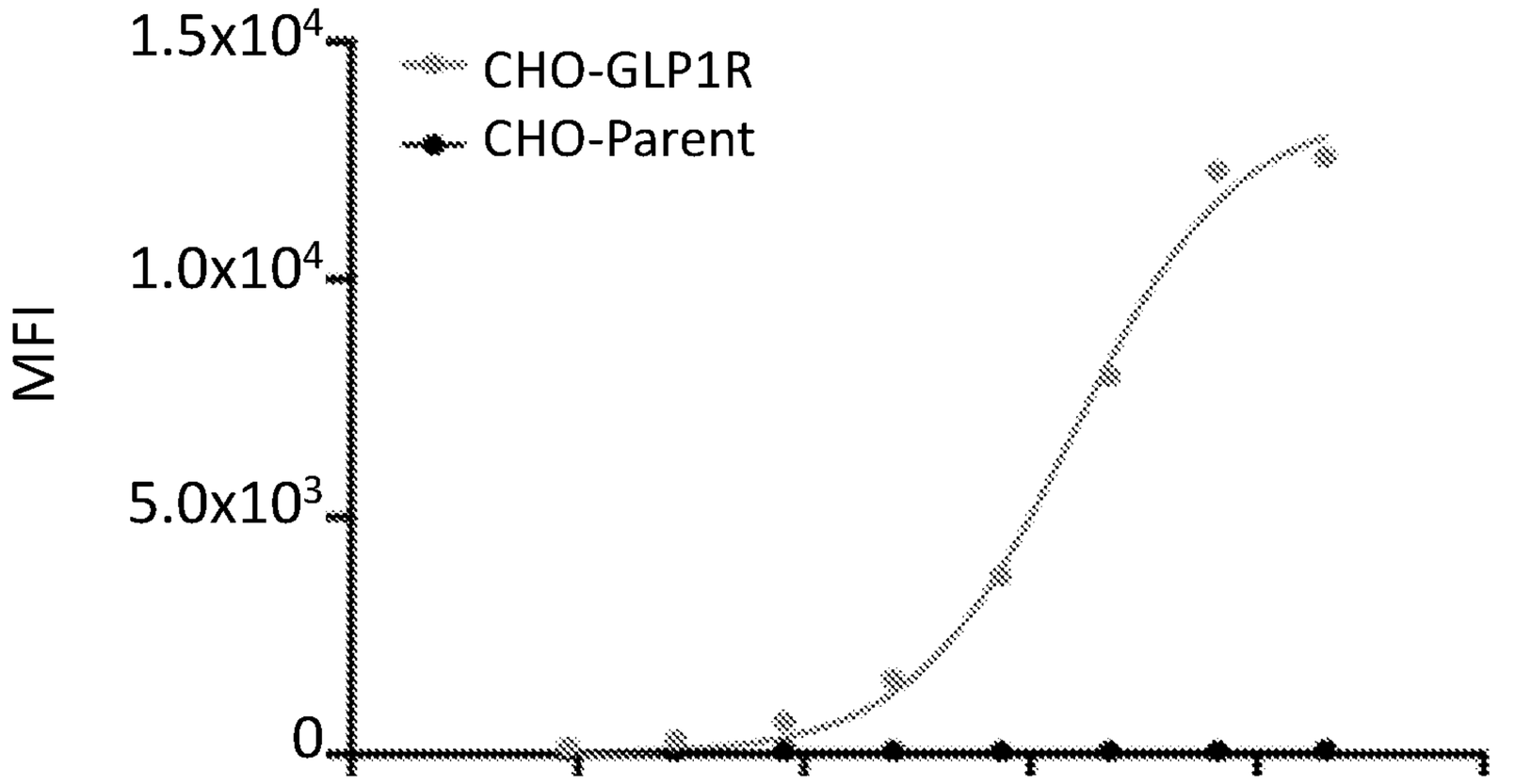
	+ no Ab	+ GLP1R-3
EC_{50}	5.6	23.4

FIG. 16C



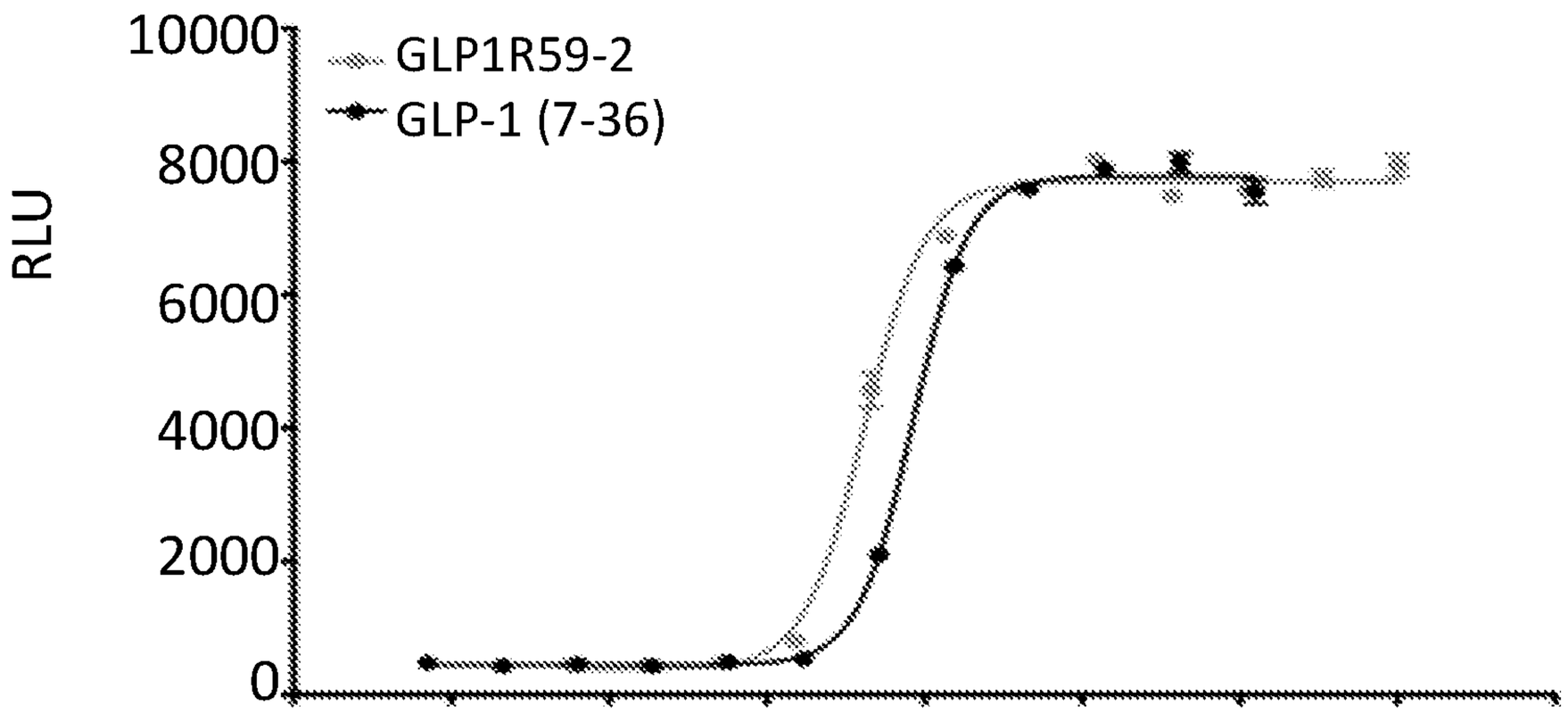
GLP1R-2

FIG. 17



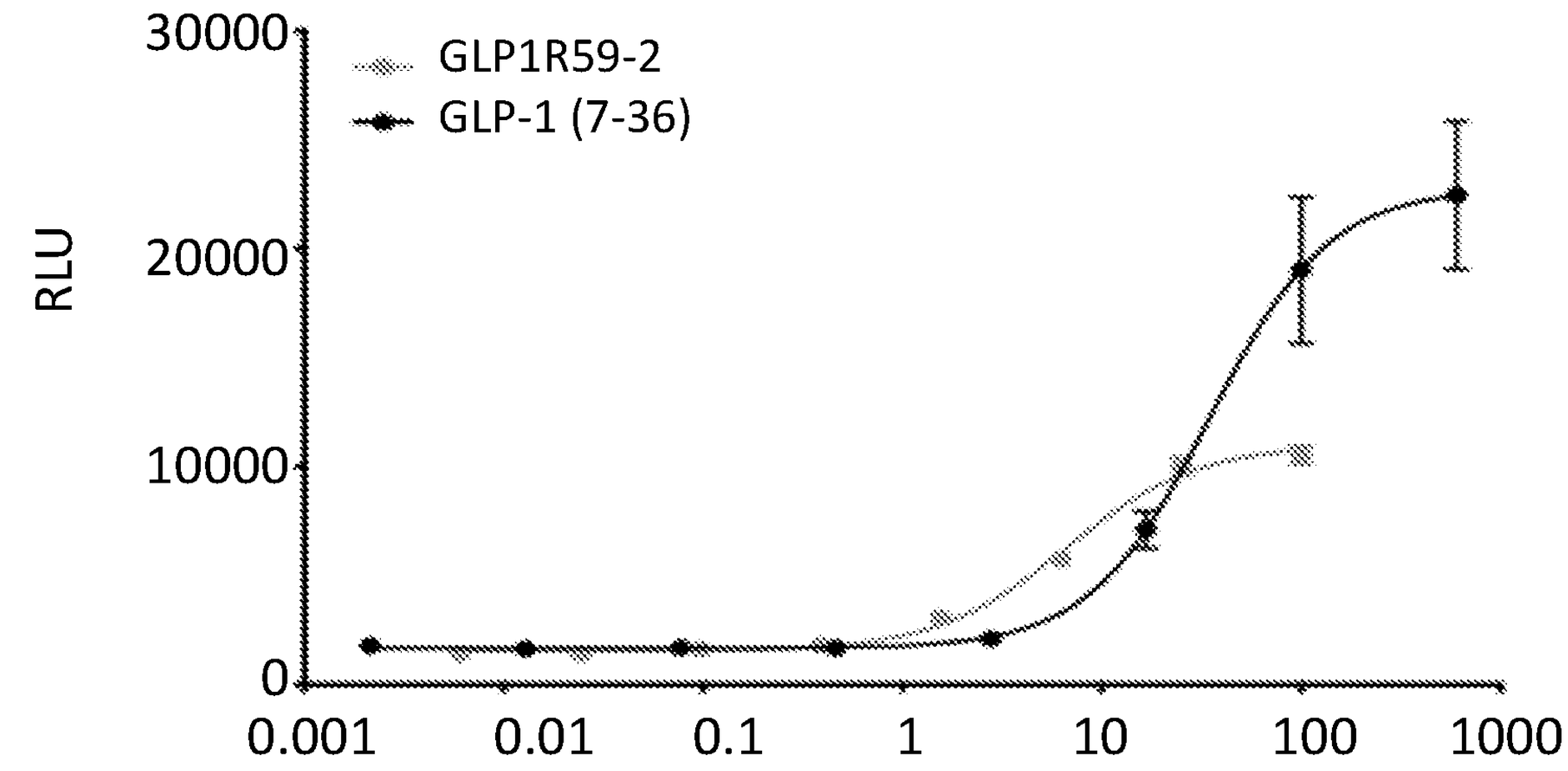
	CHO-GLP1R	CHO-Parent
EC_{50}	15.5	ND

FIG. 18A



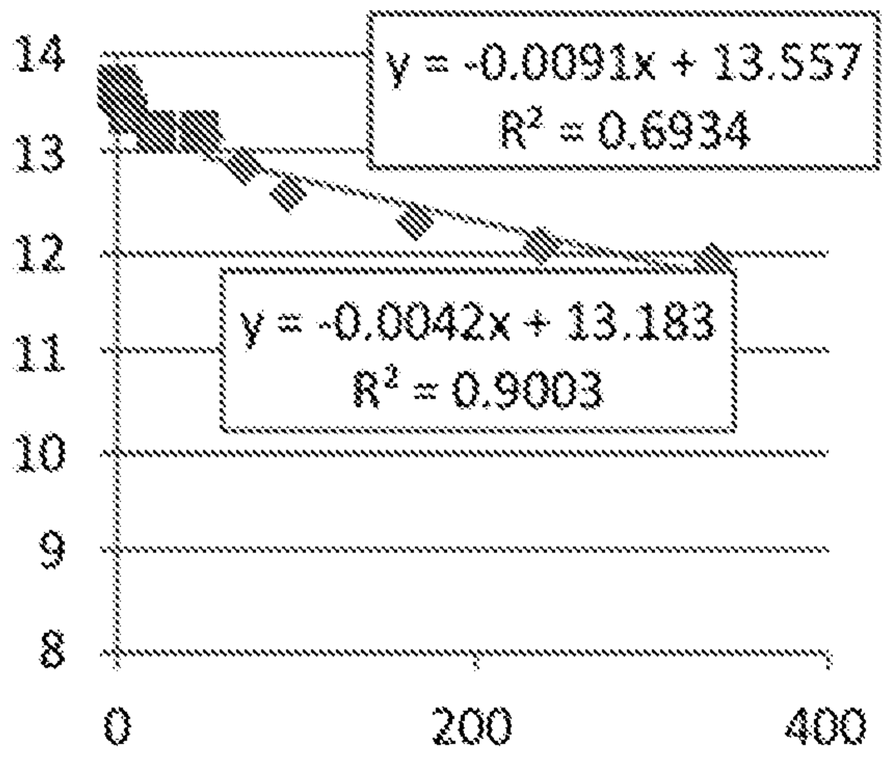
	GLP1R59-2	GLP-1 (7-36)
EC_{50}	0.042	0.085

FIG. 18B



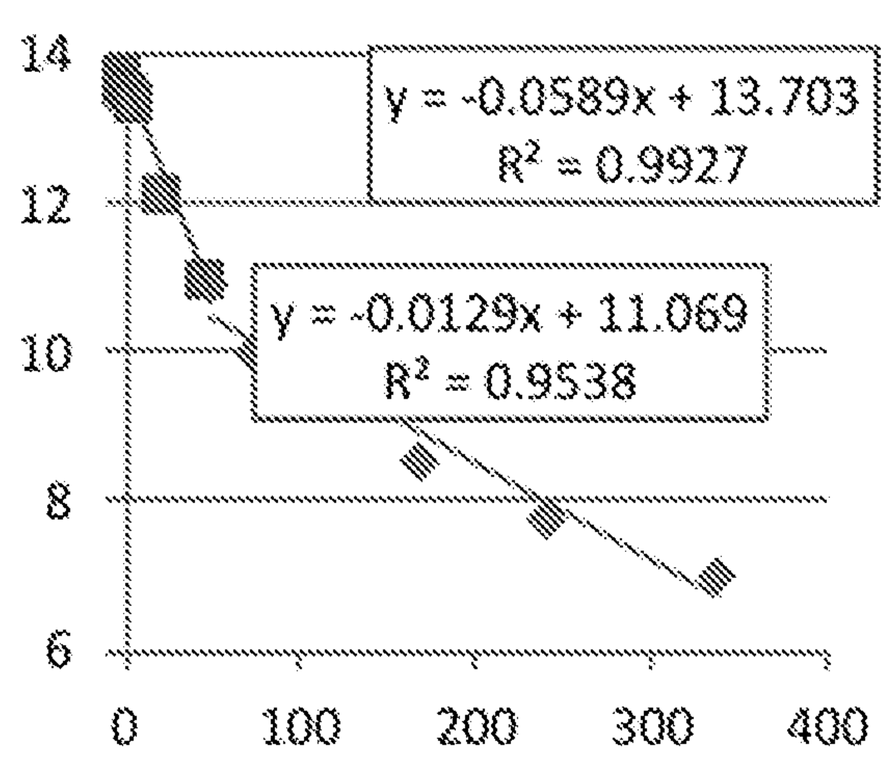
	GLP1R59-2	GLP-1 (7-36)
EC_{50}	6.7	34.6

FIG. 18C



GLP1R-3 2 Hrs

FIG. 19A



GLP1R-59-2 2 Hrs

FIG. 19B

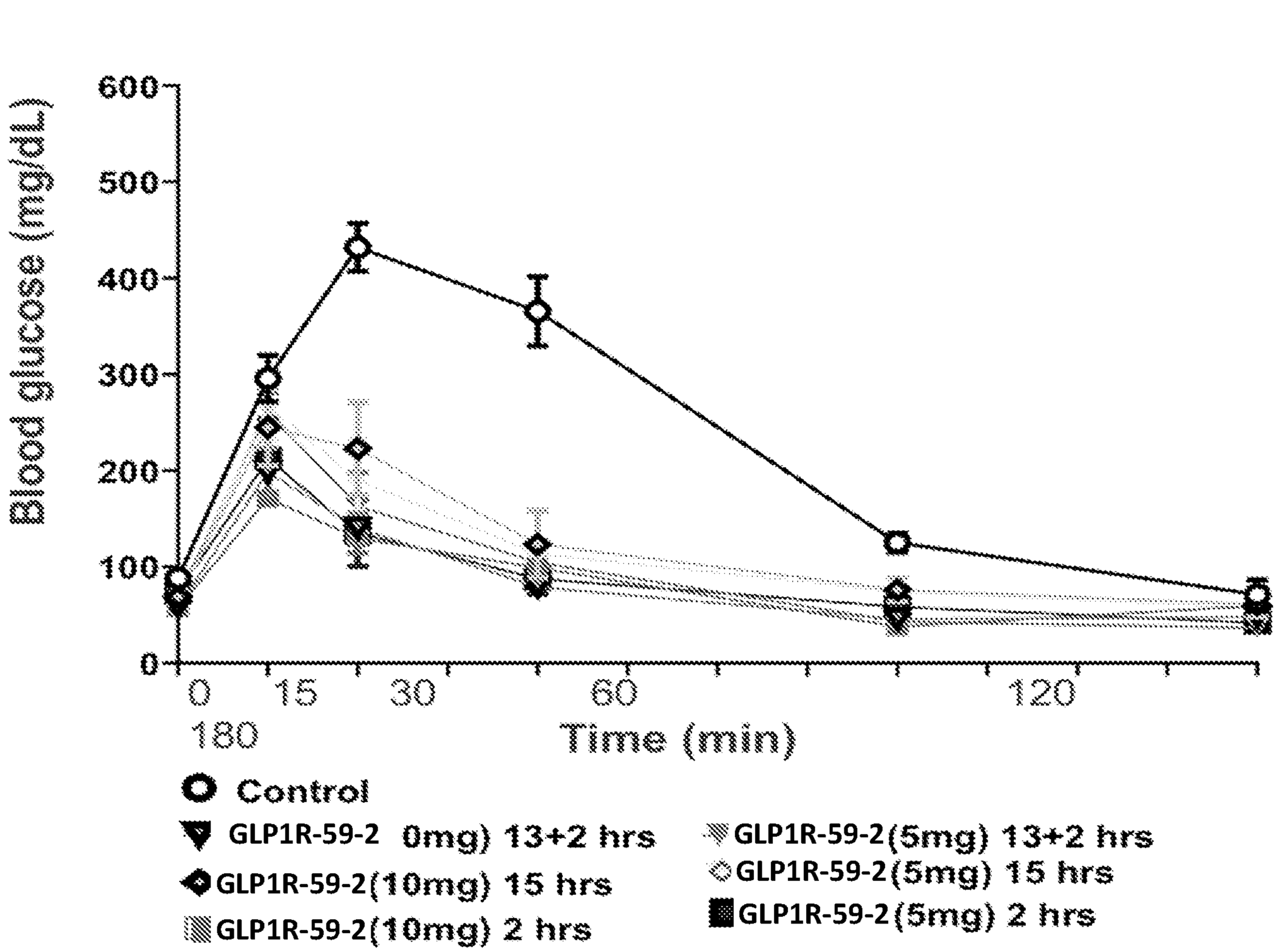


FIG. 20A

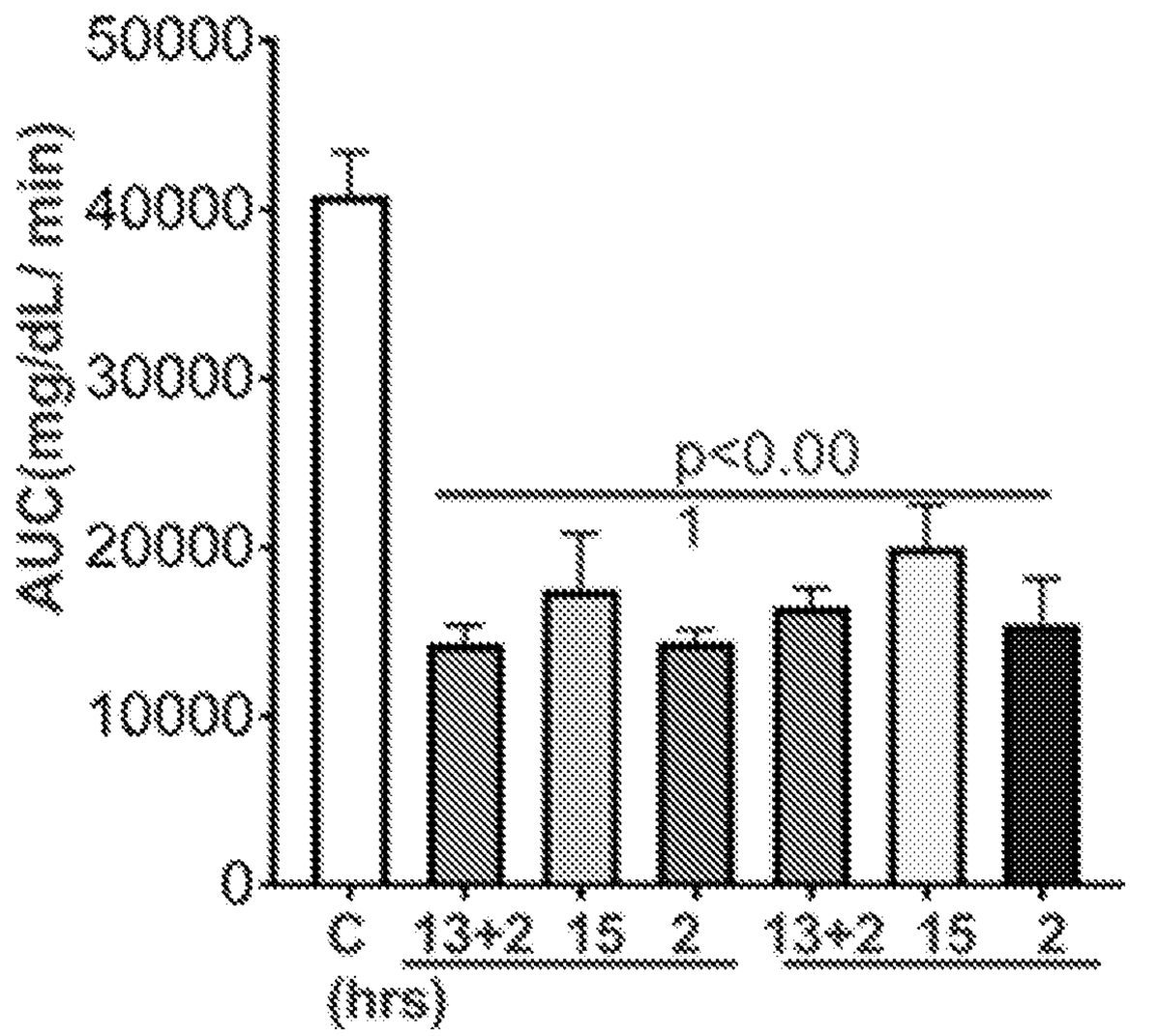


FIG. 20B

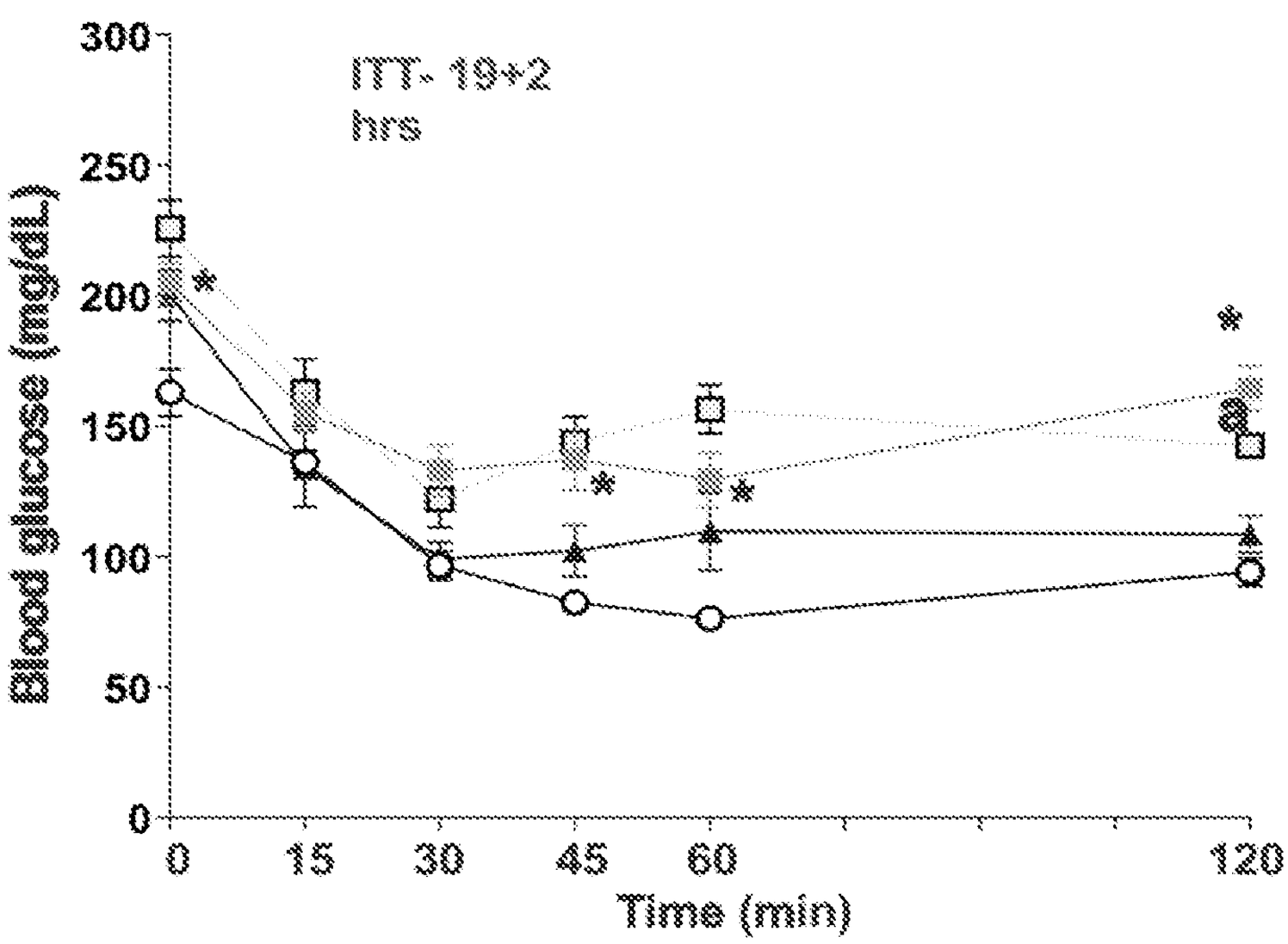
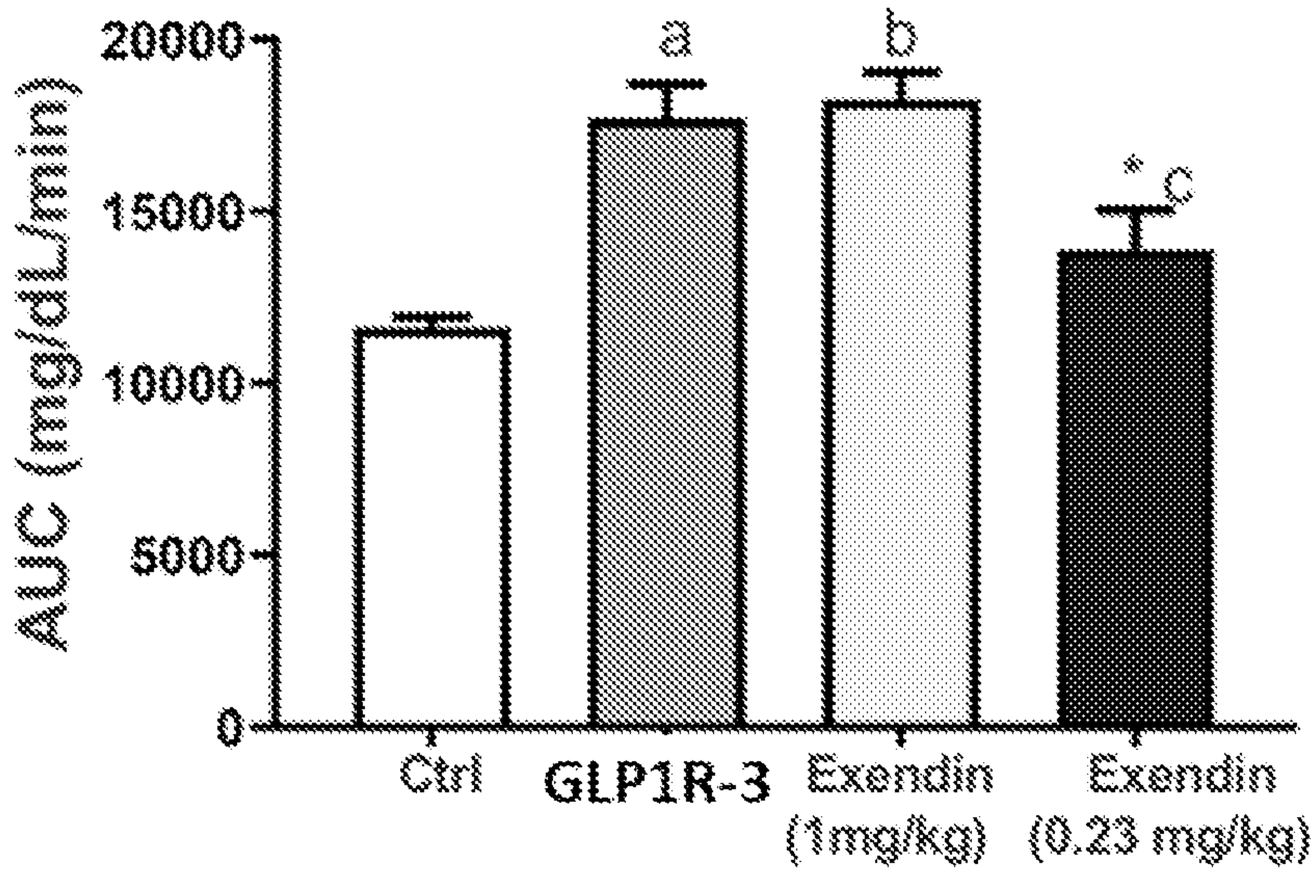


FIG. 21A



a: Ctrl vs **GLP1R-3** <0.0001
b: Ctrl vs Exendin 1 mg/kg p<0.0001
*:**GLP1R-3** vs Exendin 0.23 mg/kg p=0.03
c: Exendin 1mg/kg vs Exendin 0.23 mg/kg p=0.03

FIG. 21B

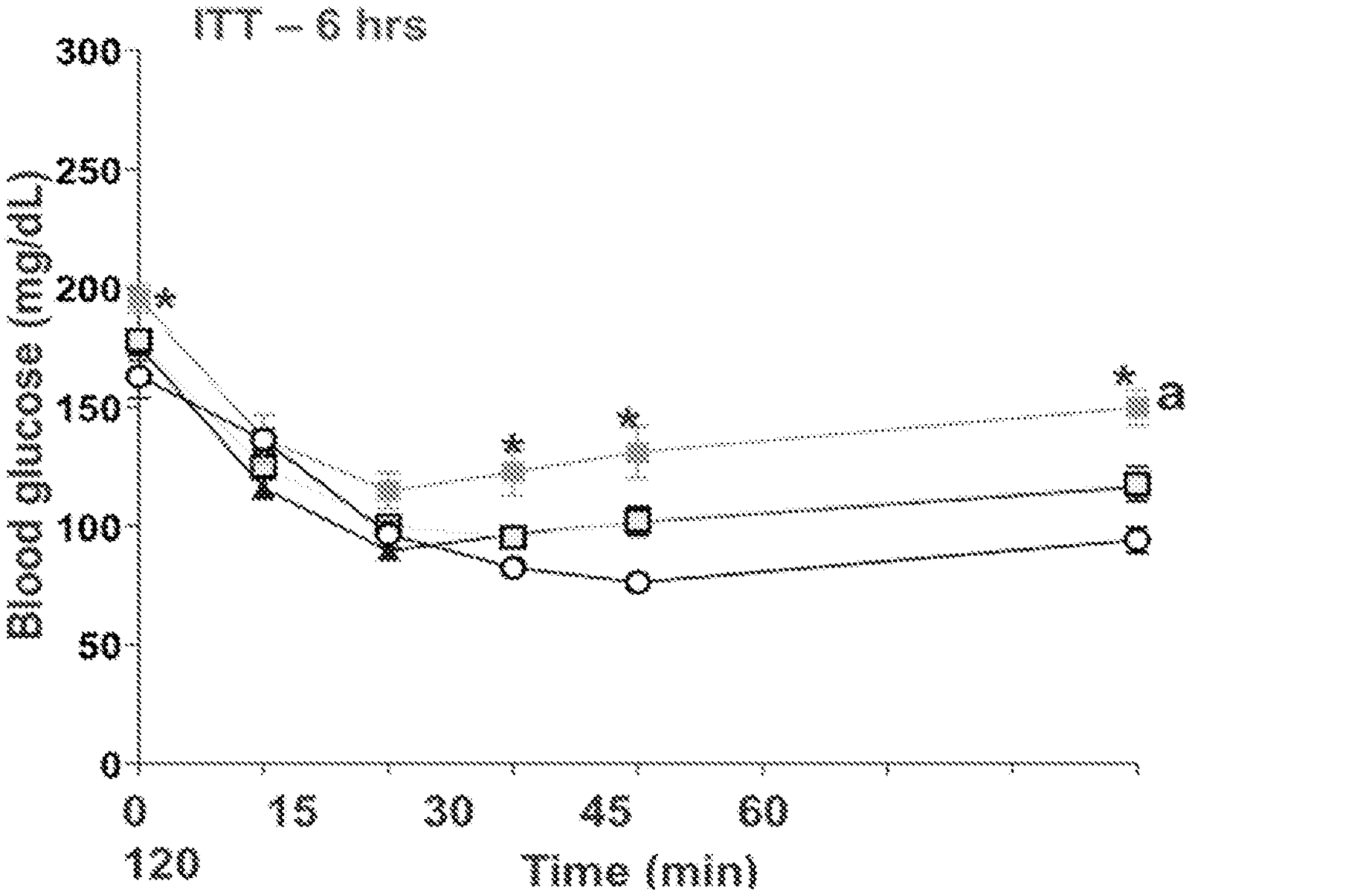
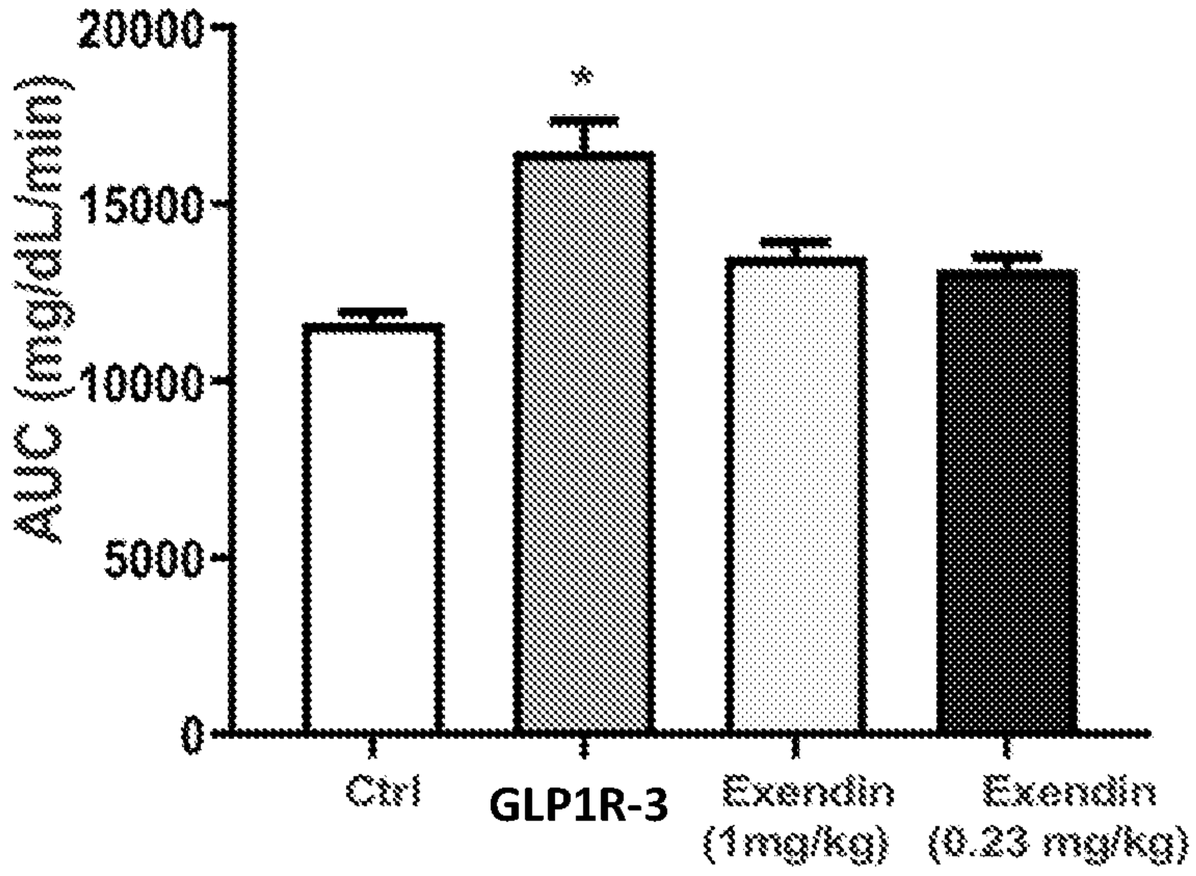


FIG. 22A



*: GLP1R-3 vs Control p=0.0003

FIG. 22B

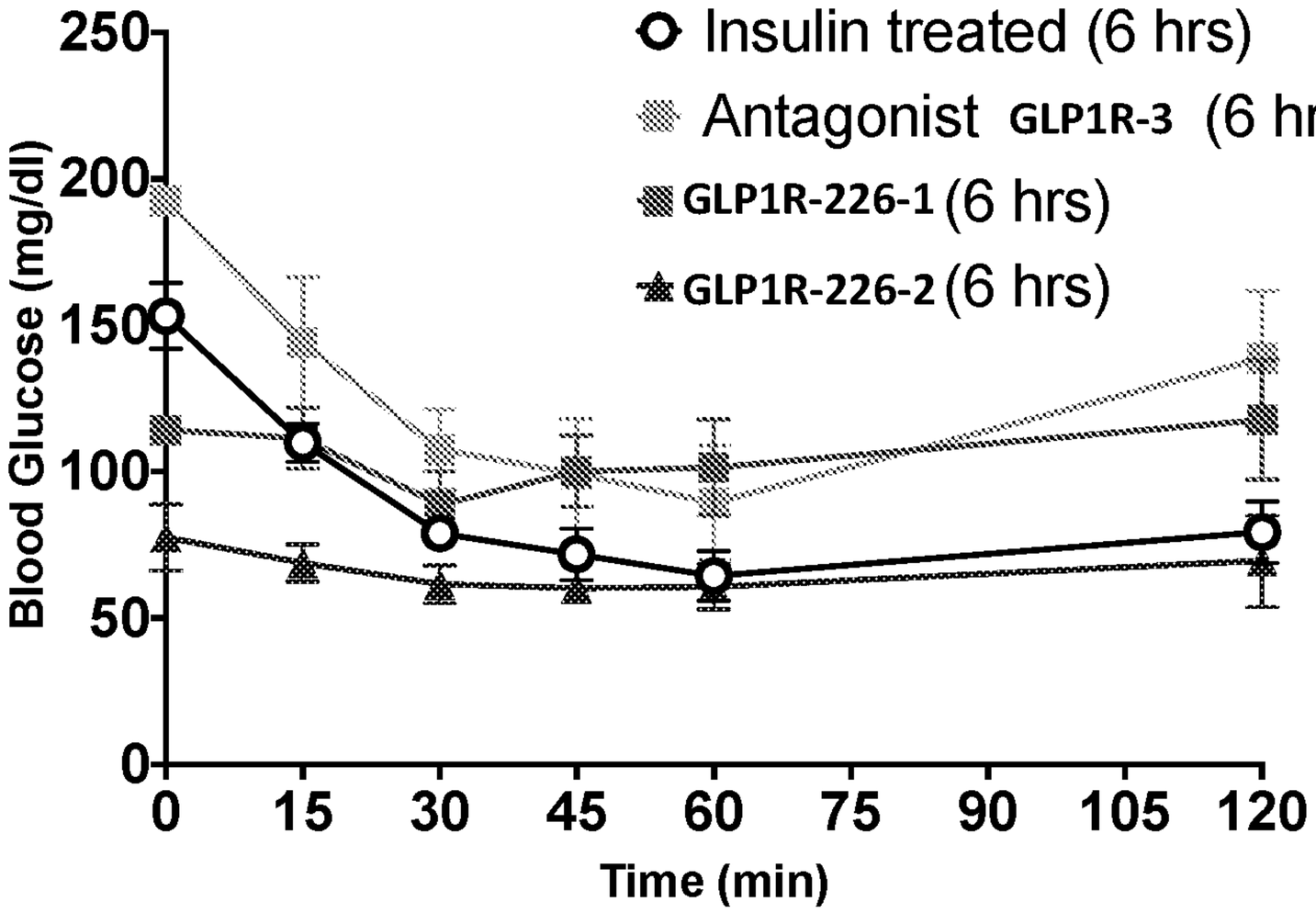


FIG. 23A

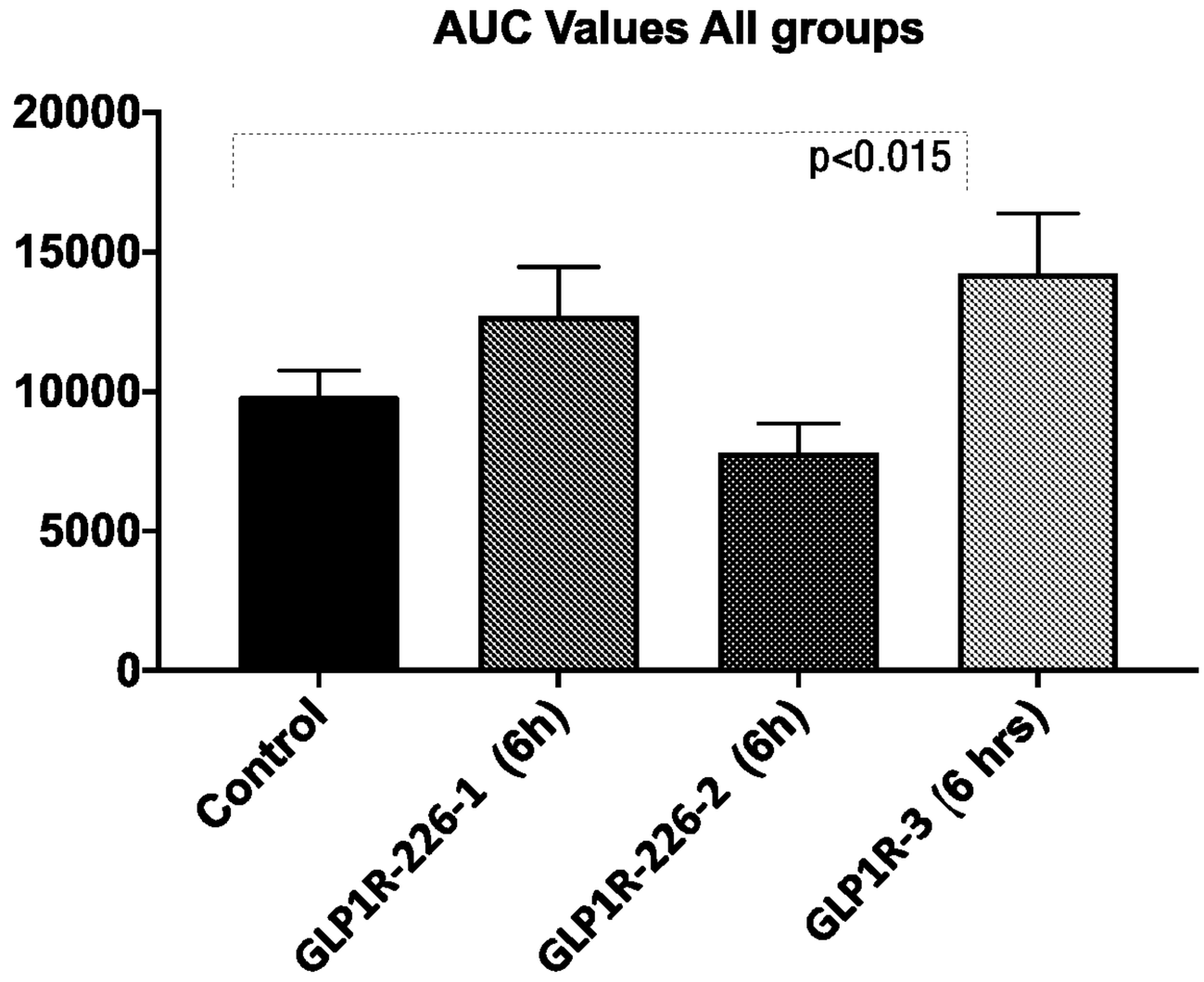
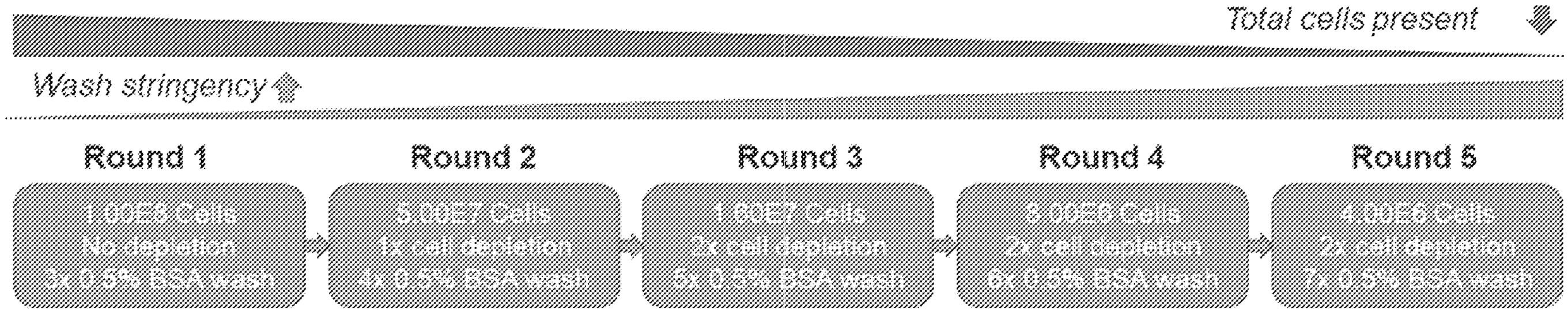


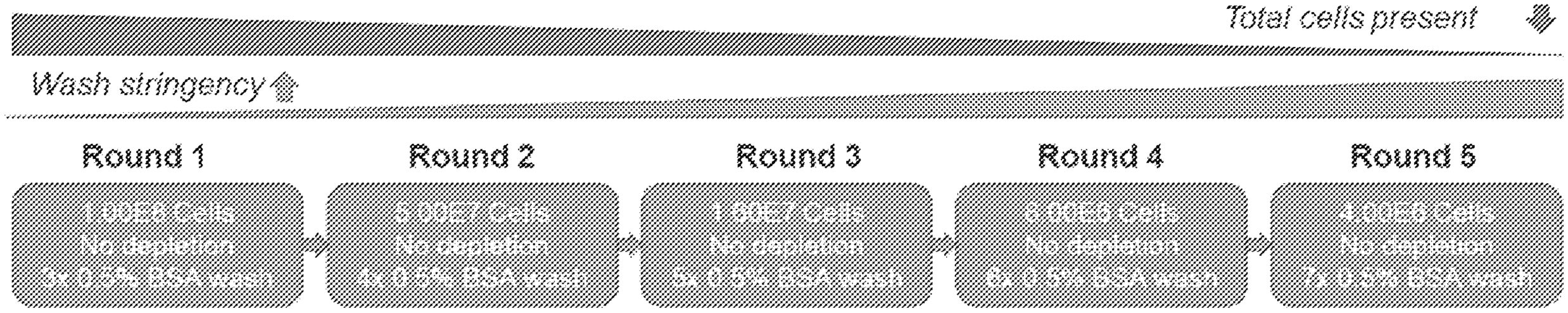
FIG. 23B



Cell based panning, GLP1R target Cells, CHO cell (1.00E8 Cells) depletion from Round 2, Elution with Trypsin

Round 1	Round 2	Round 3	Round 4	Round 5
$3.0x10^{12}$ **$4.0x10^{6}$**	$3.2x10^{13}$ **$1.9x10^{7}$**	$1.0x10^{13}$ **$3.1x10^{7}$**	$3.6x10^{12}$ **$1.5x10^{7}$**	$1.8x10^{13}$ **$7.2x10^{7}$**

FIG. 24A



Cell based panning, GLP1R target Cells, No depletion, competitive elution with GLP1R-3 Parental Antibody Lot#7492 1mg/ml

Round 1	Round 2	Round 3	Round 4	Round 5
$3.0x10^{12}$ **$2.0x10^{6}$**	$1.6x10^{13}$ **$1.8x10^{7}$**	$2.0x10^{13}$ **$1.5x10^{7}$**	$5.4x10^{12}$ **$1.7x10^{7}$**	$1.8x10^{13}$ **$4.6x10^{7}$**

FIG. 24B

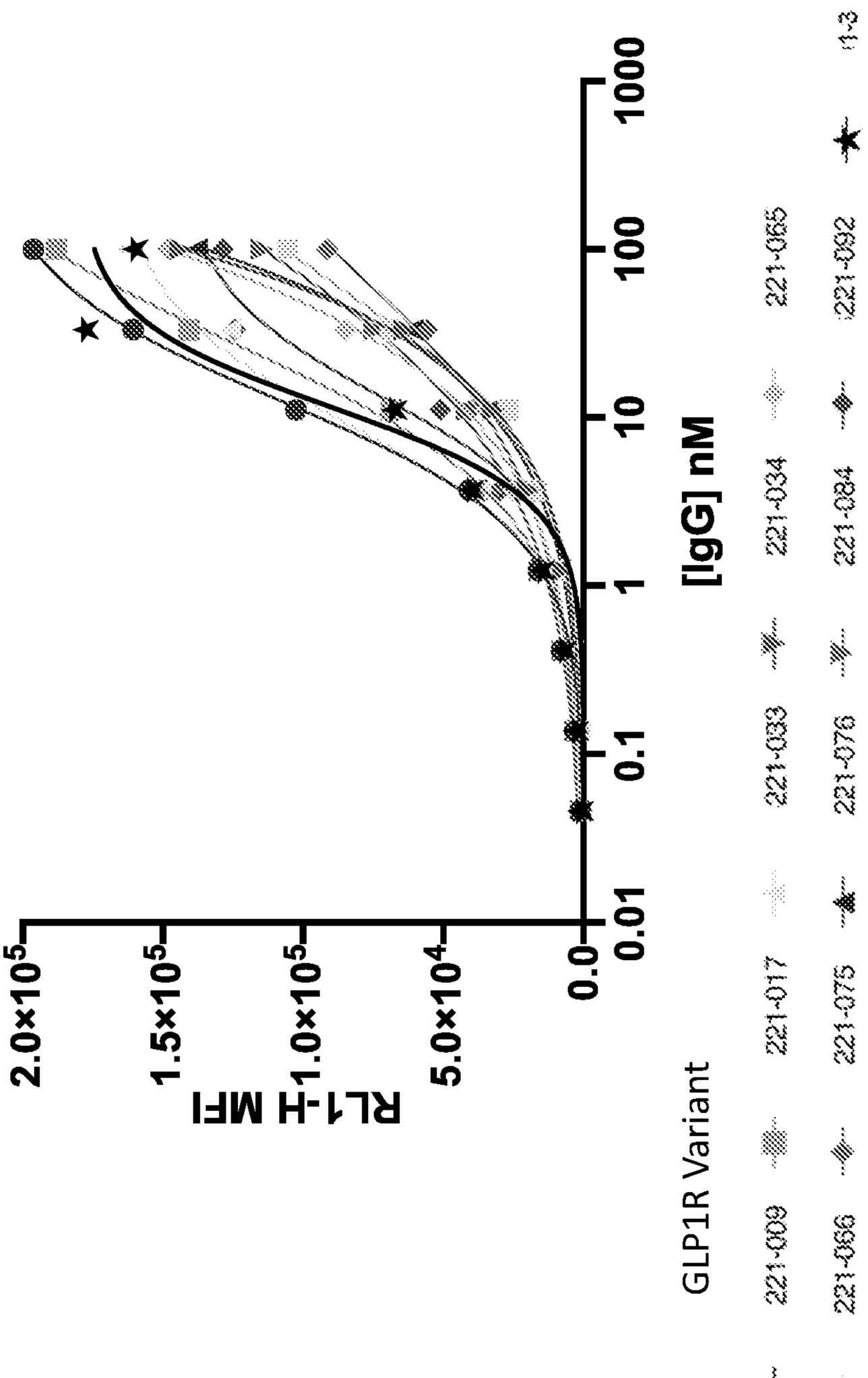

RL1-H MFI
2.0×10^5
1.5×10^5
1.0×10^5
5.0×10^4
0.0
0.01
0.1
1
10
100
[IgG] nM
GLP1R Variant
221-009
221-017
221-033
221-066
221-075
221-076
221-034
221-065
221-084
221-092

FIG. 25A

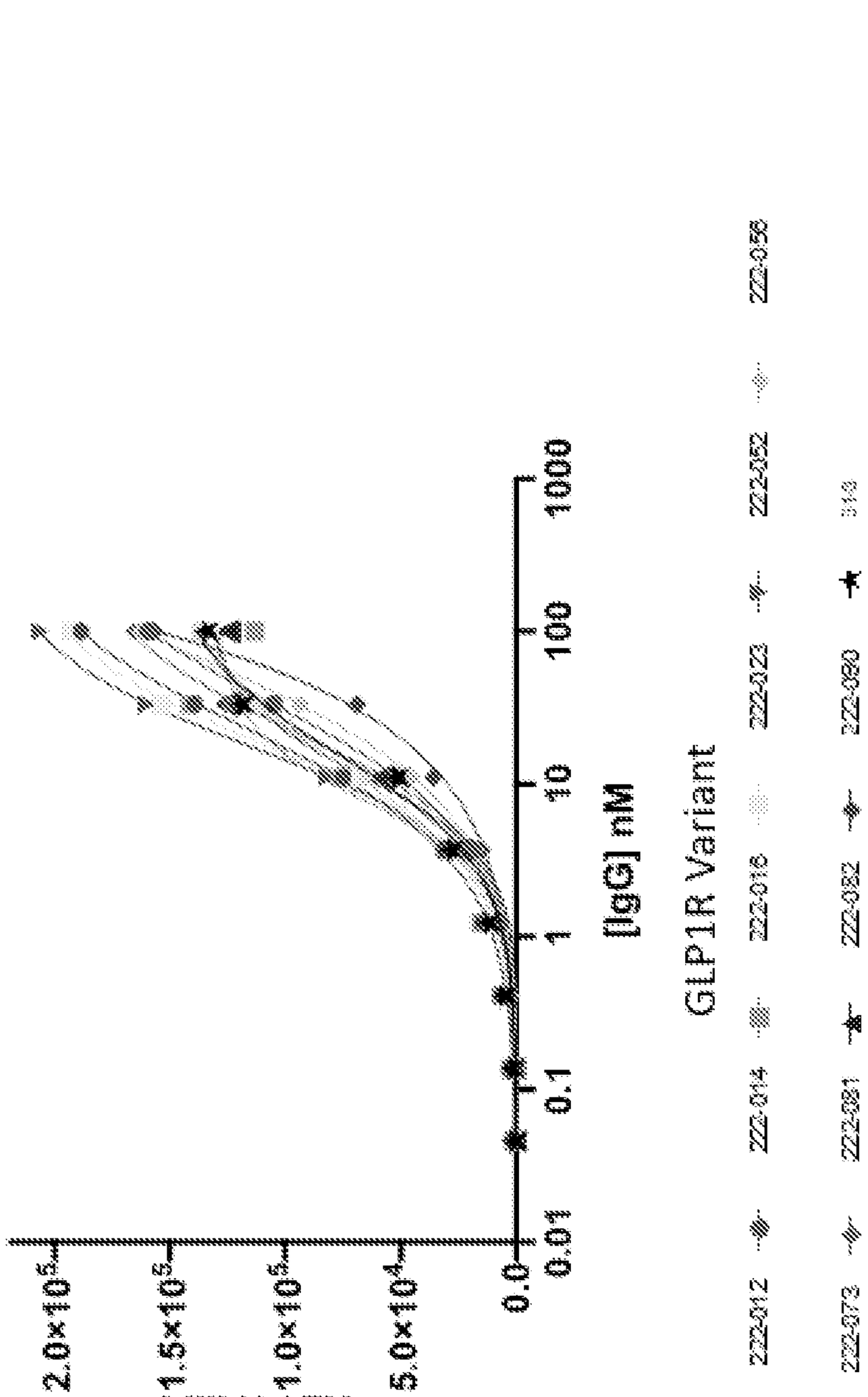

RL1-H MFI
2.0×10⁵
1.5×10⁵
1.0×10⁵
5.0×10⁴
0.0
0.01
0.1
1
10
100
1000
[IgG] nM
GLP1R Variant
ZZ2-012
ZZ2-014
ZZ2-016
ZZ2-052
ZZ2-056
ZZ2-073
ZZ2-081
ZZ2-082
ZZ2-120
ZZ2-123

FIG. 25B

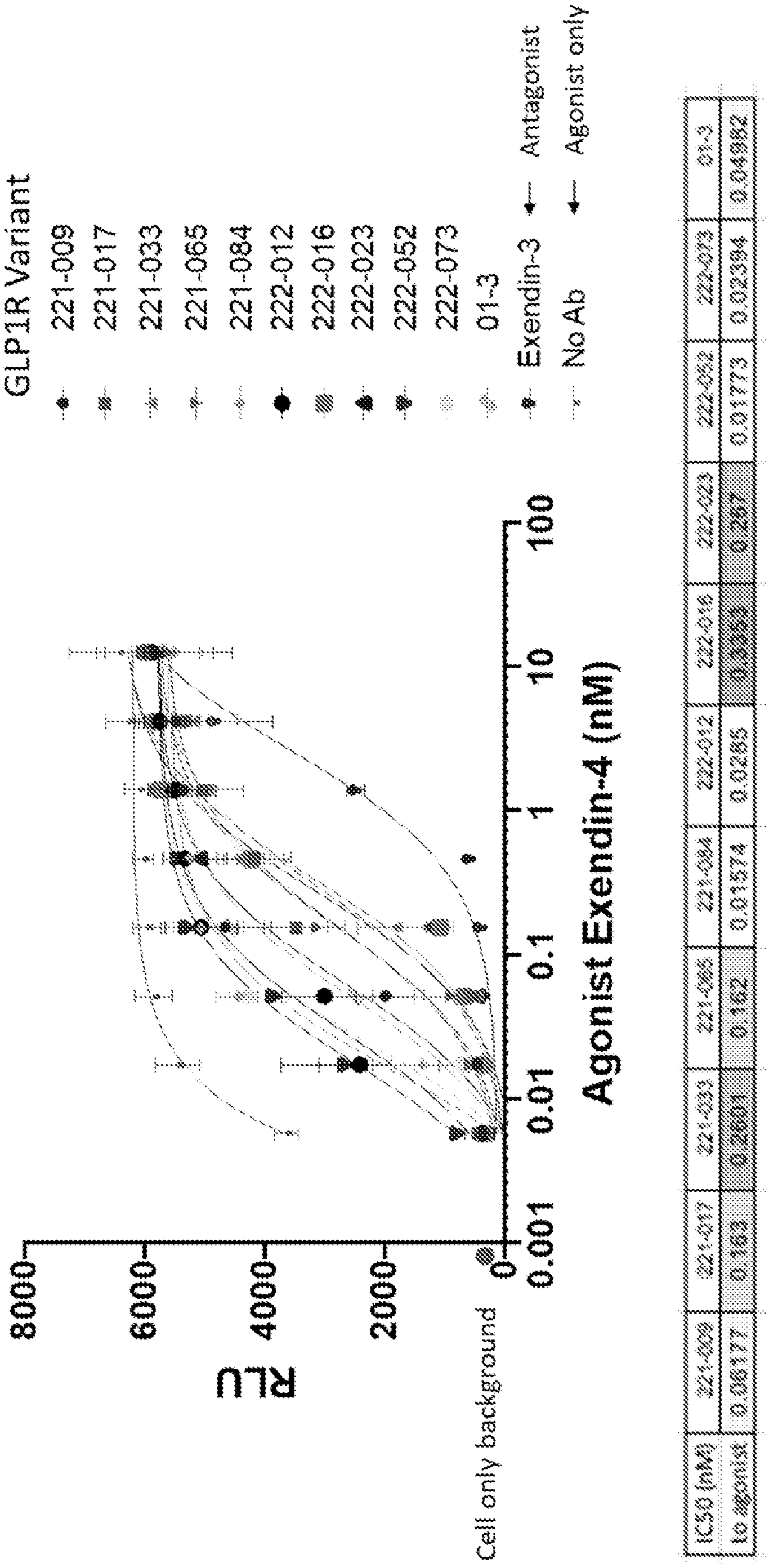

GLP1R Variant
221-009
221-017
221-033
221-065
221-084
222-012
222-016
222-023
222-052
222-073
01-3
Exendin-3
No Ab
← Antagonist
← Agonist only
Agonist Exendin-4 (nM)
0.001
0.01
0.1
1
10
100
RLU
0
200
400
600
800
Cell only background
IC50 (nM)
to agonist
221-009 0.163
221-017 0.0265
221-033 0.2001
221-065 0.207
221-084 0.162
222-012 0.01773
222-016 0.01574
222-023 0.023384
222-052 0.049862
222-073 81.3

FIG. 26