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Methods and compositions relating to GLP1R variants

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.

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Background/Summary

CROSS-REFERENCE (1) This application claims the benefit of U.S. Provisional Patent Application No. 63/070,734 filed on Aug. 26, 2020, and U.S. Provisional Patent Application No. 63/081,801 filed on Sep. 22, 2020, each of which is incorporated by reference in its entirety.

SEQUENCE LISTING

(1) The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Sep. 22, 2021, is named 44854-808_201_SL.txt and is 838,237 bytes in size.

BACKGROUND

(2) 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

(3) 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

(4) 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.

(5) 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.

(6) 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: 1157-1335; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1336-1347 and 1353-1519. 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.

(7) 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: 1157-1335; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1336-1347 and 1353-1519. 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.

(8) 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: 1157-1335; and (iii) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1336-1347 and 1353-1519.

(9) 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.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

- (1) FIG. 1A depicts a first schematic of an immunoglobulin.
- (2) FIG. 1B depicts a second schematic of an immunoglobulin.
- (3) FIG. 2 depicts a schematic of a motif for placement in an immunoglobulin.
- (4) FIG. 3 presents a diagram of steps demonstrating an exemplary process workflow for gene synthesis as disclosed herein.
- (5) FIG. 4 illustrates an example of a computer system.
- (6) FIG. 5 is a block diagram illustrating an architecture of a computer system.
- (7) FIG. 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).
- (8) FIG. 7 is a block diagram of a multiprocessor computer system using a shared virtual address memory space.
- (9) FIG. 8A depicts a schematic of an immunoglobulin comprising a VH domain attached to a VL domain using a linker.
- (10) FIG. 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.
- (11) FIG. 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.
- (12) FIG. 9A depicts a structure of Glucagon-like peptide 1 (GLP-1) in complex with GLP-1 receptor (GLP-1R), PDB entry 5VAI.
- (13) FIG. 9B depicts a crystal structure of CXCR4 chemokine receptor in complex with a cyclic peptide antagonist CVX15, PDB entry 3OR0.
- (14) FIG. 9C depicts a crystal structure of human smoothened receptor with the transmembrane domain and extracellular domain (ECD), PDB entry 5L7D. The ECD contacts the TMD through extracellular loop 3 (ECL3).
- (15) FIG. 9D depicts a structure of GLP-1R in complex with a Fab, PDB entry 6LN2.
- (16) FIG. 9E depicts a crystal structure of CXCR4 in complex with a viral chemokine antagonist Viral macrophage inflammatory protein 2 (vMIP-II), PDB entry 4RWS.
- (17) FIG. 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.
- (18) FIG. 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.
- (19) FIG. 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.

(20) FIG. 12B depicts a cell-based panning process.

(21) FIG. 13 depicts a graph of percent unique HCDR3 in the output pools of the five GLP-1R panning rounds.

(22) FIG. 14 depicts a graph of binding plots of the 13 unique GLP-1R Hits, compared to the parental CHO cell binding.

(23) FIG. 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 (bolded), residues that are similar to the GLP-1 sequence or the GLP-2 sequence are bolded and the residues that are different are left unbolded. Functional antagonists in the CAMP assay are enclosed by a box. FIG. 15 discloses SEQ ID NOS 1528, 1-2, 27, 12, 3, 32, 1529, 23, 25, 30, 1530, 19, 22 and 24, respectively, in order of appearance.

(24) FIG. 16A depicts a graph of orthosteric inhibition of GLP1R-3 binding in the absence and presence of GLP-1 (7-36).

(25) FIG. 16B depicts a graph of effects of GLP1R-3 on GLP-1 activation in the CAMP assay.

(26) FIG. 16C depicts a graph of effects of GLP1R-3 on GLP-1 induced β -arrestin recruitment.

(27) FIG. 17 depicts a design of GLP1R-59-2. The GLP1 (7-36) peptide (SEQ ID NO: 1528) was linked to the N-terminal of light chain of the functionally inactive GLP-1R binding antibody GLP1R-2.

(28) FIG. 18A depicts a graph of GLP1R-59-2 binding specifically to the GLP-1R with an EC50 of 15.5 nM.

(29) FIG. 18B depicts a graph of GLP1R-59-2 in the CAMP assay with a similar EC50 as the GLP-1 7-36 peptide.

(30) FIG. 18C depicts a graph of GLP1R-59-2 on inducing the β -arrestin recruitment in GLP-1R expression cells.

(31) FIGS. 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 (FIG. 19A). GLP1R-59-2 has a 2-day half-life in rat (FIG. 19B).

(32) FIG. 20A depicts a graph of GLP1R-59-2 on glucose after glucose challenge.

(33) FIG. 20B depicts a graph of Area Under the Curve (AUC) in a glucose tolerance test (GTT).

(34) FIG. 21A depicts a graph of GLP1R-3 and GLP-1 peptide Exendin 9-39 treatment, 19+2 hour dosing regimen

(35) FIG. 21B depicts a graph of Area Under the Curve (AUC) in an insulin tolerance test (ITT).

(36) FIG. 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.

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

(38) FIG. 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.

(39) FIG. 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.

(40) FIGS. 24A-24B are schemas of panning strategy for GLP1R-221 and GLP1R-222 variants.

(41) FIGS. 25A-25B are graphs of competition data for GLP1R-221 and GLP1R-222 variants.

(42) FIG. 26 is a graph of GLP1R-221 and GLP1R-222 variants in a CAMP assay.

DETAILED DESCRIPTION

(43) 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.

Definitions

(44) 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.

(45) 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.

(46) 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 $\pm 10\%$ thereof, or 10% below the lower listed limit and 10% above the higher listed limit for the values listed for a range.

(47) 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 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.

(48) GPCR Libraries for GLP1 Receptor

(49) 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.

(50) 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 CHI 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 CHI 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.

(51) 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.

(52) “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.

(53) “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.

(54) “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 felinized antibody.

(55) 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.

(56) 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).

(57) 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.

(58) 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.

(59) 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.

(60) 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.

(61) 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.

(62) 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.sup.1, 10.sup.2, 10.sup.3, 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, or more than 10.sup.10 variants.

(63) 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.

(64) 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.

(65) GLP1R Libraries

(66) 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.

(67) 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).

(68) 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.

(69) 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 (uniprot.org/), and IUPHAR/BPS Guide to PHARMACOLOGY (guidetopharmacology.org/).

(70) 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.

(71) 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.

(72) 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.

(73) 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.

(74) 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.

(75) TABLE-US-00001 TABLE 1 GLP1R amino acid sequences SEQ ID NO GPCR
Amino Acid Sequence 1352 GLP1R

RPQGATVSLWETVQKWREYRQCQRSLTEDPPPATDLFCNRTFDEYA
CWPDGEPGSFVNVSCPWYLPWASSVPQGHVYRFCTAEGWLQKDNS
SLPWRDLSECEESKRGERSSPEEQLLFLYIIYTVGYALSFSALVIASAIL
LGFRHLHCTRNYIHLNLFASFILRALSVFIKDAALKWMYSTAAQQHQ
WDGLLSYQDSLSCRLVFLLMQYCVAANYYWLLVEGVYLYTLLAFSV
LSEQWIFRLYVSIGWGVPLLFFVPWGVVVKYLYEDEGCWTRNSNMNY
WLIIRLPILFAIGVNFLIFVRVICIVVSKLKANLMCKTDIKCRLAKSTLT
LIPLLGTHEVIFAFVMDEHARGTLRFIKLFTLSFTSFQGLMVAILYCF
VNNEVQLEFRKSWERWRLEHLHIQRDSSMKPLKCPTSSLSSGATAGS SMYTATCQASCS

(76) 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.

(77) 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.

(78) 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.

(79) 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.

(80) 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).

(81) 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 M P et al., “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” Dev Comp Immunol, 2003 January; 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 N R and Rees A R, “WAM: an improved algorithm for modelling antibodies on the WEB,” Protein Eng. 2000 December; 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.

(82) 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.

(83) 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.

(84) 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.

(85) 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.

(86) 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.

(87) 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.

(88) 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 to about 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. (89) 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.

(90) 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.

(91) 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: 1157-1335. 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: 1157-1335. 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: 1157-1335. 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: 1157-1335. 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: 1157-1335. In some instances, an antibody or antibody fragment described herein comprises a CDRL3 sequence of any one of SEQ ID NOs: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519.

(92) 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: 1157-1335; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1336-1347 and 1353-1519. 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: 1157-1335; 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: 1336-1347 and 1353-1519.

(93) 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.

(94) 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 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 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 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.

(95) 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.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, 10.sup.13, 10.sup.14, 10.sup.15, 10.sup.16, 10.sup.17, 10.sup.18, 10.sup.19, 10.sup.20, or more than 10.sup.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.sup.5 non-identical sequences (10×237×43).

(96) 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, IGHV3-30/33m, 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.

(97) 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.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, 10.sup.13, 10.sup.14, 10.sup.15, 10.sup.16, 10.sup.17, 10.sup.18, 10.sup.19, 10.sup.20, or more than 10.sup.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.

(98) 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.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, 10.sup.13, 10.sup.14, 10.sup.15, 10.sup.16, 10.sup.17, 10.sup.18, 10.sup.19, 10.sup.20, or more than 10.sup.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.

(99) 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.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, 10.sup.13, 10.sup.14, 10.sup.15, 10.sup.16, 10.sup.17, 10.sup.18, 10.sup.19, 10.sup.20, or more than 10.sup.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.sup.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.sup.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.

(100) 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.

(101) 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.

(102) 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%.

(103) 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^{sup.7}, 10^{sup.8}, 10^{sup.9}, 10^{sup.10}, 10^{sup.11}, 10^{sup.12}, 10^{sup.13}, 10^{sup.14}, 10^{sup.15}, 10^{sup.16}, 10^{sup.17}, 10^{sup.18}, 10^{sup.19}, 10^{sup.20}, or more than 10^{sup.20} sequences. In some instances, the library has a final library diversity of at least or about 10^{sup.7}, 10^{sup.8}, 10^{sup.9}, 10^{sup.10}, 10^{sup.11}, 10^{sup.12}, 10^{sup.13}, 10^{sup.14}, 10^{sup.15}, 10^{sup.16}, 10^{sup.17}, 10^{sup.18}, 10^{sup.19}, 10^{sup.20}, or more than 10^{sup.20} sequences.

(104) 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.

(105) 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.

(106) 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.

(107) 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.

(108) 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.

(109) Expression Systems

(110) 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.

(111) 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.

(112) 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.

(113) 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.

(114) 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.

(115) 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.

(116) 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-3×FLAG, pSF-CMV-NEO-COOH-3×FLAG, 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.

(117) 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.

(118) 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 glucuronidase (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.

(119) Diseases and Disorders

(120) 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.

(121) 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.

(122) 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.

(123) 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.

(124) 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.

(125) 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.

(126) 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: 1157-1335. 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: 1157-1335. 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: 1157-1335. 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: 1157-1335. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519. 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: 1336-1347 and 1353-1519.

(127) 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: 1157-1335; and (f) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 1336-1347 and 1353-1519. 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: 1157-1335; 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: 1336-1347 and 1353-1519. 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.

(128) 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.

(129) Variant Libraries

(130) Codon Variation

(131) 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.

(132) TABLE-US-00002 TABLE 2 List of codons and amino acids One Three letter letter Amino Acids code 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

(133) 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.

(134) Highly Parallel Nucleic Acid Synthesis

(135) 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.

(136) 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.

(137) 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.

(138) 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.

(139) 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.sub.H or V.sub.L), and specific complementarity-determining regions (CDRs) of V.sub.H or V.sub.L.

(140) 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.

(141) 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.

(142) Substrates

(143) 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.

(144) 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.

(145) 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.

(146) 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 μm . 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 μm . 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 μm . 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 μm . In some cases, each locus has a width of about 0.5-100, 0.5-50, 10-75, or 0.5-50 μm .

(147) In some instances, the density of clusters within a substrate is at least or about 1 cluster per 100 mm.^{sup.2}, 1 cluster per 10 mm.^{sup.2}, 1 cluster per 5 mm.^{sup.2}, 1 cluster per 4 mm.^{sup.2}, 1 cluster per 3 mm.^{sup.2}, 1 cluster per 2 mm.^{sup.2}, 1 cluster per 1 mm.^{sup.2}, 2 clusters per 1 mm.^{sup.2}, 3 clusters per 1 mm.^{sup.2}, 4 clusters per 1 mm.^{sup.2}, 5 clusters per 1 mm.^{sup.2}, 10 clusters per 1 mm.^{sup.2}, 50 clusters per 1 mm.^{sup.2} or more. In some instances, a substrate comprises from about 1 cluster per 10 mm.^{sup.2} to about 10 clusters per 1 mm.^{sup.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 μm . 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 μm . 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.

(148) 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.^{sup.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.

(149) Surface Materials

(150) 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 polytetrafluoroethylene, 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.

(151) Surface Architecture

(152) 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.

(153) 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.

(154) 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.^{sup.2}.

(155) 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. (156) 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 μm . In some cases, the height of a well is less than about 1000, 900, 800, 700, or 600 μm .

(157) 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 μm . In some cases, the height of a channel is less than 100, 80, 60, 40, or 20 μm .

(158) 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 μm , for example, to about 90, 80, 70, 60, 50, 40, 30, 20 or 10 μm . 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 μm . 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 μm .

(159) Surface Modifications

(160) 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.

(161) 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.

(162) 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.

(163) 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. Pat. No. 5,474,796, which is herein incorporated by reference in its entirety.

(164) 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.

(165) Polynucleotide Synthesis

(166) 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.

(167) 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 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).

(168) 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.sub.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.sub.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.

(169) 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).

(170) 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.

(171) 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.

(172) 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.

(173) 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.)

(174) 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.

(175) 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.

(176) 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.

(177) 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.

(178) 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.

(179) 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 **301** 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.

(180) In situ preparation of polynucleotide arrays is generated on a solid support **301** 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.

(181) 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.

(182) 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**.

(183) 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**.

(184) 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**. (185) 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**.

(186) Computer Systems

(187) 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.

(188) 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.

(189) 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 S5PC100™ processor, ARM Cortex-A8 Apple A4™ processor, Marvell PXA 93014 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.

(190) 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.

(191) 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®, MACOS®, BlackBerry® OS™, BlackBerry® 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.

(192) 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.

(193) 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 **702** 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.

(194) 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.

(195) 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.

(196) 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

(197) 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.

Example 1: Functionalization of a Device Surface

(198) 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% H₂SO₄ and 10% H₂O₂ 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 N₂. The device was subsequently soaked in NH₄OH (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 O₂. A SAMCO PC-300 instrument was used to plasma etch O₂ at 250 watts for 1 min in downstream mode.

(199) 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. SPRTM 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 O₂ plasma etch at 250 watts for 1 min.

(200) 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.sub.2. The functionalized surface was activated to serve as a support for polynucleotide synthesis.

Example 2: Synthesis of a 50-mer Sequence on an Oligonucleotide Synthesis Device

(201) 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-TRIETHOXYSILYL)PROPYL-4-HYDROXYBUTYRAMIDE (Gelest) which was used to synthesize an exemplary polynucleotide of 50 bp (“50-mer polynucleotide”) using polynucleotide synthesis methods described herein.

(202) 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.

(203) 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.

(204) TABLE-US-00003 TABLE 3 Synthesis protocols Table 3 General DNA Synthesis Time Process Name Process Step (sec) WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) Acetonitrile to Flowcell 23 N2 System Flush 4 Acetonitrile System Flush 4 DNA BASE ADDITION Activator Manifold Flush 2 (Phosphoramidite + Activator to Flowcell 6 Activator Flow) Activator + 6 Phosphoramidite to Flowcell Activator to Flowcell 0.5 Activator + 5 Phosphoramidite to Flowcell Activator to Flowcell 0.5 Activator + 5 Phosphoramidite to Flowcell Incubate for 25 sec 25 WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) Acetonitrile to Flowcell 15 N2 System Flush 4 Acetonitrile System Flush 4 DNA BASE ADDITION Activator Manifold Flush 2 (Phosphoramidite + Activator to Flowcell 5 Activator Flow) Activator + 18 Phosphoramidite to Flowcell Incubate for 25 sec 25 WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) Acetonitrile to Flowcell 15 N2 System Flush 4 Acetonitrile System Flush 4 CAPPING (CapA + B, CapA + B to Flowcell 15 1:1, Flow) WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) Acetonitrile to Flowcell 15 Acetonitrile System Flush 4 OXIDATION (Oxidizer Oxidizer to Flowcell 18 Flow) WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) N2 System Flush 4 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 Deblock to Flowcell 36 Flow) WASH (Acetonitrile Wash Acetonitrile System Flush 4 Flow) 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

(205) 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.

(206) 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 ~100 uL/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-methylimidazole in THF), roughly ~200 uL/sec, and for Deblock (3% dichloroacetic acid in toluene), roughly ~300 uL/sec (compared to ~50 uL/sec for all reagents with flow restrictor). The time to completely push out Oxidizer was observed, the timing for chemical flow times was

Materials and Methods

(215) Stable Cell Line and Phage Library Generation

(216) 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.

(217) Germline heavy chain IGHV1-69, IGHV3-30 and germline light chain IGKV1-39, IGKV3-15, IGLV1-51, IGL V2-14 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 (SEQ ID NO: 1520). 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.

(218) Panning and Screening Strategy Used to Isolate Agonist GLP-1R scFv Clones

(219) 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/4×1000 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 1×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° 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.

(220) Next-Generation Sequencing Analysis

(221) The phagemid DNA was minipreped 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 (SEQ ID NO: 1521) and reverse primer TGAACCGCCTCCACCGCTAG (SEQ ID NO: 1522). 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 MiSeqR Reagent Kit v3 (Illumina, product #MS-102-3003) and run on the MiSeqR instrument.

(222) Reformatting and High Throughput (HT) IgG Purification

(223) 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.

(224) 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.

(225) Binding Assays and Flow Cytometry

(226) 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).

(227) Ligand Competition Assay

(228) Ligand competition assays involved co-incubating the primary IgG with 1 μ M 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 μ M) was prepared similarly with the Flow buffer (PBS+1% BSA). Each well contained 100,000 cells to which 50 μ L of IgG and 50 μ L of peptide (=plus) or buffer alone without peptide (=minus) were added. Cells and IgG/peptide mix were incubated for 1 hr 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 (50 μ L per well), before washing and resuspending in 60 μ L buffer. Finally, the assay read-out was measured on an Intellicyt® IQue3 Screener at a rate of 4 seconds per well.

(229) Cell-Based Functional Assays

(230) cAMP assays. GLP-1R IgG clones were tested for their potential effects on GLP-1R signaling by performing cAMP assays obtained from Eurofins DiscoverXX. 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 100 nM 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.

(231) Beta arrestin recruitment assay. β -arrestin recruitment assay was obtained from Eurofins DiscoverXX (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 μ L volume, and then 5 μ L 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™.

(232) In Vivo Studies

(233) 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 (22-25 C) and light controlled (12-h: 12-h light/dark cycle starting at 7 AM. 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.

(234) 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.

(235) 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.

(236) 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.

(237) Glucose Tolerance Test

(238) 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 (10 ul/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.)

(239) Insulin Tolerance Test

(240) 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 (0.75 U/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.).

(241) ELISA for Pharmacokinetic (PK) Studies.

(242) 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 100 mM Hepes, 100 mM NaCl, 50 mM NaAc, pH 6.0 vehicle. Serial blood samples were collected via jugular vein cannula with ~250 μ L 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.sub.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 (3.3 μ L for 100 μ L 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.

Results

(243) Design of GPCR-Focused Antibody Library is Based on GPCR Binding Motifs and GPCR Antibodies

(244) 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 (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 (Zhang Lab at University of Michigan), 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 (SEQ ID NO: 1523),

CARDMYYDFxxxxxEVVPADDAFDIW (SEQ ID NO: 1524),

CARDGRGSLPRPKGGPxxxxxYDSSSEDSGGAFDIW (SEQ ID NO: 1525),

CARANQHFxxxxxGYHYYGMDVW (SEQ ID NO: 1526), CAKHMSMQxxxxxRADL VGDAFDVW (SEQ ID NO: 1527).

(245) 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.

(246) 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 IGL V2-14 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 been 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 (G4S) 3 linker (SEQ ID NO: 1520). 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 sequences³¹. 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, 16aaxxxx18aa, 14aa) used to present the motifs within HCDR3.

(247) Phage Panning Against GLP-1R Over-Expressing Cell Lines Resulted in Clonal Enrichment

(248) 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 1 ml scale.

(249) IgG Binders Directed to GLP-1R Contain Either GLP-1, GLP-2 or Unique HCDR3 Motifs Identified

(250) Purified IgG clones were tested for specific binding to GLP-1R-expressing CHO cells. A single-point flow cytometry analysis using 100 nM 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 200 nM (30 µg/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.

(251) Eight IgGs of the 13 Binders are Negative Antagonists in GLP-1R Mediated cAMP Signaling
(252) 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).

(253) Characterization of Mechanisms of Action of the Antagonist IgG GLP1R-3

(254) 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:

(255) 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 (1 μ M). 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).

(256) 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.

(257) 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 (100 nM) 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.

(258) Design and Characterization of a GLP-1R Agonist IgG GLP1R-59-2

(259) 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:

(260) 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 EC₅₀ of 15.5 nM (FIG. 18A).

(261) 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 EC₅₀ values, 0.042 nM for GLP1R-59-2 and 0.085 nM for GLP-1 7-36. (FIG. 18B) supporting the hypothesis that GLP1R-59-2 can act as an effective agonist for GLP-1R.

(262) 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 EC₅₀ of 0.042 nM, and 0.085 nM for GLP-1 7-36, respectively.

(263) In Vivo PK and PD Testing of GLP1R-3 and GLP1R-59-2

(264) 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.

(265) Agonist GLP1R-59-2 was tested for its 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.

(266) 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 (20 mg/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 (0.23 mg/kg) with 19+2 hour treatment.

(267) 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).

(268) 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 (20 mg/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.

Example 5: GLP1R Variants

(269) GLP1R-3 was optimized to generate additional GLP1R variants.

(270) 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.

(271) TABLE-US-00006 TABLE 6A IgG MFI Ratio Subtraction GLP1R-3 993.31197 232201 GLP1R- 914.54027 272235 221-065 GLP1R- 1174.8495 241813 221-075 GLP1R- 1484.8457 240383 221-017 GLP1R- 1015.9153 239520 221-033 GLP1R- 746.61867 235615.5 221-076 GLP1R- 711.73926 231701 221-092 GLP1R- 711.15764 222989.5 221-034 GLP1R- 927.53542 222368.5 221-066 GLP1R- 1067.8986 220848 221-084 GLP1R- 1119.868 220417 221-009

(272) TABLE-US-00007 TABLE 6B IgG MFI Ratio Subtraction GLP1R-3 740.2 223614 GLP1R-222- 13.70825851 350309.5 052 GLP1R-222- 773.9745223 242714 016 GLP1R-222- 777.8080645 240810.5 023 GLP1R-222- 794.2474916 237181 014 GLP1R-222- 525.349537 226519 090 GLP1R-222- 983.9519651 225096 073 GLP1R-222- 774.5748709 224723.5 012 GLP1R-222- 711.0952381 223680 082 GLP1R-222- 850.1807692 220787 081 GLP1R-222- 946.2456522 217406.5 056

(273) TABLE-US-00008 TABLE 6C Median Median RL1-H of RL1-H of Expressing Parent MFI Sample Singlets Singlets 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

(274) TABLE-US-00009 TABLE 6D Median Median RL1-H of RL1-H of Expressing Parent MFI
Sample Singlets Singlets 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

(275) TABLE-US-00010 TABLE 6E GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1
GLP1 GLP1 Sample R221-009 R221-017 R221-033 R221-034 R221-065 R221-066 R221-075
R221-076 R221-084 R221-092 R01-3 EC.sub.50 12.46 27.65 9.041 ND ND 57.39 ND ND 4.091
13.29 11.51 [nM] CHO GLPIR B.sub.max 215146 249646 167203 932518 797529 171812 213495
799149 286814 144511 799671 CHO GLPIR EC.sub.50 ND ND ND ND ND ND ND ND ND ND
ND [nM] CHO Parent B.sub.max 267.4 228.7 146 279.8 261.9 112.1 234 183.2 266.6 291.2 268
CHO Parent

(276) TABLE-US-00011 TABLE 6F GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1
GLP1 GLP1 Sample R222-012 R222-014 R222-016 R222-023 R222-052 R222-056 R222-073
R222-081 R222-082 R222-090 R01-3 EC.sub.50 23.14 34.29 7.709 18.35 17.36 77.43 13.07 22.51
11.49 ND 15.4 [nM] CHO GLP1R B.sub.max 233768 213081 129918 220325 228012 292619
150681 193955 134940 1078076 152782 CHO GLP1R EC.sub.50 ND ND ND 89.37 ND ND ND
ND ND ND ND [nM] CHO Parent B.sub.max 340.6 336.4 218.5 237.9 47529 237.5 228.4 243.4
305 413.4 265.3 CHO Parent

(277) TABLE-US-00012 TABLE 6G [IgG] GLP1 GLP1 GLP1 GLP1 GLP1R GLP1R GLP1R
GLP1R GLP1R GLP1R GLP1R nM R221-009 R221-017 R221-033 R221-034 221-065 221-066
221-075 221-076 221-084 221-092 01-3 100.00 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

(278) TABLE-US-00013 TABLE 6H [IgG] GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1 GLP1
GLP1 GLP1 GLP1 nM R222-012 R222-014 R222-016 R222-023 R222-052 R222-056 R222-073
R222-081 R222-082 R222-090 R01-3 100.00 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

(279) 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 3× titration from 12.5 nM. Data is seen in FIG. 26 with improved variants highlighted in green.

Example 6: Sequences

(280) TABLE-US-00014 TABLE 7 Sequences of GLP1 embedded in CDRH3 SEQ
ID NO Sequence 1 CAKHMSMQEGAVTGEQGAAKEFIAWLKGRVRADLVGDAFDVW 2
CARDGRGSLPRPKGGPQTVGEGQAAKEFIAWLKGGGLTYDSSSEDSGGAFDIW 3
CAKHMSMQDYLVIGEGQAAKEFIAWLKGGPARADLVGDAFDVW 4
CAKHMSMQEGAVTGEQGDAKEFIAWLKGRVRADLVGDAFDVW 5
WAKHMSMQEGAVTGEQGAAKEFIAWLKGRVRADLVGDAFDVW 6
CARDGRGSLPRPKGGPQTVGEGQAAKEFIAWLKGRVRADLVGDAFDVW 7
CARANQH FYEQEGTFTSDVSSYLEGQAAKEFIAWLKGGIRGYHYYGMDVW 8
CARANQH FTELHGEGQAAKEFIAWLKGRGQIDIGYHYYGMDVW 9
CARANQH FLGAGVSSYLEGQAAKEFIAWLKGGDTTGYHYYGMDVW 10
CARANQH FLDKGTFTSDVSSYLEGQAAKEFIAWLKGGIYPGYHYYGMDVW 11
CARANQH FGTL SAGEGQAAKEFIAWLKGGSQYDSSSEDSGGAFDIW 12
CARANQH FGLHAQGEQAAKEFIAWLKGGSGTYGYHYYGMDVW 13
CARANQH FG GKGEGQAAKEFIAWLKGGGSGAGYHYYGMDVW 14

CAKQMSMQEGQAGQAAKEFIAWLVKGRVRADLVGDAFDVW 15
CAKHMSMQEGAVTGEGQAAKEFIAWLVKGGPARADLVGDAFDVW 16
CAKHMSMQEGAVTGEGQAAKEFIAWLVKGGLTYDSSSEDSGGAFDIW 17
CAKHMSMQDYLVI GEGQAAKEFIAWLVKGRVRADLVGDAFDVW
(281) TABLE-US-00015 TABLE 8 GLP1R Variants CDRH3 Sequences SEQ ID Variant
NO. Sequence GLP1R-1 18 CARANQHFDVLYGWHGVPGKYHYHYYGMDVW GLP1R-2 19
CARDMYDYDFETVVEGIQWYEALKAGKLGEVVPADDAFDIW GLP1R-3 20
CAKHMSMQEGAVTGEG**QAAKEFIAWLVKGRVRADLVGDAFDVW** GLP1R-8 21
CARDGRGSLPRPKGGPQTVGEG**QAAKEFIAWLVKGGLTYDSSSEDSGGAFDIW** GLP1R-10
22 CARANQHFFVPGSLKVWLKGVAPESSEYDSSSEDSGGAFDIW GLP1R-25 23
CARANQHFLSHAGA**AARDFINWLIQTKITGLGSGYHYHYYGMDVW** GLP1R-26 24
CAKHMSMQEGVLQGQIPSTIDWEGLLHLIRADLVGDAFDVW GLP1R-30 25
CARDMYDYDFLKIGDNLA**AARDFINWLIQTKITDGTDEVPADDAFDIW** GLP1R-50 26
CARDGRGSLPRPKGGPKFVPGKHETYGHKTGYRLRPGYHYHYYGMDVW GLP1R-56 27
CARANQHFFSGAEGEG**QAAKEFIAWLVKGIIPGYHYHYYGMDVW** GLP1R-58 28
CARANQHFLHAQGE**GQAAKEFIAWLVKGSGTYGYHYHYYGMDVW** GLP1R-60 29
CAKHMSMQDYLVI GEG**QAAKEFIAWLVKGGPARADLVGDAFDVW** GLP1R-70 30
CARDGRGSLPRPKGGPPSSGR**DFINWLIQTKITDGF**RYDSSSEDSGGAFDIW GLP1R-71 31
CARDLRELECEEWTRHGGKKHHGKRQSNRAHQGKHETYGHKTGSLVPSRGPCVD
PRGVAGSFDVW GLP1R-72 32
CARDMYDYDFHPEGTFTSDVSSYLE**GQAAKEFIAWLVKGSLIYEVVPADDAFDIW** GLP1R-
80 33 CARANQHFGPVAGGATPSEEPGSQLTRAELGWDAPPGQESLADELLQLGTEHGYH
YYGMDVW GLP1R-83 34
CAKHMSMQEGAVTGEG**QAAKEFIAWLVKGRVRADLVGDAFDVW** GLP1R-93 35
CARANQHFLSHAGA**AARDFINWLIQTKITGLGSGYHYHYYGMDVW** GLP1R-98 36
CARDGRGSLPRPKGGPHSGRLGSGYKSYDSSSEDSGGAFDIW GLP1R-238 37
CARANQHFSQAGRAARVPGPSSSLGPRGYHYHYYGMDVW GLP1R-239 38
CAKHMSMQSQGLDNLA**AARDFINWLIQTKITDGF**ELSRADLVGDAFDVW GLP1R-240 39
CARDMYDYDFFLG**TFTSDVSSYLEGQAAKEFIAWLVKGV**SPEVVPADDAFDIW GLP1R-
241 40 CAKHMSMQGSVAGGTFTSDVSSYLE**GQAAKEFIAWLVKGGPSFIRADLVGDAFD**
VW GLP1R-242 41
CAKHMSMQADT**GTFTSDVSSYLEGQAAKEFIAWLVKGEFSSRADLVGDAFDVW**
GLP1R-243 42 CARANQHFFGKGDNLA**AARDFINWLIQTKITDGS**NPGYHYHYYGMDVW
GLP1R-244 43 CARANQHFAATGAGE**GQAAKEFIAWLVKGRVEIGYHYHYYGMDVW** *bold
corresponds to GLP1 or GLP2 motif

(282) TABLE-US-00016 TABLE 9 Variable Heavy Chain Sequences SEQ ID Variant NO.
Variable Heavy Chain Sequence GLP1R- 44
MEWSWVFLFFLSVTTG VHSQVQLVQSGAEVKKPGSSVKV SCKASGGSFSSHAISW 238
VRQAPGQGLEWMGGIIPFGAPNYAQKFQGRVTITADESTSTAYMELSSLRSEDTA
VYYCARANQHFSQAGRAARVPGPSSSLGPRGYHYHYYGMDVWGQGT LVT VSSASAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDK TVERKCCVECP PCPAPPV
AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP
QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT P PMLDSD
GSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG GLP1R- 45
MEWSWVFLFFLSVTTG VHSQVQLVESGGGVVQPGRSLRLSCAASGFD FSNYGMH 239
WVRQAPGKGLEWVADISYEGSNKY YADSVKGRFTISRDN SKNTLYLQMNSLRAE
DTAVYYCAKHMSMQSQGLDNLA**AARDFINWLIQTKITDGF**ELSRADLVGDAFDVW
GQGT LVT VSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSG

ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTV
KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTFRVVSFLTUVVHQQDWLNGKEYKCKVSNKGLPAP
IEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
GLP1R- 46

MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTENNYGIS 240
WVRQAPGQGLEWMGGIIPVFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCARDMYDFFGLGTFTSDVSSYLEGQAAKEFIAWLVKGVSPPEVVPADDA
FDIWGQGTLTVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVD
KTVRKKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTFRVVSFLTUVVHQQDWLNGKEYKCKVSNK
GLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG GLP1R- 47

MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSDYAIS 241
WVRQAPGQGLEWMGGIIPVFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCAKHMSMQGSVAGGTFTSDVSSYLEGQAAKEFIAWLVKGGPSFIRADLVG
DAFDVWGQGTLTVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTK
VDKTVRKKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSFLTUVVHQQDWLNGKEYKCKV
SNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPG GLP1R- 48

MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYEISW 242
VRQAPGQGLEWMGGIIPVILGIANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCAKHMSMQADTGTFTSDVSSYLEGQAAKEFIAWLVKGEFSSRADLVGDAFD
VWGQGTLTVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTV
ERKKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTFRVVSFLTUVVHQQDWLNGKEYKCKVSNKGLP
APIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
GLP1R- 49

MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSTYGIN 243
WVRQAPGQGLEWMGGIIPVFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCARANQHFFGKGDNLAARDFINWLIQTKITDGSNPGYHYYGMDVWGQGT
LTVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVRKKCCV
ECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTFRVVSFLTUVVHQQDWLNGKEYKCKVSNKGLPAPIEKT
ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GLP1R-
50 MEWSWVFLFFLSVTTGVHSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW 244
VRQAPGQGLEWMGGIIPVFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCARANQHFAATGAGEGQAAKEFIAWLVKGRVEIGYHYYGMDVWGQGT
LTVTVSSASASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTVRKKCCVECP

PCPAPPVFLFPPKPDVTLVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GLP1R- 51
QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVAVISYD 59-2
AGNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDMYDFETVV
EGIQWYEAL KAGKLGEVVPADDAFDIWGQGT LVT VSSASTKGPSVFPLAPCSRSTS
ESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSN
FGTQTYTCNV DHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLM
ISRTP EVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLT
VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK GLP1R- 52
QVQLVQSGAEVKKPGSSVKV SCKASGGTFSDY AISWVRQAPGQGLEWMGGIIPF 59-241
GTTNYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCAKHMSMQGSVAGG
TFTSDVSSYLEGQA AKEFIAWL VKGGPSFIRADLVGDAFDVWGQGT LVT VSSASA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDK TVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GLP1R- 53
QVQLVQSGAEVKKPGSSVKV SCKASGGTFSTYGINWVRQAPGQGLEWMGGIIPF 59-243
GTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARANQHFFGKGDNL
AARDFINWLIQTKITDGSNPGYHYYGMDVWGQGT LVT VSSASASTKGPSVFPLAP
CSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSNFGTQTYTCNV DHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTP EVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GLP1R-3 54
QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSFISYDE
SNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT
GEGQA AKEFIAWL VKGRVRADLVGDAFDVWGQGT LVT VSSASTKGPSVFPLAPC
SRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSNFGTQTYTCNV DHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFLFPPK
KDTLMISRTP EVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRV
VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK GLP1R- 55
MEWSWVFLFFLSVTTGVHSEVQLVESGGGLVQAGGSLRLSCAASGSIFRINAMGW 43-8
FRQAPGKEREGVAAINNFGTTKYADSAKGRFTISADNAKNTVYLQMNSLKPEDTA
VYYCAAVRWGPHNDDRYDWGQGTQVT VSSGGGGSEPKSSDKTHTCPPCPAPELL
GGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GLP1R- 56
QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAPGKGLEWVAVISYE 10
GSDKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARANQHFFVPGSL
KVWLKGVAPESSEYDSSEDSGGAFDIWGQGT LVT VSS GLP1R- 57

QVQLVQSAGAEVKKVSSVQVNGVWVSRQAPGKGLWMMGGIIPIL 26
GTADYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCAKHMSMQEGLQG
QIPSTIDWEGLLHLIRADLVGDAFDVWGQGTLVTVSS GLP1R- 58
QVQLVESGGGVVQPGRSLRLSCAASGFTFNMYAMHWVRQAPGKGLEWVAVISY 221-065
DRSNEYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGDGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 59
QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYPMHVVRQAPGKGLEWVAVISYD 221-075
ETNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEGQAAKEFIAWLVKGIVRADLVGDAFDVWGQGTLVTVSS GLP1R- 60
QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYGVHWVRQAPGKGLEWVAFISYD 221-017
ESNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEYQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 61
QVQLVESGGGVVQPGRSLRLSCAASGFSFSNYAMHWVRQAPGKGLEWVAVISHD 221-033
RSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEGQAAKDFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 62
QVQLVESGGGVVQPGRSLRLSCAASGFTFNYPMHVVRQAPGKGLEWVAVISYD 221-076
ETNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEGQAAKEFIAWLVKGIVRADLVGDAFDVWGQGTLVTVSS GLP1R- 63
QVQLVESGGGVVQPGRSLRLSCAASGFIFNNYGMHWVRQAPGKGLEWVAFISYG 221-092
GSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGEGQAVKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 64
QVQLVESGGGVVQPGRSLRLSCAASGFPPFSNYGMHWVRQAPGKGLEWVAVISHD 221-034
RSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEGQAVKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 65
QVQLVESGGGVVQPGRSLRLSCAASGFTFNMYAMHWVRQAPGKGLEWVAVISY 221-066
DRSNEYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGEGQAIKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 66
QVQLVESGGGVVQPGRSLRLSCAASGFAFSNYGMHWVRQAPGKGLEWVAVISSD 221-084
ENNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGEMQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 67
QVQLVESGGGVVQPGRSLRLSCAASGFIFSNYGMHWVRQAPGKGLEWVAVISDE 221-009
GSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGAGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 68
QVQLVESGGGVVQPGRSLRLSCAASGFTFNYPMHVVRQAPGKGLEWVAVISYD 222-052
ESNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GGGQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 69
QVQLVESGGGVVQPGRSLRLSCAASGFTFNMYAMHWVRQAPGKGLEWVAVISDE 222-016
GSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGEYQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 70
QVQLVESGGGVVQPGRSLRLSCAASGFSFSDYGMHWVRQAPGKGLEWVAFISYD 222-023
ANNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAV
TGEWQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 71
QVQLVESGGGVVQPGRSLRLSCAASGFAFSNYGMHWVRQAPGKGLEWVSFISYD 222-014
ESNKYYADSVKGRFTISRDN SKNTLYLQMNNLRAEDNAVYYCAKHMSMQEGAV
TGEWQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 72
QVQLVESGGGVVQPGRSLRLSCAASGFSFSDYGIHWVRQAPGKGLEWVALISYEG 222-090
SNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT
GEKQAAKEFIAWLVKGRVRADLVGDAFDVWGQGTLVTVSS GLP1R- 73
QVQLVESGGGVVQPGRSLRLSCAASGFTFRDYGMHWVRQAPGKGLEWVAFIRYD 222-073
EINKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDNAVYYCAKHMSMQEGAVT

GEGQAAKEFIAWLKGRVADLVGDAFDVWGQGLTVTVSS GLP1R- 74
QVQLVESGGGVVQPGRSLRLSCAASGFTFNNGMHVWRQAPGKGLEWVAVISDE 222-012
GSNKYYADSVKGRFTISRDNSTNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV
TGVGQAAKEFIAWLKGRVADLVGDAFDVWGQGLTVTVSS GLP1R- 75
QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYSMHWVRQAPGKGLEWVALISYD 222-082
ATNKYYADSVKGRFTISRDNSTNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV
TGEFQAAKEFIAWLKGRVADLVGDAFDVWGQGLTVTVSS GLP1R- 76
QVQLVESGGGVVQPGRSLRLSCAASGFTFDNYALHWVRQAPGKGLEWVALISYD 222-081
AGNKYYADSVKGRFTISRDNSTNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAV
TGEGQAAKEFIAWLKGFVRADLVGDAFDVWGQGLTVTVSS GLP1R- 77
QVQLVESGGGVVQPGRSLRLSCAASGFPFSSYAMHWVRQAPGKGLEWVAVISYD 222-056
RSNKYYADSVKGRFTISRDNSTNTLYLQMNSLRAEDTAVYYCAKHMSMQEGAVT
GYGQAAKEFIAWLKGFVRADLVGDAFDVWGQGLTVTVSS
(283) TABLE-US-00017 TABLE 10 Variable Light Chain Sequences SEQ ID Variant
NO. Variable Light Chain Sequence GLP1R- 78
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSTSNIANNYVSW 238
YQQLPGTAPKLLIYANNRRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGAW
DVRLDVGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV
TVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLS GLP1R- 79
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSTSNIENNYVSW 239
YQQLPGTAPKLLIYGNDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW
ENRLSAVVFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV
TVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG
STVEKTVAPTECS GLP1R- 80
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSSIGNNYVSW 240
YQQLPGTAPKLLIYANNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCATW
SSSPRGWVFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV
TVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG
STVEKTVAPTECS GLP1R- 81
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGISSNIGNNYVSW 241
YQQLPGTAPKLLIYDDDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW
DNILSAAVVFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVT
VAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS GLP1R- 82
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSNIENNDVSW 242
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STVEKTVAPTECS GLP1R- 83
MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSRSNIGKNYVSW 243
YQQLPGTAPKLLIYENNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCSSYT
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MSVPTQVLGLLLLWLTDARCQSVLTQPPSVSAAPGQKVTISCSGSSSNIENNVVSW 244
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TVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG
STVEKTVAPTECS GLP1R- 85
HAEGTFTSDVSSYLEGQAAKEFIAWLKGRGGGGGSGGGGSGGGGSGSVLTQPPS 59-243

VSAAPGQKV TISCSGSR SNIGNNY VSWYQQ LPGTAPKLLIYENNERPSGIPDRFSGS
KSGTSATL GITGLQTGDEADYYCSSYTTSNTQVF GGGTKLTVLGQP KAAPSVTLFP
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SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS GLP1R- 86
HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRGGGGGSGGGGSGGGGSGSVLTQPPS 59-241
VSAAPGQKV TISCSGISSNIGNNY VSWYQQ LPGTAPKLLIYDDDQRPSGIPDRFSGS
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ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS GLP1R- 87
HGEFTFTSDVSSYLEEQAAKEFIAWLVKGGGGGGSGGGGSGGGGSGSALTQPAS 59-2
VSGSPGQSITISCTGTSNDIGTYNY VSWYQQHPGKAPKLM IYDVSGRPSGVSNRFS
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93 QSVLTQPPSVSAAPGQKV TISCSGSGSNIGNNDVSWYQQ LPGTAPKLLIYDNDKRP 221-
075 AGIPDRFSGSKSGTSATL GITGLQTGDEADYYCGTWDTSLSNYVFGGGTKLTVL
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95 QSVLTQPPSVSAAPGQKV TISCSGSSSNIGNNEY VSWYQQ LPGTAPKLLIYDNNKRV 221-
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222-012 GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSLSVGEFGGGTKLTVL
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(284) TABLE-US-00018 TABLE 11 GLP1R Sequences GLP1R SEQ ID Variant NO
Sequence GLP1R-40- 112
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GQGLTVTVSS GLP1R-40- 113
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QGTLVTVSS GLP1R-40- 114
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GLP1R-43- 253

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WDGRNAYYANSRFRFTISADNSKNTAY LQMNSLKPEDTAVYYCPRYVSPARD
HGCWGQGT LVT VSS GLP1R-41- 267
EVQLVESGGGLVQPGGSLRLSCAASGLTISTYIMGWFRQAPGKEREFVAVVNWN 02
GDSTYYADSVKGRFTISADNSKNTAY LQMNSLKPEDTAVYYCAAYYTDYDEAL
EETRGSYDWGQGT LVT VSS GLP1R-41- 268
EVQLVESGGGLVQPGGSLRLSCAASGTLFKINAMGWFRQAPGKERELVAAINRG 03
GKITHYADSVKGRFTISADNSKNTAY LQMNSLKPEDTAVYYCAASLRNSGSNVE
GRWGQGT LVT VSS GLP1R-41- 269
EVQLVESGGGLVQPGGSLRLSCAASGVTL DLYAMGWFRQAPGKEREFVAAISPS 04
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DANEYEWGQGT LVT VSS GLP1R-41- 270
EVQLVESGGGLVQPGGSLRLSCAASGRTFSDYIMGWFRQAPGKEREFVAVINRSG 05

STTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVQAYSNSDDYY
SQEGAYDWGQGTLVTVSS GLP1R-41- 271

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYVMGWFRQAPGKEREGVSYISDD 06
GRTHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYNGSWG
QGTLVTVSS GLP1R-41- 272

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRFGMGWFRQAPGKEREGVAAIGSD 07
GSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASGRDRYARDLSE
YEYVWGQGTLVTVSS GLP1R-41- 273

EVQLVESGGGLVQPGGSLRLSCAASGFTFRFNAMGWFRQAPGKEREFVAAINWR 08
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TWGQGTLVTVSS GLP1R-41- 274

EVQLVESGGGLVQPGGSLRLSCAASGGTFGVYHMGWFRQAPGKEREFVLAASVTW 09
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YRNSWVYNWGQGTLVTVSS GLP1R-41- 275

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MDWGQGTLVTVSS GLP1R-41- 276

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NQEGAYDWGQGTLVTVSS GLP1R-41- 277

EVQLVESGGGLVQPGGSLRLSCAASGPTFSNYYVGVWFRQAPGKEREFVAAILCSG 12
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GTLVTVSS GLP1R-41- 278

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YEYVWGQGTLVTVSS GLP1R-41- 279

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GQGTLVTVSS GLP1R-41- 280

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DSTKYEWQGTLVTVSS GLP1R-41- 282

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FEYDWGQGTLVTVSS GLP1R-41- 283

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YNVSEYDWGQGTLVTVSS GLP1R-41- 284

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GTLVTVSS GLP1R-41- 285

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GLP1R-41- 295

EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYGMGWFRQAPGKEREGVAAIGSD 30
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QGTTLVTVSS GLP1R-41- 298

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GLP1R-41- 347

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EVQLVESGGGLVQPGGSLRLSCAASGSIYSLDAMGWFRQAPGKEREFVAAISPAA 97
LTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAGSSRIYIYSDSLSE
RSYDWGQGTLVTVSS GLP1R-41- 363
EVQLVESGGGLVQPGGSLRLSCAASGRTFSfyGMGWFRQAPGKERELVAIKFSGG 98
TTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRWD
WGQGTLVTVSS GLP1R-41- 364
EVQLVESGGGLVQPGGSLRLSCAASGRTFSKYAMGWFRQAPGKEREFVAAIRWS 99
GGTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGGWGTGRYN
WGQGTLVTVSS GLP1R-44- 365
EVQLVESGGGLVQPGGSLRLSCAASGSIFSiyAMDWFRQAPGKEREFVAAISSDDS 01
TTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCTAVLPAYDDWGQG TLVTVSS
GLP1R-44- 366
EVQLVESGGGLVQPGGSLRLSCAASGFNSGSYTMGWFRQAPGKEREGVSYISSSD 02
GRYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGLNGAAAAGW
QGTTLVTVSS GLP1R-44- 367
EVQLVESGGGLVQPGGSLRLSCAASGRTFSNGPMGWFRQAPGKEREFVAHISTG 03
GATNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASWDGRQGWGQ
GTLVTVSS GLP1R-44- 368
EVQLVESGGGLVQPGGSLRLSCAASGRALSSYSMGWFRQAPGKEREFVALITRSG 04
GTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRHSYVDWG
QGTTLVTVSS GLP1R-44- 369
EVQLVESGGGLVQPGGSLRLSCAASGSIGSINAMGWFRQAPGKEREFVAAISWSG 05
GATNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASVAYS DYDLG
NDWGQGTLVTVSS GLP1R-44- 370
EVQLVESGGGLVQPGGSLRLSCAASGLSFDDYAMGWFRQAPGKEREFVAAISGR 06

SGNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALIQRRAPYSRLE
TWGQGTLVTVSS GLP1R-44- 371
EVQLVESGGGLVQPGGSLRLSCAASGFTFSIYAMGWFRQAPGKEREGVAAISWS 07
GGTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAAGWVAEYG
YWGQGTLVTVSS GLP1R-44- 372
EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVATISSNG 08
NTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADLRVLRLRRYE
YNYWGQGTLVTVSS GLP1R-44- 373
EVQLVESGGGLVQPGGSLRLSCAASGFTFRSNAMGWFRQAPGKEREGVAAISTS 09
GGITYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAERDGYGYWG
QGTLVTVSS GLP1R-44- 374
EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYAMGWFRQAPGKERELVAGISWN 10
GGITYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVRAGYDYWG
QGTLVTVSS GLP1R-44- 375
EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKEREWVATISWS 11
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QGTLVTVSS GLP1R-44- 376
EVQLVESGGGLVQPGGSLRLSCAASGRAFESYAMGWFRQAPGKEREFVAAIRWS 12
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WGQGTLVTVSS GLP1R-44- 377
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SWGQGTLVTVSS GLP1R-44- 378
EVQLVESGGGLVQPGGSLRLSCAASGRIFSDYAMGWFRQAPGKEREFVATINGD 14
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SWGQGTLVTVSS GLP1R-44- 379
EVQLVESGGGLVQPGGSLRLSCAASGRTLRSRNMGWFRQAPGKEREFVAAVRW 15
SGGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALGPVRRSRLE
WGQGTLVTVSS GLP1R-44- 380
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QGTLVTVSS GLP1R-44- 381
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QGTLVTVSS GLP1R-44- 382
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GQGTLVTVSS GLP1R-44- 383
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QGTLVTVSS GLP1R-44- 384
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QGTLVTVSS GLP1R-44- 385
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YWGQGTLVTVSS GLP1R-44- 386
EVQLVESGGGLVQPGGSLRLSCAASGRTEDDYAMGWFRQAPGKERELVSGITWS 22
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WGQGTLVTVSS GLP1R-44- 387

EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYAMGWFRQAPGKERELVSAISTDD 23
GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALPDDTYLATT
YDYWGQGTLVTVSS GLP1R-44- 388

EVQLVESGGGLVQPGGSLRLSCAASGSIFSDNVMGWFRQAPGKEREMVAAIRWS 24
GGITWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDLSGRGDVSE
YEYDWGQGTLVTVSS GLP1R-44- 389

EVQLVESGGGLVQPGGSLRLSCAASGEIASIIAMGWFRQAPGKEREWVSAINSGG 25
DTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADRSTIWPDWG
QGTLVTVSS GLP1R-44- 390

EVQLVESGGGLVQPGGSLRLSCAASGRTFSVSTMGWFRQAPGKEREIVAAITWSG 26
SATYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQRRWSQDWGQ
GTLVTVSS GLP1R-44- 391

EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKERELVAGITGG 27
GSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTRYGYDYW
GQGTLVTVSS GLP1R-44- 392

EVQLVESGGGLVQPGGSLRLSCAASGIPFRSRTMGWFRQAPGKEREFVAGITRNSI 28
RTRYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAPRRPYLPIRIRD
YIWGQGTLVTVSS GLP1R-44- 393

EVQLVESGGGLVQPGGSLRLSCAASGRTIVPYTMGWFRQAPGKEREFVAAISWS 29
GASTIYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAIGGTLYDRRRFE
WGQGTLVTVSS GLP1R-44- 394

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNNAMGWFRQAPGKEREGVAAINGS 30
GSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAARDDYGYWG
QGTLVTVSS GLP1R-44- 395

EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYGMGWFRQAPGKEREGVAGISWS 31
DGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAASDASFDYW
GQGTLVTVSS GLP1R-44- 396

EVQLVESGGGLVQPGGSLRLSCAASGGTFSDYGMGWFRQAPGKEREGVASISWN 32
DGSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAATADYDYWG
QGTLVTVSS GLP1R-44- 397

EVQLVESGGGLVQPGGSLRLSCAASGSTFSTYAMGWFRQAPGKERELVAAISWS 33
SGTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLVTS DGVS
YNYWGQGTLVTVSS GLP1R-44- 398

EVQLVESGGGLVQPGGSLRLSCAASGFLFDSYAMGWFRQAPGKEREPVAAISPA 34
ALTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAYYTDYDEALE
ETRGSYDWGQGTLVTVSS GLP1R-44- 399

EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYAMGWFRQAPGKEREGVAAISWN 35
SGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDARRYGYWG
QGTLVTVSS GLP1R-44- 400

EVQLVESGGGLVQPGGSLRLSCAASGSTFGNYAMGWFRQAPGKEREFVAAISRS 36
GSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDEDYALGPNE
YDWGQGTLVTVSS GLP1R-44- 401

EVQLVESGGGLVQPGGSLRLSCAASGRTFSIYAMGWFRQAPGKERELVAGISWG 37
GDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGNGYDYW
GQGTLVTVSS GLP1R-44- 402

EVQLVESGGGLVQPGGSLRLSCAASGFNSGSYTMGWFRQAPGKEREGVSYISSSD 38
GRTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAALDGYSGSWG
QGTLVTVSS GLP1R-44- 403

EVQLVESGGGLVQPGGSLRLSCAASGLTFWTSGMGWFRQAPGKEREYVAAISRS 39
GSLKGYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATVATALIWGQG TLVTVSS

GLP1R-44- 404
EVQLVESGGGLVQPGGSLRLSCAASGFTFSINAMGWFRQAPGKERELVSGISWGG 40
GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVNEDGFDYWG
QGTLVTVSS GLP1R-44- 405
EVQLVESGGGLVQPGGSLRLSCAASGFTFDDNAMGWFRQAPGKERELVAAISTS 41
GSNTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAELREYGYWG
QGTLVTVSS GLP1R-44- 406
EVQLVESGGGLVQPGGSLRLSCAASGRTFTSYNMGWFRQAPGKEREFVLSILWS 42
DDSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCASWDGRQVWGQ
GTLVTVSS GLP1R-44- 407
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NGSITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRSARNYW
GQGTLVTVSS GLP1R-44- 408
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GITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDRIEYSRGGYD
YWGGQGTLVTVSS GLP1R-44- 409
EVQLVESGGGLVQPGGSLRLSCAASGSTFRKYAMGWFRQAPGKEREFVAAISSG 45
GGSTNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGRYRERDSW
GQGTLVTVSS GLP1R-44- 410
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YDYWGGQGTLVTVSS GLP1R-44- 411
EVQLVESGGGLVQPGGSLRLSCAASGSGFSPNVMGWFRQAPGKERELVAIKFSG 47
GTTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAEEGVYRW
DWGGQGTLVTVSS GLP1R-44- 412
EVQLVESGGGLVQPGGSLRLSCAASGRTLTNHDMGWFRQAPGKEREGVSYISMS 48
DGRTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLDGYSGSW
GQGTLVTVSS GLP1R-44- 413
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DSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTLDNYGYWG
QGTLVTVSS GLP1R-44- 414
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GTSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADSITDRRSVA
VAHTSYYWGGQGTLVTVSS GLP1R-44- 415
EVQLVESGGGLVQPGGSLRLSCAASGLTFSTYAMGWFRQAPGKEREIVAAITWS 51
GGITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHGSILLDRIEW
GQGTLVTVSS GLP1R-44- 416
EVQLVESGGGLVQPGGSLRLSCAASGGTFSIYAMGWFRQAPGKERELVAAISSSG 52
SITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAAAALDGP GDMY
DYWGGQGTLVTVSS GLP1R-44- 417
EVQLVESGGGLVQPGGSLRLSCAASGGTFDNYAMGWFRQAPGKERELVSGINSD 53
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WGQGTLVTVSS GLP1R-44- 418
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WGQGTLVTVSS GLP1R-44- 419
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WNGDSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAANWKMLL
GVENDWGGQGTLVTVSS GLP1R-44- 420
EVQLVESGGGLVQPGGSLRLSCAASGFTFDIYAMGWFRQAPGKERELVAGISSSG 56

GSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLGTYDYWGQ
GTLVTVSS GLP1R-44- 421
EVQLVESGGGLVQPGGSLRLSCAASGRTFDIYAMGWFRQAPGKERELVAAINRD 57
DSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGLGNYNY
WGQGTLVTVSS GLP1R-44- 422
EVQLVESGGGLVQPGGSLRLSCAASGRSFSFNAMGWFRQAPGKERELVAAITKL 58
GFRNYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAASIEGVSGRWGQ
GTLVTVSS GLP1R-44- 423
EVQLVESGGGLVQPGGSLRLSCAASGSFFSINAMGWFRQAPGKERELVSASTWN 59
GGYTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAHRIVVGGTSV
GDWRWGQGTLVTVSS GLP1R-44- 424
EVQLVESGGGLVQPGGSLRLSCAASGRTFSDYAMGWFRQAPGKEREFVAGITSS 60
GGYTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVVYYGDWE
GSEPVQHEYDWGQGTLVTVSS GLP1R-44- 425
EVQLVESGGGLVQPGGSLRLSCAASGSIFSRNAMGWFRQAPGKEREFVAAIRWS 61
GKETWYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAKTKRTGIFTA
RMVDWGQGTLVTVSS GLP1R-44- 426
EVQLVESGGGLVQPGGSLRLSCAASGGTFTDYAMGWFRQAPGKEREFVAGISGD 62
GTITYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCATDNPYWSGYNY
WGQGTLVTVSS GLP1R-44- 427
EVQLVESGGGLVQPGGSLRLSCAASGGTFSNYAMGWFRQAPGKERELVSGINS 63
GGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVSTNDGYDY
WGQGTLVTVSS GLP1R-44- 428
EVQLVESGGGLVQPGGSLRLSCAASGGIYRVNTMGWFRQAPGKERELVAIKFSG 64
GTTDYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIAHEEGVYRW
DWGQGTLVTVSS GLP1R-44- 429
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SSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVSDDGGYDYWG
QGTLVTVSS GLP1R-44- 430
EVQLVESGGGLVQPGGSLRLSCAASGRTSSIYNMGWFRQAPGKEREFVAAISRSG 66
RSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAIVTYSYDYLGN
DWGQGTLVTVSS GLP1R-44- 431
EVQLVESGGGLVQPGGSLRLSCAASGRALSSYSMGWFRQAPGKEREFVALITRSG 67
GTTFYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCALDNRRSYVDWG
QGTLVTVSS GLP1R-44- 432
EVQLVESGGGLVQPGGSLRLSCAASGRALSRYGMVWFRQAPGKEREFVAAINRG 68
GKISHYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAGNGGRNYGHS
RARYEWQGTLVTVSS GLP1R-44- 433
EVQLVESGGGLVQPGGSLRLSCAASGFKFNDSYMRWFRQAPGKEREFVVAINWS 69
SGSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAVVNGPIFWGQG
TLVTVSS GLP1R-44- 434
EVQLVESGGGLVQPGGSLRLSCAASGRTLSDYALGWFRQAPGKERELVSGINTSG 70
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GTLVTVSS GLP1R-44- 435
EVQLVESGGGLVQPGGSLRLSCAASGSTFDIYGMGWFRQAPGKEREGVAAITGD 71
GSSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAADNDTEYGYW
GQGTLVTVSS GLP1R-44- 436
EVQLVESGGGLVQPGGSLRLSCAASGGTLDIYAMGWFRQAPGKEREFVAAISWS 72
GSTTYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVLGYDRDYW
GQGTLVTVSS GLP1R-44- 437

EVQLVESGGGLVQPGGSLRLSCAASGRTPSYSDAMGWFRQAPGKEREIVAAISRT 73
GSSIYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAQGSLYDDYDG
LPIKYDWGQGTLVTVSS GLP1R-44- 438
EVQLVESGGGLVQPGGSLRLSCAASGRFTFRTYGMGWFRQAPGKEREGVAAISWS 74
GNSTSYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAARLSKRGNRSS
RDYWGQGTLVTVSS GLP1R-44- 439
EVQLVESGGGLVQPGGSLRLSCAASGSTFDNYAMGWFRQAPGKERELVAGINWS 75
DSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVAGWGEYDY
WGQGTLVTVSS GLP1R-44- 440
EVQLVESGGGLVQPGGSLRLSCAASGSTFSIYAMGWFRQAPGKERELVAGINWS 76
DSSTYYADSVKGRFTISADNSKNTAYLQMNSLKPEDTAVYYCAAVTDYDEYNY
WGQGTLVTVSS

(285) TABLE-US-00019 TABLE 12 Variable Heavy Chain CDRs SEQ ID SEQ ID
SEQ ID Variant NO CDR1 NO CDR2 NO CDR3 GLP1R-3 441 GFTFSSYG 620 ISYDESNK
799 AKHMSMQEGAVTGEG QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 442
GFTFSDYG 621 ISYDRSNE 800 AKHMSMQEGAVTGDG 065 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 443 GFTFSDYG 622 ISYDETNK 801 AKHMSMQEGAVTGEG
075 QAAKEFIAWLVKGIVR ADLVGDAFDV GLP1R221- 444 GFTFSDYG 623 ISYDESNK
802 AKHMSMQEGAVTGEY 017 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 445
GFTFSDYG 624 ISHDRSNK 803 AKHMSMQEGAVTGEG 033 QAAKDFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 446 GFTFSDYG 625 ISYDETNK 804 AKHMSMQEGAVTGEG
076 QAAKEFIAWLVKGIVR ADLVGDAFDV GLP1R221- 447 GFTFSDYG 626 ISYGGSNK
805 AKHMSMQEGAVTGEG 092 QAVKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 448
GFTFSDYG 627 ISHDRSNK 806 AKHMSMQEGAVTGEG 034 QAVKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 449 GFTFSDYG 628 ISYDRSNE 807 AKHMSMQEGAVTGEG
066 QAIKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 450 GFTFSDYG 629 ISSDENNK
808 AKHMSMQEGAVTGEM 084 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 451
GFTFSDYG 630 ISDEGSNK 809 AKHMSMQEGAVTGAG 009 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 452 GFTFSDYG 631 ISSDENNK 810 AKHMSMQEGAVTGEF
072 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 453 GFTFSDYG 632 TSYDESNK
811 AKHMSMQEGAVTGEY 044 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 454
GFTFSDYG 633 ISSDASDK 812 AKHMSMQEGAVTGEY 012 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 455 GFTFSDYG 634 TSYDESNK 813 AKHMSMQEGAVTGVG
042 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 456 GFTFSDYG 635 ISYEGSNK
814 AKHMSMQEGAVTGMG 051 QAAKEFIAWLIKGRVR ADLVGDAFDV GLP1R221- 457
GFTFSDYG 636 ISSDASDK 815 AKHMSMQEGAVTGMG 083 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 458 GFTFSDYG 637 ISYDESNE 816 AKHMSMQEGAVTGEH
040 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 459 GFTFSDYG 638 ISYDRSNE
817 AKHMSMQEGAVHGEG 052 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 460
GFTFSDYG 639 ISDEGSNK 818 AKHMSMQEGAVTGEW 003 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 461 GFTFSDYG 640 ISSDENNK 819 AKHMSMQEGAVTGEF
094 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 462 GFTFSDYG 641 ISYDASNK
820 AKHMSMQEGAVTGEG 001 QAVKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 463
GFTFSDYG 642 ISSDASDK 821 AKHMSMQEGAVTGEW 014 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 464 GFTFSDYG 643 ISHDRSNK 822 AKHMSMQEGAVTGLG
085 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 465 GFTFSDYG 644 ISYDANNK
823 AKHMSMQEGAVTGEG 022 QAAKEFIAWLIKGRVR ADLVGDAFDV GLP1R221- 466
GFTFSDYG 645 ISYEGSNQ 824 AKHMSMQEGAVTGIG 056 QAAKEFIAWLVKGRVR
ADLVGDAFDV GLP1R221- 467 GFTFSDYG 646 TSYDESNK 825 AKHMSMQEGAVTGFG
088 QAAKEFIAWLVKGRVR ADLVGDAFDV GLP1R221- 468 GFTFSDYG 647 ISYDATNK

826 AKHMSMQEGAVTGMG 077 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 469
GFTFSDYG 648 ISYHGSNK 827 AKHMSMQEGAVTGMG 027 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 470 GFTFSDYG 649 ISYDASNK 828 AKHMSMQEGAVTGYG
019 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 471 GFTFSDYG 650 ISSDASDK
829 AKHMSMQEGAVTGEF 029 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 472
GFTFSDYG 651 TSYDESNK 830 AKHMSMQEGAVTGGG 043 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 473 GFTFSDYG 652 ISSDASNK 831 AKHMSMQEGAVTGEG
082 QAVKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 474 GFTFSDYG 653 ISYDANNK
832 AKHMSMQEGAVTGEW 079 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 475
GFTFSDYG 654 ISHDRSNK 833 AKHMSMQEGAVTGPG 080 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 476 GFTFSDYG 655 IRYGGSNK 834 AKHMSMQEGAVTGEG
059 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 477 GFTFSDYG 656 ISYDATNK
835 AKHMSMQEGAVTGYG 069 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 478
GFTFSDYG 657 ISDEGSNK 836 AKHMSMQEGAVTGMG 036 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 479 GFTFSDYG 658 ISYEGSNQ 837 AKHMSMQEGAVTGWG
057 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 480 GFTFSDYG 659 ISDEGSNK
838 AKHMSMQEGAVTGLG 035 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 481
GFTFSDYG 660 ISDEGSNK 839 AKHMSMQEGAVTGEW 063 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 482 GFTFSDYG 661 TSYDESNK 840 AKHMSMQEGAVTGEW
090 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 483 GFTFSDYG 662 ISSDASHK
841 AKHMSMQEGAVTWEG 002 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 484
GFTFSDYG 663 ISYDETNK 842 AKHMSMQEGAVTGFG 087 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 485 GFTFSDYG 664 ISDEGSNK 843 AKHMSMQEGAVTGMG
038 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 486 GFTFSDYG 665 ISYGGSNK
844 AKHMSMQEGAVTNEG 060 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 487
GFTFSDYG 666 ISSDASHK 845 AKHMSMQEGAVTWEG 015 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 488 GFTFSDYG 667 ISYDESNK 846 AKHMSMQEGAVTGEW
020 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 489 GFTFSDYG 668 ISSDASDK
847 AKHMSMQEGAVTGGG 011 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 490
GFTFSDYG 669 ISYGGSNK 848 AKHMSMQEGAVTGEW 091 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 491 GFTFSDYG 670 TSYDESNK 849 AKHMSMQEGAVTGEW
086 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 492 GFTFSDYG 671 ISHDRSNK
850 AKHMSMQEGAVTGEG 074 QALKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 493
GFTFSDYG 672 ISHDRSNK 851 AKHMSMQEGAVTGEG 032 QAAKDFIAWLKGRVR
ADLVGDAFDV GLP1R221- 494 GFTFSDYG 673 ISSDASDK 852 AKHMSMQEGAVTGWG
013 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 495 GFTFSDYG 674 ISHDRSNK
853 AKHMSMQEGAVTGWG 058 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 496
GFTFSDYG 675 ISSDASDK 854 AKHMSMQEGAVTGEG 031 QALKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 497 GFTFSDYG 676 ISSDASDK 855 AKHMSMQEGAVTGEG
054 WAAKEFIAWLKGRV RADLVGDAFDV GLP1R221- 498 GFTFSDYG 677 ISYDATNK
856 AKHMSMQEGAVTGEG 021 QFAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 499
GFTFSDYG 678 ISSDASHK 857 AKHMSMQEGAVTWEG 016 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 500 GFTFSDYG 679 ISSDASDK 858 AKHMSMQEGAVTGEG
030 QALKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 501 GFTFSDYG 680 ISSDASDK
859 AKHMSMQEGAVTGEW 018 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 502
GFTFSDYG 681 ISYDAGNK 860 AKHMSMQEGAVTGMG 028 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 503 GFTFSDYG 682 TSYEESNK 861 AKHMSMQEGAVTGMG
023 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 504 GFTFSDYG 683 ISHDRSNK
862 AKHMSMQEGAVTGIG 089 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 505
GFTFSDYG 684 ISSDASDK 863 AKHMSMQEGAVTGWG 053 QAAKEFIAWLKGRVR

ADLVGDAFDV GLP1R221- 506 GFTFSDYG 685 ISSDASNK 864 AKHMSMQEGAVTGIG
071 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 507 GFTFSDYG 686 ISYGGSNK
865 AKHMSMQEGAVTGWG 055 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 508
GFTFSDYG 687 ISSDASNK 866 AKHMSMQEGAVTGMG 046 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 509 GFTFSDYG 688 IRYDESNK 867 AKHMSMQEGAVTGEG
039 QALKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 510 GFTFSDYG 689 ISSDASNK
868 AKHMSMQEGAVMGEG 078 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 511
GFTFSDYG 690 ISSDASDK 869 AKHMSMQEGAVTGIG 010 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 512 GFTFSDYG 691 ISDEGSNK 870 AKHMSMQEGAVTGLG
005 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 513 GFTFSDYG 692 ISHDRSNK
871 AKHMSMQEGAVTGFG 073 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 514
GFTFSDYG 693 ISYDETNK 872 AKHMSMQEGAVTGIG 041 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 515 GFTFSDYG 694 ISYDESNK 873 AKHMSMQEGAVTEEG
025 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 516 GFTFSDYG 695 ISDEGSNK
874 AKHMSMQEGAVTGWG 007 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 517
GFTFSDYG 696 ISYDESNK 875 AKHMSMQEGAVTGFG 093 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 518 GFTFSDYG 697 ISYDAGNK 876 AKHMSMQEGAVTGEG
024 QAVKEFIAWLKGDVR ADLVGDAFDV GLP1R221- 519 GFTFSDYG 698 ISDEGSNK
877 AKHMSMQEGAVTGLG 008 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 520
GFTFSDYG 699 ISYDENNK 878 AKHMSMQEGAVTGMG 050 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 521 GFTFSDYG 700 TSYDESNK 879 AKHMSMQEGAVTGWG
062 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 522 GFTFSDYG 701 ISYDAGNK
880 AKHMSMQEGAVTGFG 068 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 523
GFTFSDYG 702 ISNDENNK 881 AKHMSMQEGAVTGFG 067 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 524 GFTFSDYG 703 TSYDESNK 882 AKHMSMQEGAVTGWG
061 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 525 GFTFSDYG 704 ISDEGSNK
883 AKHMSMQEGAVTGYG 064 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 526
GFTFSDYG 705 ISYDATNK 884 AKHMSMQEGAVTGIG 070 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 527 GFTFSDYG 706 ISDEGSNK 885 AKHMSMQEGAVTGFG
006 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 528 GFTFSDYG 707 ISSDASNK
886 AKHMSMQEGAVTGEG 045 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R221- 529
GFTFSDYG 708 ISDEGSNK 887 AKHMSMQEGAVTGFG 004 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R221- 530 GFTFSDYG 709 ISSDASDK 888 AKHMSMQEGAVTGEG
047 QAWKEFIAWLKGRV RADLVGDAFDV GLP1R221- 531 GFTFSDYG 710 ISSDASDK
889 AKHMSMQEGAVTGEY 048 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 532
GFTFNYP 711 ISYDESNK 890 AKHMSMQEGAVTGGG 052 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 533 GFTFNYP 712 ISDEGSNK 891 AKHMSMQEGAVTGEY
016 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 534 GFTFSDYG 713 ISYDANNK
892 AKHMSMQEGAVTGEW 023 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 535
GFAFSNYG 714 ISYDESNK 893 AKHMSMQEGAVTGEW 014 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 536 GFTFSDYG 715 ISYEGSNK 894 AKHMSMQEGAVTGEK
090 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 537 GFTFRDYG 716 IRYDEINK
895 AKHMSMQEGAVTGEG 073 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 538
GFTFNYP 717 ISDEGSNK 896 AKHMSMQEGAVTGVG 012 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 539 GFTFSAYS 718 ISYDATNK 897 AKHMSMQEGAVTGEF
082 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 540 GFTFDNYA 719 ISYDAGNK
898 AKHMSMQEGAVTGEG 081 QAAKEFIAWLKGFVR ADLVGDAFDV GLP1R-222- 541
GFPFSSYA 720 ISYDRSNK 899 AKHMSMQEGAVTGYG 056 QAAKEFIAWLKGFVR
ADLVGDAFDV GLP1R-222- 542 GFTFRDYA 721 ISFDESNK 900 AKHMSMQEGAVTGEW
058 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 543 GFTFNYP 722 ISHDRSNK

901 AKHMSMQEGAVTGTG 063 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 544
GLTFSNYA 723 TSYDESNK 902 AKHMSMQEGAVTREG 042 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 545 GFTFGSYA 724 TSYDESNK 903 AKHMSMQEGAVTGEG
092 QAAKEFIAWLVMGRVR ADLVGDAFDV GLP1R-222- 546 GFTFSSYG 725 ISSDASDK
904 AKHMSMQEGAVTGEG 007 QAAKEFIAWLKGVV RADLVGDAFDV GLP1R-222- 547
GFNFNNYG 726 ISYDASNK 905 AKHMSMQEGAVTGEF 008 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 548 GFTSSSYA 727 ISDEGSNK 906 AKHMSMQEGAVTGEG
024 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 549 GFTFSDYP 728 ISYDESNK
907 AKHMSMQEGAVTGEG 062 QAAKEFIAWLKGRVR NDLVGDAFDV GLP1R-222- 550
GFTFGNYG 729 ISYDASNK 908 AKHMSMQEGAVTGEF 077 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 551 GFTFNNTYA 730 ISYAGSNE 909 AKHMSMQEGAVTGEG
064 QALKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 552 GFSFRSYG 731 ISSDASNK
910 AKHMSMQEGAQTGEG 074 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 553
GFSFSNYA 732 TSYDESNK 911 AKHMSMQEGAVTGEG 029 QAAKEFIAWLLKGRVR
ADLVGDAFDV GLP1R-222- 554 GFAFSSYA 733 ISYDENNK 912 AKHMSMQEGAVTGYG
046 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 555 GFTFNNTYP 734 IWSDASQK
913 AKHMSMQEGAVTGEG 005 WAAKEFIAWLKGRV RADLVGDAFDV GLP1R-222- 556
GFTFGNYA 735 ISSDASDK 914 AKHMSMQEGAVTGEW 004 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 557 GFAFSNYG 736 ISYDASNK 915 AKHMSMQEGAVTGEG
022 QAAKNFIAWLKGRVR ADLVGDAFDV GLP1R-222- 558 GFTFSNYA 737 ISYDASNK
916 AKHMSMQEGAVTGYG 087 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 559
GFSFGSYA 738 TSYDESNK 917 AKHMSMQEGAVTGEW 048 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 560 GFTFSSYP 739 ISYEGTNK 918 AKHMSMQEGAVTGEG
072 QAAKDFIAWLKGRVR ADLVGDAFDV GLP1R-222- 561 GFSFSNYA 740 ISYDESNE
919 AKHMSMQEGAVTGEG 089 QAAKEFIAWLKGDVR ADLVGDAFDV GLP1R-222- 562
GFSFSSYG 741 ISYGGSNK 920 AKHMSMQEGAVTGEW 083 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 563 GFSFSNYA 742 TSYDESNK 921 AKHMSMQEGAVTGEG
001 QAAKEFIAWLLKGRVR ADLVGDAFDV GLP1R-222- 564 GFTFSDYG 743 ISYDESNK
922 AKHMSMQEGAVTGEG 075 WAAKEFIAWLKGRV RADLVGDAFDV GLP1R-222- 565
GFTFSDFA 744 ISYEGSNK 923 AKHMSMQEGAVQGEG 071 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 566 GFTFSDYP 745 ISDEGSNK 924 AKHMSMQEGAVTGEIQ
069 AAKEFIAWLKGRVRA DLVGDAFDV GLP1R-222- 567 GFTFRDYA 746 ISYDATNK
925 AKHMSMQEGAVTGMG 002 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 568
GFTFNRYG 747 ISYDASNK 926 AKHMSMQEGAVTGEG 006 QAAWEFIAWLKGRV
RADLVGDAFDV GLP1R-222- 569 GFPFSSYG 748 ISYDATNK 927 AKHMSMQEGAVTGEG
055 QAAKSFIWLKGRVR ADLVGDAFDV GLP1R-222- 570 GFSFGSYA 749 ISYDASNK
928 AKHMSMQEGAVTGMG 027 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 571
GFTFSNYD 750 ISYAGSNK 929 AKHMSMQEGAVTGTG 066 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 572 GFSFRTYG 751 ISDEGSNK 930 AKHMSMQEGAVTGEG
015 YAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 573 GFTFSTYG 752 ISYDANNK
931 AKHMSMQEGAVTGEG 076 QAAVEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 574
GFSFSDYA 753 ISSDASNK 932 AKHMSMQEGAVTGYG 011 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 575 GFTFSNYA 754 ISYDATNK 933 AKHMSMQEGAVTGEA
065 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 576 GFTFSNYD 755 TSYDESKK
934 AKHMSMQEGAVTGKG 041 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 577
GFSFSNYA 756 TSYDESNK 935 AKHMSMQEGAVTGEG 028 QAAYEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 578 GFTFSDYP 757 ISYAGSNE 936 AKHMSMQEGAVTGYG
086 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 579 GFPFSSYA 758 ISYDANNK
937 AKHMSMQEGAVTGYG 033 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 580
GFAFSSYA 759 ISYDESNK 938 AKHMSMQEGAVTGEG 035 WAAKEFIFWLKGRVR

ADLVGDAFDV GLP1R-222- 581 GFSFSNYA 760 ISYDESNK 939 AKHMSMQEGAVTYG
045 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 582 GFTFSDYP 761 ISYDRSNE
940 AKHMSMQEGAVTGTG 085 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 583
GFSFSNYG 762 ISSDASNK 941 AKHMSMQEGAVTGEW 049 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 584 GFSFRNYG 763 ISYDESNK 942 AKHMSMQEGAVTGEG
078 QAAKEFIAWLKGRVR PDLVGDAFDV GLP1R-222- 585 GFTFNDYG 764 ISSDASNK
943 AKHMSMQEGAVTGTG 021 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 586
GFTFGNYA 765 ISSDASNK 944 AKHMSMQEGAVTGEF 009 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 587 GFTFTNYG 766 ISSDASDK 945 AKHMSMQEGAVTGMG
036 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 588 GFSFSNYG 767 ISYGGSNK
946 AKHMSMQEGAVTGEG 084 FAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 589
GFTFSDYP 768 ISSDASDK 947 AKHMSMQEGAVTGEG 010 QAAKEFIAWLKGVV
RADLVGDAFDV GLP1R-222- 590 GFSFSNYA 769 ISYDASNK 948 AKHMSMQEGAVTGGG
088 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 591 GFPFSNYA 770 ISSDASNK
949 AKHMSMQEGAVTGEW 079 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 592
GFSFSDYG 771 ISYDANNK 950 AKHMSMQEGAVTGGLG 040 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 593 GFTFGSYG 772 ISDEGSNK 951 AKHMSMQEGAVTNEG
070 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 594 GFTFNDYG 773 ISSDENNK
952 AKHMSMQEGAVTGEG 032 QWAKEFIAWLKGRV RADLVGDAFDV GLP1R-222- 595
GFTFRDYG 774 ISSDENNK 953 AKHMSMQEGAVTGWG 030 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 596 GFTFGNYG 775 ISSDASHK 954 AKHMSMQEGAVTWEG
038 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 597 GFTFSGYA 776 ISSDENNK
955 AKHMSMQEGAVTGWG 031 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 598
GFTFSNYA 777 ISDEGSNK 956 AKHMSMQEGAVTGAG 026 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 599 GFNFNNYG 778 ISYDESNK 957 AKHMSMQEGAVTGEW
054 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 600 GFTFSDYP 779 ISSDASDK
958 AKHMSMQEGAVTGHG 093 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 601
GFTFNNYP 780 ISYGGSDK 959 AKHMSMQEGAVTGEG 051 WAAKEFIAWLKGRV
RADLVGDAFDV GLP1R-222- 602 GFTFSDYA 781 IPYDESNK 960 AKHMSMQEGAVTGEG
067 QAAKNFIAWLKGRVR ADLVGDAFDV GLP1R-222- 603 GFAFSNYG 782 ISDEGSNK
961 AKHMSMQEGAVTGHG 059 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 604
GFTFNRYG 783 ISDEGSNK 962 AKHMSMQEGAVTGVG 025 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 605 GFIFSNYA 784 ISYDASNK 963 AKHMSMQEGAVTGEY
068 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 606 GFNFNNYG 785 ISSDASNK
964 AKHMSMQEGAVTGEG 053 QAVKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 607
GFTFGSYG 786 ISSDENNK 965 AKHMSMQEGAVTGEG 018 FAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 608 GFTFGSYA 787 TSYDESNK 966 AKHMSMQEGAVTGYG
047 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 609 GFTFSNYD 788 ISDEGSNK
967 AKHMSMQEGAVTGEG 060 WAAKEFIAWLKGRV RADLVGDAFDV GLP1R-222- 610
GFTFKNYG 789 ISYGGSNK 968 AKHMSMQEGAVTGEG 020 PAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 611 GFSFSDYA 790 ISDDGSNK 969 AKHMSMQEGAVTGEG
044 QAAKEFIAWLKGFVR ADLVGDAFDV GLP1R-222- 612 GFSFSDYG 791 ISSDASDK
970 AKHMSMQEGAVTGEG 080 QALKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 613
GFTFGSYG 792 ISSDENNK 971 AKHMSMQEGAVTGMG 057 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 614 GFTLSNYA 793 IPYDESNK 972 AKHMSMQEGAVTGVG
043 QAAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 615 GFTFSNFA 794 ISSDASNK
973 AKHMSMQEGAVTGEG 003 QSAKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 616
GFTFRNFG 795 ISSDASNK 974 AKHMSMQEGAVTGIG 037 QAAKEFIAWLKGRVR
ADLVGDAFDV GLP1R-222- 617 GFTFGSHG 796 ISSDENNK 975 AKHMSMQEGAVTGEG
091 QAIKEFIAWLKGRVR ADLVGDAFDV GLP1R-222- 618 GFNFNNYG 797 ISDEGSNK

976 AKHMSMQEAGVTGEG 019 QAAKEFIWLVKGRVR PDLVGDAFDV GLP1R-222- 619
GFTFGSYG 798 ISYDASNK 977 AKHMSMQEAGVTGWG 094 QAAKEFIWLVKGRVR
ADLVGDAFDV

(286) TABLE-US-00020 TABLE 13 Variable Light Chain CDRs SEQ ID SEQ ID
SEQ ID Variant NO CDR1 NO CDR2 NO CDR3 GLP1R-3 978 SSNIADNY 1157 DNN 1336
GTWDNYLGAGV GLP1R221-065 979 TSNIANNF 1158 DHN 1337 GTWDTSLSAGA
GLP1R221-075 980 GSNIGNND 1159 DND 1338 GTWDTSLSNYV GLP1R221-017 981
SSNIGNTY 1160 DDY 1339 ATWDATLNTGV GLP1R221-033 982 SSNIGNEY 1161 DNN
1340 ATWDTSLNVGV GLP1R221-076 983 SSNIGNND 1162 ENN 1341 LTWDHSLTAYV
GLP1R221-092 984 TSNIANNF 1163 DNN 1342 GTWDTSLSVGM GLP1R221-034 985
SSNIGNNP 1164 END 1343 ATWDRGLSTGV GLP1R221-066 986 SSNIGNNY 1165 ENN
1344 GIWDRSLSAWV GLP1R221-084 987 SSNIADNY 1166 ENN 1345 GTWDVSLSVGM
GLP1R221-009 988 SSNIGNQY 1167 DDH 1346 GTWDTSLSVGE GLP1R221-072 989
SSNIGRNF 1168 DHN 1347 GTWDVTLHTGV GLP1R221-044 990 SSNIGNND 1169 DNN
1515 GTWDTSLSGGV GLP1R221-012 991 SSTIGNNY 1170 EDD 1516 ATWDRGLSTGV
GLP1R221-042 992 SSNIGNKY 1171 DDD 1517 GTWDTSLSVGM GLP1R221-051 993
SSNIGNDY 1172 DNN 1518 GTWDRGPNTGV GLP1R221-083 994 SSNIGSKD 1173 DDD
1519 GTWDRSLGGWV GLP1R221-040 995 SSNIGDND 1174 DNN 1353 GTWDRSLNVGV
GLP1R221-052 996 SSNIGSKY 1175 DNN 1354 GTWDRGPNTGV GLP1R221-003 997
SSNIGNNP 1176 DND 1355 ATWDHSLRVGV GLP1R221-094 998 SSNIGNKY 1177 DNN
1356 GTWDTALTAGV GLP1R221-001 999 SSNIGSHY 1178 DTN 1357 ATWDRGLSTGV
GLP1R221-014 1000 SSTIGNNY 1179 DND 1358 ATWDTSLNVGV GLP1R221-085 1001
TSNIGNNH 1180 DNN 1359 GTWDRSLSSAV GLP1R221-022 1002 SSNIGSNY 1181 DNN
1360 GTWDTSVSAGV GLP1R221-056 1003 GSNIGNND 1182 DTN 1361 ATWDRTLSIGV
GLP1R221-088 1004 SSNIGSKY 1183 DNN 1362 GTWDTTLNIGV GLP1R221-077 1005
SSNIGNND 1184 GDD 1363 ATWDRSLRAGV GLP1R221-027 1006 SSNIGNDF 1185 DNN
1364 GTWDTSLSTGV GLP1R221-019 1007 SSNIGNNF 1186 DNN 1365 GTWETSLSAGV
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GLP1R-222-094 1156 SSNIGNTY 1335 ENK 1514 ATWDTSLSEGV

(287) 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

1. An antibody or antibody fragment that binds to glucagon-like peptide-1 receptor (GLP1R) comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region (VH), and the light chain comprises a light chain variable region (VL), wherein: (a) the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 441, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 620, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 799, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 978, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1157, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1336; (b) the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 534, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 713, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 892, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1071, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1250, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1429; (c) the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 561, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 740, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 919, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1098, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1277, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1456; or (d) the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 592, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 771, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 950, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1129, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1308, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1487.
2. The antibody or antibody fragment of claim 1, wherein the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 441, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 620, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 799, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 978, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1157, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1336.
3. The antibody or antibody fragment of claim 1, wherein the VH comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 534, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 713, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 892, and wherein the VL comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1071, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 1250, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 1429.
4. The antibody or antibody fragment of claim 1, wherein the VH comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 70.
5. The antibody or antibody fragment of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO: 70.
6. The antibody or antibody fragment of claim 1, wherein the VL comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 104.
7. The antibody or antibody fragment of claim 1, wherein the VL comprises the amino acid sequence of SEQ ID NO: 104.
8. The antibody or antibody fragment of claim 1, wherein the VH comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 70, and wherein the VL comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 104.
9. The antibody or antibody fragment of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO: 70, and wherein the VL comprises the amino acid sequence of SEQ ID

NO: 104.

10. The antibody or antibody fragment of claim 1, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 54, and wherein the light chain comprises the amino acid sequence of SEQ ID NO: 89.

11. The antibody or antibody fragment of claim 1, wherein the antibody is a monoclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab')₂ fragment, a Fv fragment, a single-domain antibody, a diabody, disulfide-linked Fvs (sdFv), an intrabody, or an antigen-binding fragment thereof.

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

13. 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.

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

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

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