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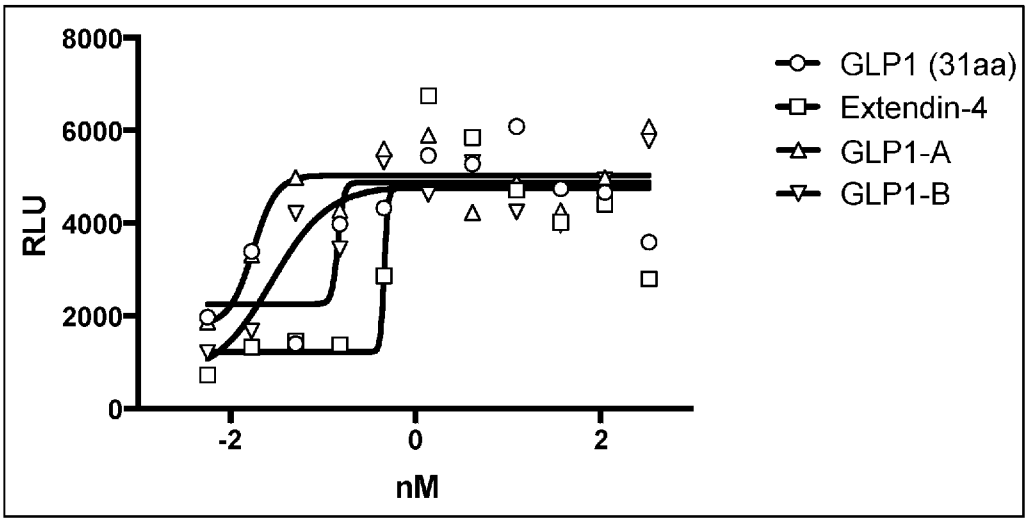

Fig. 3

(57) Abstract: Provided are various embodiments relating to variant IgG Fc polypeptides of companion animals having increased Protein A binding for ease of purification, decreased C1q binding for reduced complement-mediated immune responses, decreased CD16 binding (e.g., for reduced antibody-dependent cellular cytotoxicity (ADCC) induction, increased stability, and/or the ability to form heterodimeric proteins. In addition, various embodiments relating to antibodies and fusion proteins comprising such variant IgG Fc polypeptides are provided. Also provided are various embodiments relating to contiguous polypeptides comprising one or more variant GLP1 polypeptide(s) having improved serum half-life. Further provided are various embodiments relating to contiguous polypeptides or heterodimeric polypeptides comprising a GLP1 polypeptide and a glucagon polypeptide as a dual GLP1 receptor and glucagon receptor agonist. In various embodiments, such polypeptides may be used to treat, for example, diabetes, obesity, or related indications, in companion animals, such as canines, felines, and equines.

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IGG FC VARIANTS FOR VETERINARY USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 62/545,858, filed August 15, 2017, which is incorporated by reference herein in its entirety for any purpose.

FIELD

[0002] The present disclosure relates to variant IgG Fc polypeptides of companion animals with enhanced features, including increased Protein A binding (e.g., for ease of purification), decreased C1q binding (e.g., for reduced complement-mediated immune responses), decreased CD16 binding (e.g., for reduced antibody-dependent cellular cytotoxicity (ADCC) induction, increased stability, and/or the ability to form heterodimeric proteins. The variant IgG Fc polypeptides of the present disclosure may have broad applicability in companion animal therapeutics. For example, variant IgG Fc polypeptides may be used in the design and production of long-acting GLP1 polypeptides for treating, for example, diabetes, obesity, or related indications, in companion animals, such as canines, felines, and equines. In addition, variant IgG Fc polypeptides may be used in the design and production of antibodies or fusion proteins for treating various disorders in companion animals.

BACKGROUND

[0003] IgG Fc plays an important role in Fc-mediated functions though interactions with FcRn, Fc receptor, and C1q. In companion animals, various IgG subtypes possess differences in these functions, which are often considered when choosing a particular IgG antibody or IgG Fc fusion protein for therapeutic or diagnostic applications. For example, the ability of an IgG subtype to have weak or no measurable binding affinity to C1q or CD16 may be advantageous. In addition, IgG Fc's ability to bind Protein A may be useful for purification using a Protein A affinity purification platform.

[0004] However, most IgG Fc subtypes of canine, feline, and equine do not possess Protein A binding properties, weak or no measurable binding affinity to CD16, and weak or no measurable binding affinity to C1q. For example, of the four canine IgG Fc subtypes (IgG-A, IgG-B, IgG-C, and IgG-D), only canine IgG-B Fc has appreciable affinity to Protein A. Meanwhile only canine IgG-A Fc and IgG-D Fc have no or weak C1q binding or CD16 binding. Antibodies

and Fc fusion proteins comprising variant IgG Fc polypeptides that have reduced binding to C1q and/or CD16, and/or that able to bind Protein A are desirable.

[0005] Glucagon-like peptide-1 (GLP1) is a potent antihyperglycemic hormone, which plays an important role in regulating blood glucose level. Native GLP1 has an in vivo half-life of approximately 2 minutes. Long-acting GLP1 polypeptides can be used to treat diabetes and obesity, prevent diabetes, control hyperglycemic conditions, lower lipids, treat conditions that would benefit from lowered blood glucose levels, suppress gastric or intestinal movement, slow gastric emptying, and/or decrease food intake. There remains a need for long-acting GLP1 polypeptides for treating high blood glucose or uncontrollable blood glucose-induced conditions in companion animals, such as canines, felines, and equines.

SUMMARY OF THE INVENTION

Embodiment 1. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification relative to a wild-type IgG Fc polypeptide of a companion animal species, wherein the variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

Embodiment 2. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification relative to a wild-type IgG Fc polypeptide of a companion animal species, wherein the variant IgG Fc polypeptide has reduced binding affinity to C1q and/or CD16 relative to the wild-type IgG Fc polypeptide.

Embodiment 3. The polypeptide of embodiment 1 or embodiment 2, wherein the variant IgG Fc polypeptide binds to C1q and/or CD16 with a dissociation constant (K_d) of greater than 5×10^{-6} M, greater than 1×10^{-5} M, greater than 5×10^{-5} M, greater than 1×10^{-4} M, greater than 5×10^{-4} M, or greater than 1×10^{-3} M, as measured by biolayer interferometry.

Embodiment 4. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

Embodiment 5. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide binds to Protein A with a dissociation constant (K_d) of less than 5×10^{-6} M, less than 1×10^{-6} M, less than 5×10^{-7} M, less than 1×10^{-7} M, less than 5×10^{-8} M, less than 1×10^{-8} M, less than 5×10^{-9} M, less than 1×10^{-9} M, less than 5×10^{-10} M, less than 1×10^{-10} M, less than 5×10^{-11} M, less than 1×10^{-11} M, less than 5×10^{-12} M, or less than 1×10^{-12} M, as measured by biolayer interferometry.

Embodiment 6. The polypeptide of any one of the preceding embodiments, wherein the companion animal species is canine, feline, or equine.

Embodiment 7. The polypeptide of any one of the preceding embodiments, wherein the wild-type IgG Fc polypeptide is

a) a canine IgG-A Fc, IgG-B Fc, IgG-C Fc, or IgG-D Fc;

b) an equine IgG1 Fc, IgG2 Fc, IgG3 Fc, IgG4 Fc, IgG5 Fc, IgG6 Fc, or IgG7 Fc; or

c) a feline IgG1a Fc, IgG1b Fc, or IgG2 Fc.

Embodiment 8. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification to a hinge region relative to a wild-type feline or equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide has increased recombinant production and/or increased hinge disulfide formation relative to the wild-type IgG Fc polypeptide, as determined by SDS-PAGE analysis under reducing and/or nonreducing conditions.

Embodiment 9. The polypeptide of any one the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 20 of SEQ ID NO: 129.

Embodiment 10. The polypeptide of any one the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 20 of SEQ ID NO: 129.

Embodiment 11. The polypeptide of any one the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a proline at a position corresponding to position 16 or at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a serine at a position corresponding to position 3 or at position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a proline at a position corresponding to position 20 or at position 20 of SEQ ID NO: 129.

Embodiment 12. The polypeptide of any one the preceding embodiments, wherein the variant IgG Fc polypeptide comprises a hinge region or a portion of a hinge region from an IgG Fc polypeptide of a different isotype.

Embodiment 13. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises a hinge region or a portion of a hinge region from a wild-type feline IgG-1a Fc polypeptide, from a wild-type feline IgG-1b Fc polypeptide, or from a wild-type equine IgG1 Fc polypeptide.

Embodiment 14. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises SEQ ID NO: 19, SEQ ID NO: 125 or SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID N: 134, SEQ ID NO: 135.

Embodiment 15. A polypeptide comprising an amino acid sequence of SEQ ID NO: 19, SEQ ID NO: 125 or SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID N: 134, SEQ ID NO: 135.

Embodiment 16. A polypeptide comprising a variant IgG2 Fc polypeptide comprising at least one amino acid substitution relative to a wild-type feline IgG2 Fc polypeptide, wherein the at least one amino acid substitution is a cysteine, and wherein the variant IgG2 Fc polypeptide is capable of forming at least one additional inter-chain disulfide linkage relative to the wild-type feline IgG2 Fc polypeptide.

Embodiment 17. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises at least one amino acid substitution relative to

a wild-type feline IgG Fc polypeptide, wherein the at least one amino acid substitution is a cysteine, and wherein the variant IgG Fc polypeptide is capable of forming at least one additional inter-chain disulfide linkage relative to the wild-type feline IgG Fc polypeptide.

Embodiment 18. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises a cysteine at a position corresponding to position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, or position 16 of SEQ ID NO: 16.

Embodiment 19. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises a cysteine at a position corresponding to position 14 of SEQ ID NO: 16.

Embodiment 20. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises a cysteine at position 14 of SEQ ID NO: 16.

Embodiment 21. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide is at least 90% identical, at least 95% identical, at least 97% identical, or at least 99% identical to the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 100, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO:122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

Embodiment 22. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises SEQ ID NO: 17.

Embodiment 23. A polypeptide comprising an amino acid sequence of SEQ ID NO: 17.

Embodiment 24. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 205 of SEQ ID NO: 1, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 1;

b) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 24 of SEQ ID NO: 3;

c) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 4, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 4;

d) an amino acid substitution at a position corresponding to position 15 of SEQ ID NO: 64, and/or an amino acid substitution at a position corresponding to position 203 of SEQ ID NO: 64;

e) an amino acid substitution at a position corresponding to position 199 of SEQ ID NO: 67, and/or an amino acid substitution at a position corresponding to position 200 of SEQ ID NO: 67; and/or

f) an amino acid substitution at a position corresponding to position 199 of SEQ ID NO: 68, an amino acid substitution at a position corresponding to position 200 of SEQ ID NO: 68, an amino acid substitution at a position corresponding to position 201 of SEQ ID NO: 68, and/or an amino acid substitution at a position corresponding to position 202 of SEQ ID NO: 68.

Embodiment 25. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 21 of SEQ ID NO: 1, an amino acid substitution at position 23 of SEQ ID NO: 1, an amino acid substitution at position 25 of SEQ

ID NO: 1, an amino acid substitution at position 80 of SEQ ID NO: 1, an amino acid substitution at position 205 of SEQ ID NO: 1, and/or an amino acid substitution at position 207 of SEQ ID NO: 1;

b) an amino acid substitution at position 21 of SEQ ID NO: 3, an amino acid substitution at position 23 of SEQ ID NO: 3, and/or an amino acid substitution at position 24 of SEQ ID NO: 3;

c) an amino acid substitution at position 21 of SEQ ID NO: 4, an amino acid substitution at position 23 of SEQ ID NO: 4, an amino acid substitution at position 25 of SEQ ID NO: 4, an amino acid substitution at position 80 of SEQ ID NO: 4, and/or an amino acid substitution at position 207 of SEQ ID NO: 4;

d) an amino acid substitution at position 15 of SEQ ID NO: 64, and/or an amino acid substitution at position 203 of SEQ ID NO: 64;

e) an amino acid substitution at position 199 of SEQ ID NO: 67, and/or an amino acid substitution at position 200 of SEQ ID NO: 67; and/or

f) an amino acid substitution at position 199 of SEQ ID NO: 68, an amino acid substitution at position 200 of SEQ ID NO: 68, an amino acid substitution at position 201 of SEQ ID NO: 68, and/or an amino acid substitution at position 202 of SEQ ID NO: 68.

Embodiment 26. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a threonine at a position corresponding to position 21 of SEQ ID NO: 1, a leucine at a position corresponding to position 23 of SEQ ID NO: 1, an alanine at a position corresponding to position 25 of SEQ ID NO: 1, a glycine at a position corresponding to position 80 of SEQ ID NO: 1, an alanine at a position corresponding to position 205 of SEQ ID NO: 1, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 1;

b) a threonine at a position corresponding to position 21 of SEQ ID NO: 3, a leucine at a position corresponding to position 23 of SEQ ID NO: 3, and/or an isoleucine at a position corresponding to position 24 of SEQ ID NO: 3;

c) a threonine at a position corresponding to position 21 of SEQ ID NO: 4, a leucine at a position corresponding to position 23 of SEQ ID NO: 4, an alanine at a position corresponding to position 25 of SEQ ID NO: 4, a glycine at a position corresponding to position 80 of SEQ ID NO: 4, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 4;

d) a threonine or a valine at a position corresponding to position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at a position corresponding to position 203 of SEQ ID NO: 64;

e) a leucine at a position corresponding to position 199 of SEQ ID NO: 67, and/or a histidine at a position corresponding to position 200 of SEQ ID NO: 67; and/or

f) a leucine at a position corresponding to position 199 of SEQ ID NO: 68, a histidine at a position corresponding to position 200 of SEQ ID NO: 68, an asparagine at a position corresponding to position 201 of SEQ ID NO: 68, and/or a histidine at a position corresponding to position 202 of SEQ ID NO: 68.

Embodiment 27. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a threonine at position 21 of SEQ ID NO: 1, a leucine at position 23 of SEQ ID NO: 1, an alanine at position 25 of SEQ ID NO: 1, a glycine at position 80 of SEQ ID NO: 1, an alanine at position 205 of SEQ ID NO: 1, and/or a histidine at position 207 of SEQ ID NO: 1;

b) a threonine at position 21 of SEQ ID NO: 3, a leucine at position 23 of SEQ ID NO: 3, and/or an isoleucine at position 24 of SEQ ID NO: 3;

c) a threonine at a position 21 of SEQ ID NO: 4, a leucine at position 23 of SEQ ID NO: 4, an alanine at position 25 of SEQ ID NO: 4, a glycine at position 80 of SEQ ID NO: 4, and/or a histidine at position 207 of SEQ ID NO: 4;

d) a threonine or a valine at position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at position 203 of SEQ ID NO: 64;

e) a leucine at position 199 of SEQ ID NO: 67, and/or a histidine at position 200 of SEQ ID NO: 67; and/or

f) a leucine at position 199 of SEQ ID NO: 68, a histidine at position 200 of SEQ ID NO: 68, an asparagine at position 201 of SEQ ID NO: 68, and/or a histidine at position 202 of SEQ ID NO: 68.

Embodiment 28. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of:

a) SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, or SEQ ID NO: 84; or

b) SEQ ID NO: 19, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 75, or SEQ ID NO: 76.

Embodiment 29. A polypeptide comprising an amino sequence of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 84, SEQ ID NO: 19, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 75, or SEQ ID NO: 76.

Embodiment 30. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 2, or an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 3;

b) an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 63, an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 65, an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 66, or an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 69; or

c) an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 80, or an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 81.

Embodiment 31. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 93 of SEQ ID NO: 2, or an amino acid substitution at position 93 of SEQ ID NO: 3;

b) an amino acid substitution at position 87 of SEQ ID NO: 63, an amino acid substitution at position 87 of SEQ ID NO: 65, an amino acid substitution at position 87 of SEQ ID NO: 66, or an amino acid substitution at position 87 of SEQ ID NO: 69; or

c) an amino acid substitution at position 198 of SEQ ID NO: 80, or an amino acid substitution at position 198 of SEQ ID NO: 81.

Embodiment 32. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an arginine at a position corresponding to position 93 of SEQ ID NO: 2, or an arginine at a position corresponding to position 93 of SEQ ID NO: 3;

b) a serine at a position corresponding to position 87 of SEQ ID NO: 63, a serine substitution at a position corresponding to position 87 of SEQ ID NO: 65, a serine at a position corresponding to position 87 of SEQ ID NO: 66, or a serine at a position corresponding to position 87 of SEQ ID NO: 69; or

c) an alanine at a position corresponding to position 198 of SEQ ID NO: 80, or an alanine at a position corresponding to position 198 of SEQ ID NO: 81.

Embodiment 33. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an arginine at position 93 of SEQ ID NO: 2, or an arginine at position 93 of SEQ ID NO: 3;

b) a serine at position 87 of SEQ ID NO: 63, a serine at position 87 of SEQ ID NO: 65, a serine at position 87 of SEQ ID NO: 66, or a serine at position 87 of SEQ ID NO: 69; or

c) an alanine at position 198 of SEQ ID NO: 80, or alanine at position 198 of SEQ ID NO: 81.

Embodiment 34. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises the amino acid sequence of:

a) SEQ ID NO: 78, SEQ ID NO: 79, or SEQ ID NO: 84; or

b) SEQ ID NO: 70, SEQ ID NO: 73, SEQ ID NO: 74, or SEQ ID NO: 77; or

c) SEQ ID NO: 82 or SEQ ID NO: 83.

Embodiment 35. A polypeptide comprising an amino sequence of SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 70, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 82, or SEQ ID NO: 83.

Embodiment 36. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 2, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 3.

Embodiment 37. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 5 of SEQ ID NO: 2, an amino acid substitution at position 38 of SEQ ID NO: 2, an amino acid substitution at position 39 of SEQ ID NO: 2, an amino acid substitution at position 97 of SEQ ID NO: 2, and/or an amino acid substitution at position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at position 5 of SEQ ID NO: 3, an amino acid substitution at position 38 of SEQ ID NO: 3, an amino acid substitution at position 39 of SEQ ID NO: 3, an amino acid substitution at position 97 of SEQ ID NO: 3, and/or an amino acid substitution at position 98 of SEQ ID NO: 3.

Embodiment 38. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a proline at a position corresponding to position 5 of SEQ ID NO: 2, a glycine at a position corresponding to position 38 of SEQ ID NO: 2, an arginine at a position corresponding to position 39 of SEQ ID NO: 2, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 2, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 2; or

b) a proline at a position corresponding to position 5 of SEQ ID NO: 3, a glycine at a position corresponding to position 38 of SEQ ID NO: 3, an arginine at a position corresponding to position 39 of SEQ ID NO: 3, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 3, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 3.

Embodiment 39. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a proline at position 5 of SEQ ID NO: 2, a glycine at position 38 of SEQ ID NO: 2, an arginine at position 39 of SEQ ID NO: 2, an isoleucine at position 97 of SEQ ID NO: 2, and/or a glycine at position 98 of SEQ ID NO: 2; or

b) a proline at position 5 of SEQ ID NO: 3, a glycine at position 38 of SEQ ID NO: 3, an arginine at position 39 of SEQ ID NO: 3, an isoleucine at position 97 of SEQ ID NO: 3, and/or a glycine at position 98 of SEQ ID NO: 3.

Embodiment 40. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of:

a) SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, or SEQ ID NO: 147; or

b) SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

Embodiment 41. A polypeptide comprising an amino sequence of SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO:

149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

Embodiment 42. A polypeptide comprising a variant IgG Fc polypeptide comprising:

a) a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 1, a tyrosine or a tryptophan at aposition corresponding to position 137 of SEQ ID NO: 2, a tyrosine or a tryptophan at a position corresponding to position 137 of SEQ ID NO: 3, or a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 4; or

b) a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 16, a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118.

Embodiment 43. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a tyrosine or a tryptophan at position 138 of SEQ ID NO: 1, a tyrosine or a tryptophan at position 137 of SEQ ID NO: 2, a tyrosine or a tryptophan at position 137 of SEQ ID NO: 3, or a tyrosine or a tryptophan at position 138 of SEQ ID NO: 4; or

b) a tyrosine or a tryptophan at position 154 of SEQ ID NO: 16, a tyrosine or a tryptophan at position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118.

Embodiment 44. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

Embodiment 45. A polypeptide comprising an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

Embodiment 46. A contiguous polypeptide comprising the polypeptide of any one of the preceding embodiments and a glucagon-like peptide-1 (GLP1) polypeptide.

Embodiment 47. A contiguous polypeptide comprising the polypeptide of any one of the preceding embodiments and a glucagon polypeptide.

Embodiment 48. A polypeptide comprising a variant IgG Fc polypeptide comprising:

a) a serine at a position corresponding to position 138 of SEQ ID NO: 1, a serine at a position corresponding to position 137 of SEQ ID NO: 2, a serine at a position corresponding to position 137 of SEQ ID NO: 3, a serine at a position corresponding to position 138 of SEQ ID NO: 4, a serine at a position corresponding to position 154 of SEQ ID NO: 16, a serine at a position corresponding to position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a serine at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118;

b) an alanine at a position corresponding to position 140 of SEQ ID NO: 1, an alanine at a position corresponding to position 139 of SEQ ID NO: 2, an alanine at a position corresponding to position 139 of SEQ ID NO: 3, an alanine at a position corresponding to position 140 of SEQ ID NO: 4, an alanine at a position corresponding to position 156 of SEQ ID NO: 16, an alanine at a position corresponding to position 156 of SEQ ID NO: 80 or SEQ ID NO: 117, or an alanine at a position corresponding to position 156 of SEQ ID NO: 81 or SEQ ID NO: 118; and/or

c) a threonine at a position corresponding to position 181 of SEQ ID NO: 1, a threonine at a position corresponding to position 180 of SEQ ID NO: 2, a threonine at a position corresponding to position 180 of SEQ ID NO: 3, a threonine at a position corresponding to position 181 of SEQ ID NO: 4, a threonine at a position corresponding to position 197 of SEQ ID NO: 16, a threonine at a position corresponding to position 197 of SEQ ID NO: 80 or SEQ ID NO: 117, or a threonine at a position corresponding to position 197 of SEQ ID NO: 81 or SEQ ID NO: 118.

Embodiment 49. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises:

a) a serine at position 138 of SEQ ID NO: 1, a serine at position 137 of SEQ ID NO: 2, a serine at position 137 of SEQ ID NO: 3, a serine at position 138 of SEQ ID NO: 4, a serine at position 154 of SEQ ID NO: 16, a serine at position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a serine at position 154 of SEQ ID NO: 81 or SEQ ID NO: 118;

b) an alanine at position 140 of SEQ ID NO: 1, an alanine at position 139 of SEQ ID NO: 2, an alanine at position 139 of SEQ ID NO: 3, an alanine at position 140 of SEQ ID NO: 4, an alanine at position 156 of SEQ ID NO: 16, an alanine at position 156 of SEQ ID NO: 80 or SEQ ID NO: 117, or an alanine at position 156 of SEQ ID NO: 81 or SEQ ID NO: 118; and/or;

c) a threonine at position 181 of SEQ ID NO: 1, a threonine at position 181 of SEQ ID NO: 2, a threonine at position 181 of SEQ ID NO: 3, a threonine at position 181 of SEQ ID NO: 4, a threonine at position 197 of SEQ ID NO: 16, a threonine at position 197 of SEQ ID NO: 80 or SEQ ID NO: 117, or a threonine at position 197 of SEQ ID NO: 81 or SEQ ID NO: 118.

Embodiment 50. The polypeptide of any one of the preceding embodiments, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 124.

Embodiment 51. A polypeptide comprising an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 124.

Embodiment 52. The polypeptide of any one of the preceding embodiments, wherein the polypeptide is glycoslylated.

Embodiment 53. The polypeptide of any one of embodiments 1 to 51, wherein the polypeptide is aglycosylated.

Embodiment 54. A contiguous polypeptide comprising the polypeptide of any one of embodiments 48 to 53 and a glucagon-like peptide-1 (GLP1) polypeptide.

Embodiment 55. A contiguous polypeptide comprising the polypeptide of any one of embodiments 48 to 53 and a glucagon polypeptide.

Embodiment 56. A heterodimeric protein comprising the contiguous polypeptide of embodiment 46 and the contiguous polypeptide of embodiment 54.

Embodiment 57. A heterodimeric protein comprising the contiguous polypeptide of embodiment 47 and the contiguous polypeptide of embodiment 55.

Embodiment 58. The contiguous polypeptide or heterodimeric protein of any one of embodiments 46, 47, or 54 to 57, wherein the GLP1 polypeptide is a wild-type GLP1 polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 85.

Embodiment 59. The contiguous polypeptide or heterodimeric protein of any one of embodiments 46, 47, or 54 to 58, wherein the GLP1 polypeptide is a variant GLP1 polypeptide.

Embodiment 60. The contiguous polypeptide or heterodimeric protein of any one of embodiments 46, 47, or 54 to 59, wherein the GLP1 polypeptide comprises the amino acid sequence of SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 98, or SEQ ID NO: 99.

Embodiment 61. The contiguous polypeptide or heterodimeric protein of any one of embodiments 46, 47, or 54 to 60, wherein the glucagon polypeptide is a wild-type glucagon polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 21.

Embodiment 62. The contiguous polypeptide or heterodimeric protein of any one of embodiments 46, 47, or 54 to 61, wherein the glucagon polypeptide is a variant glucagon polypeptide.

Embodiment 63. A heterodimeric protein comprising:

i) a first variant canine IgG Fc polypeptide comprising at least one amino acid modification relative to a first wild-type canine IgG Fc polypeptide and a second variant canine IgG Fc polypeptide comprising at least one amino acid modification relative to a second wild-type canine IgG Fc polypeptide; or

ii) a first variant feline IgG Fc polypeptide comprising at least one amino acid modification relative to a first wild-type feline IgG Fc polypeptide and a second variant feline IgG Fc polypeptide comprising at least one amino acid modification relative to a second wild-type feline IgG Fc polypeptide, wherein:

a) the first variant canine IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 138 of SEQ ID NO: 1, position 137 of SEQ ID NO: 2, position 137 of SEQ ID NO: 3, or position 138 of SEQ ID NO: 4;

b) the second variant canine IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 138, position 140, and/or position 181 of SEQ ID NO: 1, position 137, position 139, and/or position 180 of SEQ ID NO: 2, position 137, position 139, and/or position 180 of SEQ ID NO: 3, or position 138, position 140, and/or position 181 of SEQ ID NO: 4;

c) the first variant feline IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 154 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118; and/or

d) the second variant feline IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 154, position 156, and/or position 197 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

Embodiment 64. The heterodimeric protein of embodiment 63, wherein the first wild-type canine IgG Fc polypeptide and the second wild-type canine IgG Fc polypeptide are from the same IgG subtype and/or the first wild-type feline IgG Fc polypeptide and the second wild-type feline IgG Fc polypeptide are from the same IgG subtype.

Embodiment 65. The heterodimeric protein of embodiment 63, wherein the first wild-type canine IgG Fc polypeptide and the second wild-type canine IgG Fc polypeptide are from a different IgG subtype and/or the first wild-type feline IgG Fc polypeptide and the second wild-type feline IgG Fc polypeptide are from the same IgG subtype.

Embodiment 66. The heterodimeric protein of any one of embodiments 63 to 65, wherein:

a) the first variant canine IgG Fc polypeptide comprises a tyrosine or tryptophan at a position corresponding to position 138 of SEQ ID NO: 1, position 137 of SEQ ID NO: 2, position 137 of SEQ ID NO: 3, or position 138 of SEQ ID NO: 4; and/or

b) the first variant feline IgG Fc polypeptide comprises a tryptophan at a position corresponding to position 154 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

Embodiment 67. The heterodimeric protein of any one of embodiments 63 to 66, wherein:

a) the second variant canine IgG Fc polypeptide comprises a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 1, a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 2, a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 3, and/or a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 4; and/or

b) the second variant feline IgG Fc polypeptide comprises a serine at a position corresponding to position 154, an alanine at a position corresponding to position 156, and/or a threonine at a position corresponding to position 197 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

Embodiment 68. The heterodimeric protein of any one of embodiments 63 to 67, wherein:

a) the first variant canine IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, or SEQ ID NO: 115; and/or

b) the first variant feline IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

Embodiment 69. The heterodimeric protein of any one of embodiments 63 to 68, wherein:

a) the second variant canine IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, or SEQ ID NO: 116; and/or

b) the second variant feline IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 123.

Embodiment 70. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 69, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type IgG Fc polypeptide and has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

Embodiment 71. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 70, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 205 of SEQ ID NO: 1, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 1;

b) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 24 of SEQ ID NO: 3; or

c) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 4, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 4.

Embodiment 72. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 71, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 21 of SEQ ID NO: 1, an amino acid substitution at position 23 of SEQ ID NO: 1, an amino acid substitution at position 25 of SEQ ID NO: 1, an amino acid substitution at position 80 of SEQ ID NO: 1, an amino acid substitution at position 205 of SEQ ID NO: 1, and/or an amino acid substitution at position 207 of SEQ ID NO: 1;

b) an amino acid substitution at position 21 of SEQ ID NO: 3, an amino acid substitution at position 23 of SEQ ID NO: 3, and/or an amino acid substitution at position 24 of SEQ ID NO: 3; or

c) an amino acid substitution at position 21 of SEQ ID NO: 4, an amino acid substitution at position 23 of SEQ ID NO: 4, an amino acid substitution at position 25 of SEQ ID NO: 4, an amino acid substitution at position 80 of SEQ ID NO: 4, and/or an amino acid substitution at position 207 of SEQ ID NO: 4.

Embodiment 73. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 72, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a threonine at a position corresponding to position 21 of SEQ ID NO: 1, a leucine at a position corresponding to position 23 of SEQ ID NO: 1, an alanine at a position corresponding to position 25 of SEQ ID NO: 1, a glycine at a position corresponding to position 80 of SEQ ID NO: 1, an alanine at a position corresponding to position 205 of SEQ ID NO: 1, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 1;

b) a threonine at a position corresponding to position 21 of SEQ ID NO: 3, a leucine at a position corresponding to position 23 of SEQ ID NO: 3, and/or an isoleucine at a position corresponding to position 24 of SEQ ID NO: 3; or

c) a threonine at a position corresponding to position 21 of SEQ ID NO: 4, a leucine at a position corresponding to position 23 of SEQ ID NO: 4, an alanine at a position corresponding to position 25 of SEQ ID NO: 4, a glycine at a position corresponding to position 80 of SEQ ID NO: 4, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 4.

Embodiment 74. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 73, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a threonine at position 21 of SEQ ID NO: 1, a leucine at position 23 of SEQ ID NO: 1, an alanine at position 25 of SEQ ID NO: 1, a glycine at position 80 of SEQ ID NO: 1, an alanine at position 205 of SEQ ID NO: 1, and/or a histidine at position 207 of SEQ ID NO: 1;

b) a threonine at position 21 of SEQ ID NO: 3, a leucine at position 23 of SEQ ID NO: 3, and/or an isoleucine at position 24 of SEQ ID NO: 3; or

c) a threonine at position 21 of SEQ ID NO: 4, a leucine at position 23 of SEQ ID NO: 4, an alanine at position 25 of SEQ ID NO: 4, a glycine at position 80 of SEQ ID NO: 4, and/or a histidine at position 207 of SEQ ID NO: 4.

Embodiment 75. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 74, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type IgG Fc polypeptide and has decreased binding affinity to CD16 relative to the wild-type IgG Fc polypeptide.

Embodiment 76. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 75, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 2, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 3.

Embodiment 77. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 76, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 5 of SEQ ID NO: 2, an amino acid substitution at position 38 of SEQ ID NO: 2, an amino acid substitution at position 39 of SEQ ID NO: 2, an amino acid substitution at position 97 of SEQ ID NO: 2, and/or an amino acid substitution at position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at position 5 of SEQ ID NO: 3, an amino acid substitution at position 38 of SEQ ID NO: 3, an amino acid substitution at position 39 of SEQ ID NO: 3, an amino acid substitution at position 97 of SEQ ID NO: 3, and/or an amino acid substitution at position 98 of SEQ ID NO: 3.

Embodiment 78. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 77, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a proline at a position corresponding to position 5 of SEQ ID NO: 2, a glycine at a position corresponding to position 38 of SEQ ID NO: 2, an arginine at a position

corresponding to position 39 of SEQ ID NO: 2, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 2, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 2; or

b) a proline at a position corresponding to position 5 of SEQ ID NO: 3, a glycine at a position corresponding to position 38 of SEQ ID NO: 3, an arginine at a position corresponding to position 39 of SEQ ID NO: 3, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 3, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 3.

Embodiment 79. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 78, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a proline at position 5 of SEQ ID NO: 2, a glycine at position 38 of SEQ ID NO: 2, an arginine at position 39 of SEQ ID NO: 2, an isoleucine at position 97 of SEQ ID NO: 2, and/or a glycine at position 98 of SEQ ID NO: 2; or

b) a proline at position 5 of SEQ ID NO: 3, a glycine at position 38 of SEQ ID NO: 3, an arginine at position 39 of SEQ ID NO: 3, an isoleucine at position 97 of SEQ ID NO: 3, and/or a glycine at position 98 of SEQ ID NO: 3.

Embodiment 80. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 79, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type canine IgG Fc polypeptide and has decreased binding affinity to C1q relative to the wild-type canine IgG Fc polypeptide.

Embodiment 81. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 80, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 2, or an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 3.

Embodiment 82. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 81, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an amino acid substitution at position 93 of SEQ ID NO: 2, or an amino acid substitution at position 93 of SEQ ID NO: 3.

Embodiment 83. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 82, wherein the variant IgG Fc polypeptide, the first

variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an arginine at a position corresponding to position 93 of SEQ ID NO: 2, or an arginine at a position corresponding to position 93 of SEQ ID NO: 3.

Embodiment 84. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 42 to 83, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an arginine at position 93 of SEQ ID NO: 2, or an arginine at position 93 of SEQ ID NO: 3.

Embodiment 85. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 1 to 84, wherein the polypeptide is an antibody, an antibody fusion, or a fusion polypeptide.

Embodiment 86. A contiguous polypeptide comprising:

a) a first glucagon-like peptide-1 (GLP1) polypeptide (GLP1A);

b) a first linker (L1);

c) an Fc polypeptide (Fc) of a companion animal species;

d) optionally, a second linker (L2); and

e) optionally, a second GLP1 polypeptide (GLP1B).

Embodiment 87. The contiguous polypeptide of embodiment 65 comprising:

formula (I): GLP1A—L1—Fc; or

formula (II): Fc—L1—GLP1A.

Embodiment 88. The contiguous polypeptide of embodiment 65 comprising:

formula (III): GLP1A—L1—Fc—L2—GLP1B.

Embodiment 89. The contiguous polypeptide of any one of embodiments 86 to 88, wherein GLP1B, if present, comprises the same amino acid sequence as GLP1A.

Embodiment 90. A contiguous polypeptide comprising:

a) a glucagon-like peptide-1 (GLP1) polypeptide;

b) a first linker (L1);

c) an Fc polypeptide (Fc);

d) a second linker (L2); and

e) a glucagon polypeptide (Gluc).

Embodiment 91. The contiguous polypeptide of embodiment 90 comprising:

Formula (IV): GLP1—L1—Fc—L2—Gluc; or

Formula (V): Gluc—L1—Fc—L2—GLP1.

Embodiment 92. The contiguous polypeptide of any one of embodiments 86 to 91, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises a wild-type GLP1 polypeptide.

Embodiment 93. The contiguous polypeptide of any one of embodiments 86 to 92, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises a variant GLP1 polypeptide.

Embodiment 94. The contiguous polypeptide of any one of embodiments 86 to 93, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises an amino acid sequence of SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 98, or SEQ ID NO: 99.

Embodiment 95. The contiguous polypeptide of any one of embodiments 86 to 94, wherein the glucagon polypeptide comprises a wild-type glucagon polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 21.

Embodiment 96. The contiguous polypeptide of any one of embodiments 86 to 95, wherein the glucagon polypeptide is a variant glucagon polypeptide.

Embodiment 97. The contiguous polypeptide of any one of embodiments 86 to 96, wherein the Fc polypeptide is a human IgG Fc.

Embodiment 98. The contiguous polypeptide of any one of embodiments 86 to 97, wherein the Fc polypeptide is a human IgG1 Fc, IgG2 Fc, IgG3 Fc, or IgG4 Fc.

Embodiment 99. The contiguous polypeptide of any one of embodiments 86 to 98, wherein the Fc polypeptide is an Fc of a companion animal species.

Embodiment 100. The contiguous polypeptide of any one of embodiments 86 to 97 or 99, wherein the Fc polypeptide comprises:

a) a canine IgG-A Fc, IgG-B Fc, IgG-C Fc, or IgG-D Fc;

b) an equine IgG1 Fc, IgG2 Fc, IgG3 Fc, IgG4 Fc, IgG5 Fc, IgG6 Fc, or IgG7 Fc; or

c) a feline IgG1a Fc, IgG1b Fc, or IgG2 Fc.

Embodiment 101. The contiguous polypeptide of any one of embodiments 86 to 100, wherein the Fc polypeptide is a wild-type IgG Fc polypeptide.

Embodiment 102. The contiguous polypeptide of any one of embodiments 86 to 100, wherein the Fc polypeptide is a variant IgG Fc polypeptide.

Embodiment 103. The contiguous polypeptide of any one of embodiments 86 to 102, wherein the Fc polypeptide comprises the polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of embodiments 1 to 84.

Embodiment 104. The contiguous polypeptide of any one of embodiments 85 to 102, wherein the contiguous polypeptide has a longer serum half-life than a wild-type GLP1 polypeptide.

Embodiment 105. The contiguous polypeptide of any one of embodiments 86 to 104, wherein L1 and L2, if present, each independently is a flexible linker.

Embodiment 106. The contiguous polypeptide of any one of embodiments 86 to 105, wherein the amino acid sequence of L1 and L2, if present, each independently comprises 100%, at least 95%, at least 90%, at least 85% serine and/or glycine amino acid residues.

Embodiment 107. The contiguous polypeptide of any one of embodiments 86 to 106, wherein the contiguous polypeptide comprises an extension at its C-terminus.

Embodiment 108. The contiguous polypeptide of any one of embodiments 86 to 107, wherein the contiguous polypeptide comprises a glycine residue, two glycine residues, three glycine residues, four glycine residues, five glycine residues, six glycine residues, seven glycine residues, eight glycine residues, or greater than eight glycine residues at its C-terminus.

Embodiment 109. The contiguous polypeptide of any one of embodiments 86 to 108, wherein the contiguous polypeptide comprises an amino acid sequence of SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, or SEQ ID NO: 95 at its C-terminus.

Embodiment 110. The contiguous polypeptide of any one of embodiments 86 to 109, wherein the contiguous polypeptide comprises:

a) the amino acid sequence of SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 46; SEQ ID NO: 47, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, or SEQ ID NO: 106; or

b) the amino acid sequence of SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; or SEQ ID NO: 59.

Embodiment 111. A polypeptide comprising an amino acid sequence of SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 46; SEQ ID NO: 47, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 103; SEQ ID NO: 104, SEQ ID NO: 105, or SEQ ID NO: 106.

Embodiment 112. The polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of the preceding embodiments, wherein the at least one amino acid modification or substitution comprises an amino acid substitution with an amino acid derivative.

Embodiment 113. An isolated nucleic acid encoding the polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of the preceding embodiments.

Embodiment 114. A host cell comprising the nucleic acid of embodiment 113.

Embodiment 115. A method of producing a polypeptide comprising culturing the host cell of embodiment 114 and isolating the polypeptide.

Embodiment 116. A pharmaceutical composition comprising the polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of embodiments 1 to 112, and a pharmaceutically acceptable carrier.

Embodiment 117. A method of increasing production of cAMP in a cell, the method comprising exposing the cell to the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of embodiments 1 to 112 or 116 under conditions permissive for binding of the polypeptide, heterodimeric protein, or contiguous polypeptide to GLP1R.

Embodiment 118. The method of embodiment 117, wherein the cell is exposed to the polypeptide, heterodimeric protein, contiguous polypeptide, or the pharmaceutical composition ex vivo.

Embodiment 119. The method of embodiment 117, wherein the cell is exposed to the polypeptide, heterodimeric protein, contiguous polypeptide, or the pharmaceutical composition in vivo.

Embodiment 120. The method of any one of embodiments 118 to 119, whererin the cell is a human cell, a canine cell, a feline cell, or an equine cell.

Embodiment 121. A method of delivering a polypeptide to a subject comprising administering the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of embodiments 1 to 112 or 116 parenterally.

Embodiment 122. A method of delivering a polypeptide to a subject comprising administering the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of embodiments 1 to 112 or 116 by an intramuscular route, an intraperitoneal route, an intracerebrospinal route, a subcutaneous route, an intra-arterial route, an intrasynovial route, an intrathecal route, or an inhalation route.

Embodiment 123. A method of treating a subject having diabetes or obesity, the method comprising administering to the subject a therapeutically effective amount of the

polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of embodiments 1 to 112 or 116.

Embodiment 124. The method of embodiment 123, comprising administering insulin, a DPP4 inhibitor, a SGLT2 inhibitor, a biguanides sulfonylureas meglitinide derivative, an alpha-glucosidase inhibitor, a thiazolidinedion (TZD), an amylinomimetic, a bile acid sequestrant, a dopamine agonist.

Embodiment 125. The method of any one of embodiments 121 to 124, wherein the subject is a human subject.

Embodiment 126. The method of any one of embodiments 121 to 124, wherein the subject is a companion animal species.

Embodiment 127. The method of embodiment 126, wherein the companion animal species is canine, equine, or feline.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Figure 1 shows an alignment of canine IgG-A, B, C, and D Fc sequences. The boxes indicate the regions likely in contact with Protein A.

[0007] Figure 2A shows an SDS-PAGE analysis of GLP1-G8/GLP-2G_III_WTfeIgG2 (SEQ ID NO: 23; "GLP1 A variant" in this figure) and GLP1-G8_I_WTfeIgG2 (SEQ ID NO: 24; "GLP1 B variant" in this figure) having wild-type feline IgG2 hinge with one disulfide bond in the absence and presence of reducing agent (DTT).

[0008] Figure 2B shows an SDS-PAGE analysis of GLP1-G8/GLP-2G_III_VARfeIgG2 (SEQ ID NO: 25; "GLP1 MA variant" in this figure) of GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26; "GLP1 MB variant" in this figure) having variant feline IgG2 hinge with two disulfide bonds in the absence and presence of reducing agent (DTT).

[0009] Figure 3 shows a cAMP CHO-K1 GLP1R Bioassay to evaluate activity of GLP1-G8/GLP1-2G_III_VARfeIgG2 (SEQ ID NO: 25) and GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) compared to controls (GLP1 (7-37) and Extendin-4).

[0010] Figure 4 shows a cell-based bioassay to evaluate activity of GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) ("GLP1-B" in this figure) after 1 year of storage with CHOK1-GLP1R cells and cAMP-glo (n=2).

[0011] Figure 5 shows a Western Blot analysis of GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) ("GLP1B" in this figure) after incubation in serum for 24 hours at 37°C (lane 1), in PBS for 24 hours at 37°C (lane 2), in PBS for 24 hours at 4°C (lane 9). A mouse anti-GLP1 antibody was used.

[0012] Figure 6 is a plot of GLP1-G8_I_VARfeIgG2 (SEQ ID NO:26) concentration in the serum over time after subcutaneous administration to 5 cats, as measured by quantitative ELISA.

[0013] Figure 7 shows a plot of GLP1-G8_I_VARfeIgG2 (SEQ ID NO:26) concentration in the serum over time after subcutaneous administration to 5 cats, as measured by cell-based activity assay. The mean AUC from 0 to 168 hours was about 840 μg(h)/mL and the mean $t_{1/2}$ was 36 hours.

DESCRIPTION OF THE SEQUENCES

[0014] Table 1 provides a listing of exemplary sequences referenced herein.

Table 1: Description of the Sequences

SEQ ID NO:	SEQUENCE	DESCRIPTION
1	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary wild-type canine IgG-A Fc Protein A – C1q – CD16 –
2	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary wild-type canine IgG-B Fc Protein A + C1q + CD16 +
107	PKRENGRVPRPPDCPKCPAPEMLGGPSVFIFPP KPKDTLLIARTPEVTCVVVDLDPEDPEVQISW FVDGKQMQTAKTQPREEQFNGTYRVVSVLPIG HQDWLKGKQFTCKVNNKALPSPIERTISKARG QAHQPSVYVLPPSREELSKNTVSLTCLIKDFF PPDIDVEWQSNGQQEPESKYRTTPPQLDEDGS YFLYSKLSVDKSRWQRGDTFICAVMHEALHNH YTQESLSHSPGK	Exemplary wild-type canine IgG-B Fc with hinge Protein A + C1q + CD16 +
3	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary wild-type canine IgG-C Fc Protein A – C1q + CD16 +
108	AKECECKCNCNNCPCPGCGLLGGPSVFIFPPK PKDILVTARTPTVTCVVVDLDPENPEVQISWF VDSKQVQTANTQPREEQSNGTYRVVSVLPIGH QDWLSGKQFKCKVNNKALPSPIEEIISKTPGQ AHQPNVYVLPPSRDEMSKNTVTLTCLVKDFFP	Exemplary wild-type canine IgG-C Fc with hinge Protein A – C1q +

	PEIDVEWQSNGQQEPESKYRMTPPQLDEDGSY FLYSKLSVDKSRWQRGDTFICAVMHEALHNHY TQISLSHSPGK	CD16 +
4	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary wild-type canine IgG-D Fc Protein A – C1q – CD16 –
5	PVPEPLGGPSVLIFPPKPKD**T**L**L**I**A**RTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPI**G**HQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHE**A**L**H**NHYTDLSLSHSPGK	Exemplary variant canine IgG-A Fc C1q – Protein A + I(21)T R(23)L T(25)A E(80)G T(205)A Q(207)H
6	PGCGLLGGPSVFIFPPKPKD**T**L**LI**ARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc C1q + Protein A + I(21)T V(23)L T(24)I
7	PVPESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPI**G**HQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEAL**H**NHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc C1q – Protein A + I(21)T R(23)L T(25)A E(80)G Q(207)H
8	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSI**Y**CLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary variant canine IgG-A Fc Heterodimer chain 1 T(138)Y
9	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFL**T**SKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary variant canine IgG-A Fc Heterodimer chain 2 Y(181)T

10	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSL**Y**CLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Heterodimer chain 1 T(137)Y
11	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFL**T**SKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Heterodimer chain 2 Y(180)T
12	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTL**Y**CLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Heterodimer chain 1 T(137)Y
13	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFL**T**SKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Heterodimer chain 2 Y(180)T
14	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTL**Y**CLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc Heterodimer chain 1 T(138)Y
15	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFL**T**SKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc Heterodimer chain 2 Y(181)T
109	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSI**W**CLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary variant canine IgG-A Fc Heterodimer chain 3 T(138)W
110	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH	Exemplary variant canine IgG-A Fc

	IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSI**S**C**A**IKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFL**T**SKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Heterodimer chain 4 T(138)S L(140)A Y(181)T
111	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSL**W**CLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Heterodimer chain 3 T(137)W
112	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSL**S**C**A**IKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFL**T**SKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Heterodimer chain 4 T(137)S L(139)A Y(180)T
113	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTL**W**CLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Heterodimer chain 3 T(137)W
114	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTL**S**C**A**VKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFL**T**SKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Heterodimer chain 4 T(137)S L(139)A Y(180)T
115	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTL**W**CLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc Heterodimer chain 3 T(138)W
116	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTL**S**C**A**IKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFL**T**SKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc Heterodimer chain 4 T(138)S L(140)A Y(181)T
16	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF	Exemplary wild-type feline IgG2 Fc Protein A + C1q –

	HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	
117	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary wild-type feline IgG1a Fc Protein A + C1q +
118	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary wild-type feline IgG1b Fc Protein A + C1q +
119	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSV**W**CLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG2 Fc Heterodimer chain 1 T(154)W
120	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSV**S**C**A**IKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFL**T**SRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG2 Fc Heterodimer chain 2 T(154)S L(156)A Y(197)T
121	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSV**W**CLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1a Fc Heterodimer chain 1 T(154)W
122	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSV**S**C**A**IKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFV**T**SKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1a Fc Heterodimer chain 2 T(154)S L(156)A Y(197)T

123	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSV**W**CLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1b Fc Heterodimer chain 1 T(154)W
124	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSV**S**C**A**IEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFL**T**SRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1b Fc Heterodimer chain 2 T(154)S L(156)A Y(197)T
17	PKTASTIESKTGE**C**PKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG2 Fc Hinge Cys G(14)C
125	*RKTDHPPGPKPCDCPKCPPPEMLGGP*SVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG2 Fc with feline IgG1 hinge
126	PKTASTIESKTGEGP**P**CPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG2 Fc with modified hinge K(16)P
127	RKTDHPPGPKPCDCP**P**CPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1a Fc with modified hinge K(16)P
128	RKTDHPPGPKPCDCP**P**CPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK	Exemplary variant feline IgG1b Fc with modified hinge

	GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	K(16)P
18	*DMSKCPKCPAPELL*GGPSVFIFPPNPKDALMI SRTPVVTCVVVNLSDQYPDVQFSWYVDNTEVH SAITKQREAQFNSTYRVVSVLPIQHQDWLSGK EFKCSVTNVGVPQPISRAISRGKGPSRVPQVY VLPPHPDELAKSKVSVTCLVKDFYPPDISVEW QSNRWPELEGKYSTTPAQLDGDGSYFLYSKLS LETSRWQQVESFTCAVMHEALHNHFTKTDISE SLGK	Exemplary variant equine Fc IgG2 (with equine IgG1 hinge) Protein A – C1q –
19	*DMSKCPKCPAPELL*GGPSVFIFPPNPKD**T**LMI SRTPVVTCVVVNLSDQYPDVQFSWYVDNTEVH SAITKQREAQFNSTYRVVSVLPIQHQDWLSGK EFKCSVTNVGVPQPISRAISRGKGPSRVPQVY VLPPHPDELAKSKVSVTCLVKDFYPPDISVEW QSNRWPELEGKYSTTPAQLDGDGSYFLYSKLS LETSRWQQVESFTCAVMHEALHNH**Y**TKTDISE SLGK	Exemplary variant equine IgG2 Fc (with equine IgG1 hinge) C1q – Protein A + A(29)T F(217)Y
20	H**X**EGTFTSDVSSYLEGQAAKEFIAWLVKG	Exemplary variant GLP1 (7-35) X8 may be G or S
21	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT	Glucagon (Gluc)
22	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPS SGAPPPS	Extendin-4
23	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG SGGGGSGGGGSGGGGS*PKTASTIESKTGEGPK CPVPEIPGAPSVFIFPPKPKDTLSISRTPEVT CLVVDLGPDDSNVQITWFVDNTEMHTAKTRPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVN SKSLPSAMERTISKAKGQPHEPQVYVLPPTQE ELSENKVSVTCLIKGFHPPDIAVEWEITGQPE PENNYQTTPPQLDSDGTYFLYSRLSVDRSHWQ RGNTYTCSVSHEALHSHHTQKSLTQSPGK*GGG GSGGGG*HAEGTFTSDVSSYLEGQAAKEFIAWL VKGGG	GLP1-G8/GLP-2G_III_ WTfeIgG2
24	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG SGGGGSGGGGSGGGGS*PKTASTIESKTGEGPK CPVPEIPGAPSVFIFPPKPKDTLSISRTPEVT CLVVDLGPDDSNVQITWFVDNTEMHTAKTRPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVN SKSLPSAMERTISKAKGQPHEPQVYVLPPTQE ELSENKVSVTCLIKGFHPPDIAVEWEITGQPE PENNYQTTPPQLDSDGTYFLYSRLSVDRSHWQ RGNTYTCSVSHEALHSHHTQKSLTQSPGK	GLP1-G8_I_WTfeIgG2
25	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG SGGGGSGGGGSGGGGS*PKTASTIESKTGE**C**PK CPVPEIPGAPSVFIFPPKPKDTLSISRTPEVT CLVVDLGPDDSNVQITWFVDNTEMHTAKTRPR	GLP1-G8/GLP1-2G_III_ VARfeIgG2

	EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVN SKSLPSAMERTISKAKGQPHEPQVYVLPPTQE ELSENKVSVTCLIKGFHPPDIAVEWEITGQPE PENNYQTTPPQLDSDGTYFLYSRLSVDRSHWQ RGNTYTCSVSHEALHSHHTQKSLTQSPGK*GGG GSGGGG*HAEGTFTSDVSSYLEGQAAKEFIAWL VKGGG	
26	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG SGGGGSGGGGSGGGGS*PKTASTIESKTGE**C**PK CPVPEIPGAPSVFIFPPKPKDTLSISRTPEVT CLVVDLGPDDSNVQITWFVDNTEMHTAKTRPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVN SKSLPSAMERTISKAKGQPHEPQVYVLPPTQE ELSENKVSVTCLIKGFHPPDIAVEWEITGQPE PENNYQTTPPQLDSDGTYFLYSRLSVDRSHWQ RGNTYTCSVSHEALHSHHTQKSLTQSPGK	GLP1-G8_I_VARfeIgG2
27	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*PKTASTIESKTGEGP KCPVPEIPGAPSVFIFPPKPKDTLSISRTPEV TCLVVDLGPDDSNVQITWFVDNTEMHTAKTRP REEQFNSTYRVVSVLPILHQDWLKGKEFKCKV NSKSLPSAMERTISKAKGQPHEPQVYVLPPTQ EELSENKVSVTCLIKGFHPPDIAVEWEITGQP EPENNYQTTPPQLDSDGTYFLYSRLSVDRSHW QRGNTYTCSVSHEALHSHHTQKSLTQSPGK*GG GGSGGGG*HAEGTFTSDVSSYLEGQAAKEFIAW LVKGGGG	GLP1-S8/GLP1-3G_III_ WTfeIgG2
28	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*PKTASTIESKTGEGP KCPVPEIPGAPSVFIFPPKPKDTLSISRTPEV TCLVVDLGPDDSNVQITWFVDNTEMHTAKTRP REEQFNSTYRVVSVLPILHQDWLKGKEFKCKV NSKSLPSAMERTISKAKGQPHEPQVYVLPPTQ EELSENKVSVTCLIKGFHPPDIAVEWEITGQP EPENNYQTTPPQLDSDGTYFLYSRLSVDRSHW QRGNTYTCSVSHEALHSHHTQKSLTQSPGK	GLP1-S8_I_WTfeIgG2
29	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*PKESTSKCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSG GGG*HAEGTFTSDVSSYLEGQAAKEFIAWLVKG GGG	GLP1-G8/GLP1-3G_III_ VARcaIgGD
30	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*PKESTCKCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL	GLP1-G8_I_VARcaIgGD

	PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK	
31	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG* *GGGGSGGGSGGGSGGGS*PKESTSKCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSG* *GGG*HAEGTFTSDVSSYLEGQAAKEFIAWLVKG GGG	GLP1-S8/GLP1-3G_III_ VARcaIgGD
32	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG* *GGGGSGGGSGGGSGGGS*PKESTCKCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK	GLP1-S8_I_VARcaIgGD
33	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG* *GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK*GGGGSGGGG*HA EGTFTSDVSSYLEGQAAKEFIAWLVKGGGG	GLP1-G8/GLPL1-3G_III_ VAReqIgG2
34	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG* *GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK	GLP1-G8_I_VAReqIgG2
35	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG* *GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK*GGGGSGGGG*HA	GLP1-S8/GLP1-3G_III_ VAReqIgG2

	EGTFTSDVSSYLEGQAAKEFIAWLVKGGGG	
36	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK	GLP1-S8_I_VAReqIgG2
37	*MAVLGLLFCLVTFPSCVLS*H**S**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*PKTASTIESKTGEGPKCPVPEIPGAPSV FIFPPKPKDTLSISRTPEVTCLVVDLGPDDSN VQITWFVDNTEMHTAKTRPREEQFNSTYRVVS VLPILHQDWLKGKEFKCKVNSKSLPSAMERTI SKAKGQPHEPQVYVLPPTQEELSENKVSVTCL IKGFHPPDIAVEWEITGQPEPENNYQTTPPQL DSDGTYFLYSRLSVDRSHWQRGNTYTCSVSHE ALHSHHTQKSLTQSPGK*GGGGSGGGG*HAEGTF TSDVSSYLEGQAAKEFIAWLVKGGGG	ssGLP1-S8/GLP1-3G_III_ WTfeIgG2
38	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GGGSGGGGSGGGGSGG GGS*PKTASTIESKTGE**C**PKCPVPEIPGAPSVF IFPPKPKDTLSISRTPEVTCLVVDLGPDDSNV QITWFVDNTEMHTAKTRPREEQFNSTYRVVSV LPILHQDWLKGKEFKCKVNSKSLPSAMERTIS KAKGQPHEPQVYVLPPTQEELSENKVSVTCLI KGFHPPDIAVEWEITGQPEPENNYQTTPPQLD SDGTYFLYSRLSVDRSHWQRGNTYTCSVSHEA LHSHHTQKSLTQSPGK*GGGGSGGGG*HAEGTFT SDVSSYLEGQAAKEFIAWLVKGGG	ssGLP1-G8/GLP1-2G_III_ VARfeIgG2
39	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GGGSGGGGSGGGGSGG GGS*PKTASTIESKTGE**C**PKCPVPEIPGAPSVF IFPPKPKDTLSISRTPEVTCLVVDLGPDDSNV QITWFVDNTEMHTAKTRPREEQFNSTYRVVSV LPILHQDWLKGKEFKCKVNSKSLPSAMERTIS KAKGQPHEPQVYVLPPTQEELSENKVSVTCLI KGFHPPDIAVEWEITGQPEPENNYQTTPPQLD SDGTYFLYSRLSVDRSHWQRGNTYTCSVSHEA LHSHHTQKSLTQSPGK	ssGLP1-G8_I_VARfeIgG2
40	*MAVLGLLFCLVTFPSCVLS*H**S**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*PKTASTIESKTGEGPKCPVPEIPGAPSV FIFPPKPKDTLSISRTPEVTCLVVDLGPDDSN VQITWFVDNTEMHTAKTRPREEQFNSTYRVVS VLPILHQDWLKGKEFKCKVNSKSLPSAMERTI SKAKGQPHEPQVYVLPPTQEELSENKVSVTCL IKGFHPPDIAVEWEITGQPEPENNYQTTPPQL DSDGTYFLYSRLSVDRSHWQRGNTYTCSVSHE ALHSHHTQKSLTQSPGK	ssGLP1-S8_I_WTfeIgG2

41	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GGGSGGGGSGGGGSGG GGS*PKESTCKCISPCPVPESLGGPSVFIFPPK PKD**T**L**L**I**A**RTPEITCVVLDLGREDPEVQISWF VDGKEVHTAKTQPREQQFNSTYRVVSVLPI**G**H QDWLTGKEFKCRVNHIGLPSPIERTISKARGQ AHQPSVYVLPPSPKELSSSDTVTLTCLIKDFF PPEIDVEWQSNGQPEPESKYHTTAPQLDEDGS YFLYSKLSVDKSRWQQGDTFTCAVMHEAL**H**NH YTDLSLSHSPGK*GGGGSGGGG*HAEGTFTSDVS SYLEGQAAKEFIAWLVKGGG	ssGLP1-G8/GLP1-2G_III_ VARcaIgGD
42	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GGGSGGGGSGGGGSGG GGS*PKEST**S**KCISPCPVPESLGGPSVFIFPPK PKD**T**L**L**I**A**RTPEITCVVLDLGREDPEVQISWF VDGKEVHTAKTQPREQQFNSTYRVVSVLPI**G**H QDWLTGKEFKCRVNHIGLPSPIERTISKARGQ AHQPSVYVLPPSPKELSSSDTVTLTCLIKDFF PPEIDVEWQSNGQPEPESKYHTTAPQLDEDGS YFLYSKLSVDKSRWQQGDTFTCAVMHEAL**H**NH YTDLSLSHSPGK*GGGGSGGGG*HAEGTFTSDVS SYLEGQAAKEFIAWLVKGGG	ssGLP1-G8/GLP1-2G_III_ VARcaIgGD
43	*MAVLGLLFCLVTFPSCVLS*H**S**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*PKEST**S**KCISPCPVPESLGGPSVFIFPP KPKD**T**L**L**I**A**RTPEITCVVLDLGREDPEVQISW FVDGKEVHTAKTQPREQQFNSTYRVVSVLPI**G** HQDWLTGKEFKCRVNHIGLPSPIERTISKARG QAHQPSVYVLPPSPKELSSSDTVTLTCLIKDF FPPEIDVEWQSNGQPEPESKYHTTAPQLDEDG SYFLYSKLSVDKSRWQQGDTFTCAVMHEAL**H**N HYTDLSLSHSPGK*GGGGSGGGG*HAEGTFTSDV SSYLEGQAAKEFIAWLVKGGGG	ssGLP1-S8/GLP1-3G_III_ VARcaIgGD
44	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*DMSKCPKCPAPELLGGPSVFIFPPNPKD **T**LMISRTPVVTCVVVNLSDQYPDVQFSWYVDN TEVHSAITKQREAQFNSTYRVVSVLPIQHQDW LSGKEFKCSVTNVGVPQPISRAISRGKGPSRV PQVYVLPPHPDELAKSKVSVTCLVKDFYPPDI SVEWQSNRWPELEGKYSTTPAQLDGDGSYFLY SKLSLETSRWQQVESFTCAVMHEALHNH**Y**TKT DISESLGK*GGGGSGGGG*HAEGTFTSDVSSYLE GQAAKEFIAWLVKGGGG	ssGLP1-G8/GLP1-3G_III_ VAReqIgG2
45	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGSS*VPKPQCPPYTHSKFLGGPSVFIFPPNP KD**T**LMISRTPVVTCVVVNLSDQYPDVQFSWYV DNTEVHSAITKQREAQFNSTYRVVSVLPIQHQ DWLSGKEFKCSVTNVGVPQPISRAISRGKGPS RVPQVYVLPPHPDELAKSKVSVTCLVKDFYPP DISVEWQSNRWPELEGKYSTTPAQLDGDGSYF	ssGLP1-G8_I_VAReqIgG2

	LYSKLSLETSRWQQVESFTCAVMHEALHNH**Y**T KTDISESLGK	
46	*MAVLGLLFCLVTFPSCVLS*H**S**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*DMSKCPKCPAPELLGGPSVFIFPPNPKD **T**LMISRTPVVTCVVVNLSDQYPDVQFSWYVDN TEVHSAITKQREAQFNSTYRVVSVLPIQHQDW LSGKEFKCSVTNVGVPQPISRAISRGKGPSRV PQVYVLPPHPDELAKSKVSVTCLVKDFYPPDI SVEWQSNRWPELEGKYSTTPAQLDGDGSYFLY SKLSLETSRWQQVESFTCAVMHEALHNH**Y**TKT DISESLGK*GGGGSGGGG*HAEGTFTSDVSSYLE GQAAKEFIAWLVKGGGG	ssGLP1-S8/GLP1-3G_III_ VAReqIgG2
47	*MAVLGLLFCLVTFPSCVLS*H**S**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGSS*VPKPQCPPYTHSKFLGGPSVFIFPPNP KD**T**LMISRTPVVTCVVVNLSDQYPDVQFSWYV DNTEVHSAITKQREAQFNSTYRVVSVLPIQHQ DWLSGKEFKCSVTNVGVPQPISRAISRGKGPS RVPQVYVLPPHPDELAKSKVSVTCLVKDFYPP DISVEWQSNRWPELEGKYSTTPAQLDGDGSYF LYSKLSLETSRWQQVESFTCAVMHEALHNH**Y**T KTDISESLGK	ssGLP1-S8_I_VAReqIgG2
48	MGLVAPVVLLHQDDEEHGQDEGPEDGSGYLLG TLTRFSSDFDSAPEVILAPDDQLQLPHPSSRE NFWARTGLCAESFLLRPVGPVGPVMGWSEGFH KRNSRQEFLRRRLFAGGLCAASTQESRNRCSS RGCKSSPADCPELDRTQHLGNSVGPIQAAHQE LALGAGGPGDECQCCSVSNSLFIPEPQSTCPY NGYTSWPLEGNLRVACAPPPPPPARTLFGGSR RGAVDKKAGGGNRSPGGGAGTGEFGAPGAGGG LGRRPEVGAWTAAEGTNPADLASSPPPPSTRP PAAPRPPCADFCAASPQTTFPTPSPR*RPLPAS GGATVSLSETVQKWREYRHQCQRFLTEAPPPA TGLFCNRTFDEYACWPDGLPGSFVNVSCPWYL PWASSVLQGHVYRFCTAEGLWLRQDNSSLPWR NLSECEESKRGERSSPEEQLLSFS*IIYTVGYT LSFSALVIASAILLSFRHLHCTRNYIHLNLFA SFILRALSVFIRDAVLKWMYSTAPQQHQWDGL LSYQDSLGCRLVFLLMQYCVAANYYWLLVEGV YLYTLLAFSVFSEQRIFRLYLSIGWGVPLLFV IWGIVKYLYEDEGCWTRNSNMNYWLIIRLPIL FAIGVNFLIFVRVICIVVSKLKANLMCKTDIK CRLAKSTLTLIPLLGTHEVVFAFVMDEHARGT LRFIKLFTELSFTSFQGLMVAILYCFVNNEVQ MEFRRSWERWRLKHLHIQRDSSMKPLKCPTSS LTSGGTVGSSVYAASCQASCS	Feline glucagon-like peptide 1 receptor (GLP1R)
49	RPLPASGGATVSLSETVQKWREYRHQCQRFLT EAPPPATGLFCNRTFDEYACWPDGLPGSFVNV SCPWYLPWASSVLQGHVYRFCTAEGLWLRQDN SSLPWRNLSECEESKRGERSSPEEQLLSFS	Mature feline glucagon-like peptide 1 receptor-N-terminal domain (GLP1R-N)

50	*METDTLLLWVLLLWVPGSTG*RPLPASGGATVS LSETVQKWREYRHQCQRFLTEAPPPATGLFCN RTFDEYACWPDGLPGSFVNVSCPWYLPWASSV LQGHVYRFCTAEGLWLRQDNSSLPWRNLSECE ESKRGERSSPEEQLLSFSGSENLYFQGPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKHHHHHH	ssFeGLP1R-N_huFc_ PolyHis
51	*METDTLLLWVLLLWVPGSTG*RPLPASGGATVS LSETVQKWREYRHQCQRFLTEAPPPATGLFCN RTFDEYACWPDGLPGSFVNVSCPWYLPWASSV LQGHVYRFCTAEGLWLRQDNSSLPWRNLSECE ESKRGERSSPEEQLLSFSGGGSHHHHHH	ssFeGLP1R-N_PolyHis
52	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG SGGGGSGGGGSGGGGS*PKTASTIESKTGEGPK CPVPEIPGAPSVFIFPPKPKDTLSISRTPEVT CLVVDLGPDDSNVQITWFVDNTEMHTAKTRPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVN SKSLPSAMERTISKAKGQPHEPQVYVLPPTQE ELSENKVSVTCLIKGFHPPDIAVEWEITGQPE PENNYQTTPPQLDSDGTYFLYSRLSVDRSHWQ RGNTYTCSVSHEALHSHHTQKSLTQSPGK*GGG GSGGGG*HSQGTFTSDYSKYLDSRRAQDFVQWL MNT*GGG*	GLP1-G8/Gluc-3G_IV_ WTfeIgG2
53	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT*GGG GSGGGGSGGGGSGGGGS*PKTASTIESKTGEGP KCPVPEIPGAPSVFIFPPKPKDTLSISRTPEV TCLVVDLGPDDSNVQITWFVDNTEMHTAKTRP REEQFNSTYRVVSVLPILHQDWLKGKEFKCKV NSKSLPSAMERTISKAKGQPHEPQVYVLPPTQ EELSENKVSVTCLIKGFHPPDIAVEWEITGQP EPENNYQTTPPQLDSDGTYFLYSRLSVDRSHW QRGNTYTCSVSHEALHSHHTQKSLTQSPGK*GG GGSGGGG*HAEGTFTSDVSSYLEGQAAKEFIAW LVKG*GG*	Gluc/GLP1-2G_V_ WTfeIgG2
54	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*PKEST**S**KCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSG GGG*HSQGTFTSDYSKYLDSRRAQDFVQWLMNT *GGGG*	GLP1-G8/Glu-4G_IV_ VARcaIgGD

55	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT*GAG GGGGSGGGSGGGSGGGS*PKEST**S**KCISPCPVP ESLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVL DLGREDPEVQISWFVDGKEVHTAKTQPREQQF NSTYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGL PSPIERTISKARGQAHQPSVYVLPPSPKELSS SDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGD TFTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSG GGG*HAEGTFTSDVSSYLEGQAAKEFIAWLVKG *GGG*	Gluc/GLP1-3G_V_ VARcaIgGD
56	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK*GGGGSGGGG*HS QGTFTSDYSKYLDSRRAQDFVQWLMNT*GGGG*	GLP1-G8/Gluc-4G_IV_ VAReqIgGD
57	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT*GAG GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK*GGGGSGGGG*HA EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG*	Gluc/GLP1-3G_V_ VAReqIgG2
58	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGSS*ESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK*GGGGSGGGG* HSQGTFTSDYSKYLDSRRAQDFVQWLMNT*GGG G*	GLP1-G8/Glu-4G_IV_ huIgG4
59	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT*GGG GGSGGGSGGGSGGGSS*ESKYGPPCPPCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLGK*GGGGSGGGG*HA	Gluc/GLP1-3G_V_huIgG4

	EGTFTSDVSSYLEGQAAKEFIAWLVKGGAG*GG G*	
60	PVPEPLGGPSVLIFPPKPKD**T**LRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETL**H**NHYTDLSLSHSPGK	Exemplary variant canine IgG-A Fc C1q – Protein A + I(21)T Q(207)H
61	PGCGLLGGPSVFIFPPKPKD**T**LVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc C1q + Protein A + I(21)T
62	PVPESLGGPSVFIFPPKPKD**T**LRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEAL**H**NHYTDLSLSHSPGK	Exemplary variant canine IgG-D Fc C1q – Protein A + I(21)T Q(207)H
63	GGPSVFLFPPNPKDTLMITRTPEVTCVVVDVS QENPDVKFNWYMDGVEVRTATTRPKEEQFNST YRVVSVLRIQHQDWLSGKEFKCKVNNQALPQP IERTITKTKGRSQEPQVYVLAPHPDESKKSKV SVTCLVKDFYPPEINIEWQSNGQPELETKYST TQAQQDSDGSYFLYSKLSVDRNRWQQGTTFTC GVMHEALHNHYTQKNVSKNPGK	Exemplary wild-type equine IgG1 Fc Protein A + C1q +
64	GGPSVFIFPPNPKDALMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQFNST YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQVESFTC AVMHEALHNHFTKTDISESLGK	Exemplary wild-type equine IgG2 Fc Protein A – C1q –
65	GGPSVFIFPPKPKDVLMITRMPEVTCLVVDVS HDSSDVLFTWYVDGTEVKTAKTMPNEEQNNST YRVVSVLRIQHQDWLNGKKFKCKVNNQALPAP VERTISKATGQTRVPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDITVEWQSNEHPEPEGKYRT TEAQKDSDGSYFLYSKLTVEKDRWQQGTTFTC VVMHEALHNHVMQKNISKNPGK	Exemplary wild-type equine IgG3 Fc Protein A + C1q+
66	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQFNST YRVVSVLPIQHKDWLSGKEFKCKVNNKALPAP VERTISAPTGQPREPQVYVLAPHRDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDSDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary wild-type equine IgG4 Fc Protein A + C1q +

67	GGPSVFIFPPKPKDVLMISRKPEVTCVVVDLG HDDPDVQFTWFVDGVETHTATTEPKEEQFNST YRVVSVLPIQHQDWLSGKEFKCSVTSKALPAP VERTISKAKGQLRVPQVYVLAPHPDELAKNTV SVTCLVKDFYPPEIDVEWQSNEHPEPEGKYST TPAQLNSDGSYFLYSKLSVETSRWKQGESFTC GVMHEAVENHYTQKNVSHSPGK	Exemplary wild-type equine IgG5 Fc Protein A – C1q –
68	GRPSVFIFPPNPKDTLMISRTPEVTCVVVDVS QENPDVKFNWYVDGVEAHTATTKAKEKQDNST YRVVSVLPIQHQDWRRGKEFKCKVNNRALPAP VERTITKAKGELQDPQVYILAPHPDEVTKNTV SVTCLVKDFYPPDINVEWQSNEEPEPEVKYST TPAQLDGDGSYFLYSKLTVETDRWEQGESFTC VVMHEAIRHTYRQKSITNFPGK	Exemplary wild-type equine IgG6 Fc Protein A – C1q –
69	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQNNST YRVVSILAIQHKDWLSGKEFKCKVNNQALPAP VQKTISKPTGQPREPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDGDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary wild-type equine IgG7 Fc Protein A + C1q +
70	GGPSVFLFPPNPKDTLMITRTPEVTCVVVDVS QENPDVKFNWYMDGVEVRTATTRPKEEQFNST YRVVSVLRIQHQDWLSGKEFKC**S**VNNQALPQP IERTITKTKGRSQEPQVYVLAPHPDESKKSKV SVTCLVKDFYPPEINIEWQSNGQPELETKYST TQAQQDSDGSYFLYSKLSVDRNRWQQGTTFTC GVMHEALHNHYTQKNVSKNPGK	Exemplary variant equine IgG1 Fc Protein A + C1q – K(87)S
71	GGPSVFIFPPNPKDALMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQFNST YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQGESFTC AVMHEALHNH**Y**TKTDISESLGK	Exemplary variant equine IgG2 Fc C1q – Protein A + F(203)Y
72	GGPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQFNST YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQVESFTC AVMHEALHNH**Y**TKTDISESLGK	Exemplary variant equine IgG2 Fc C1q – Protein A + A(15)T F(203)Y
129	PPCVLSAEGVIPIPSVPKPQCPPYTHSKFLGG PSVFIFPPNPKDALMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNHFTKTDISESLGK	Exemplary wild-type equine IgG2 Fc with hinge Protein A – C1q –

130	PPCVLSAEGVIPIPSVPKP**P**CPPYTHSKFLGG PSVFIFPPNPKDALMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNHFTKTDISESLGK	Exemplary variant equine IgG2 Fc with modified hinge Protein A – C1q – Q(20)P
131	PP**S**VLSAEGVIPIPSVPKPQCPPYTHSKFLGG PSVFIFPPNPKDALMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNHFTKTDISESLGK	Exemplary variant equine IgG2 Fc with modified hinge Protein A – C1q – C(3)S
132	PP**S**VLSAEGVIPIPSVPKP**P**CPPYTHSKFLGG PSVFIFPPNPKDALMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNHFTKTDISESLGK	Exemplary variant equine IgG2 Fc with modified hinge Protein A – C1q – C(3)S Q(20)P
133	PPCVLSAEGVIPIPSVPKPQCPPYTHSKFLGG PSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNH**Y**TKTDISESLGK	Exemplary variant equine IgG2 Fc with hinge Protein A + C1q – A(45)T F(233)Y
134	PPCVLSAEGVIPIPSVPKP**P**CPPYTHSKFLGG PSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNH**Y**TKTDISESLGK	Exemplary variant equine IgG2 Fc with modified hinge Protein A + C1q – Q(20)P A(45)T F(233)Y
135	PP**S**VLSAEGVIPIPSVPKP**P**CPPYTHSKFLGG PSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSDQ YPDVQFSWYVDNTEVHSAITKQREAQFNSTYR VVSVLPIQHQDWLSGKEFKCSVTNVGVPQPIS RAISRGKGPSRVPQVYVLPPHPDELAKSKVSV TCLVKDFYPPDISVEWQSNRWPELEGKYSTTP AQLDGDGSYFLYSKLSLETSRWQQVESFTCAV MHEALHNH**Y**TKTDISESLGK	Exemplary variant equine IgG2 Fc with modified hinge Protein A + C1q – C(3)S Q(20)P A(45)T F(233)Y
73	GGPSVFIFPPKPKDVLMITRMPEVTCLVVDVS HDSSDVLFTWYVDGTEVKTAKTMPNEEQNNST	Exemplary variant equine IgG3 Fc

	YRVVSVLRIQHQDWLNGKKFKC**S**VNNQALPAP VERTISKATGQTRVPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDITVEWQSNEHPEPEGKYRT TEAQKDSDGSYFLYSKLTVEKDRWQQGTTFTC VVMHEALHNHVMQKNISKNPGK	Protein A + C1q – K(87)S
74	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQFNST YRVVSVLPIQHKDWLSGKEFKC**S**VNNKALPAP VERTISAPTGQPREPQVYVLAPHRDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDSDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary variant equine IgG4 Fc Protein A + C1q – K(87)S
75	GGPSVFIFPPKPKDVLMISRKPEVTCVVVDLG HDDPDVQFTWFVDGVETHTATTEPKEEQFNST YRVVSVLPIQHQDWLSGKEFKCSVTSKALPAP VERTISKAKGQLRVPQVYVLAPHPDELAKNTV SVTCLVKDFYPPEIDVEWQSNEHPEPEGKYST TPAQLNSDGSYFLYSKLSVETSRWKQGESFTC GVMHEA**LH**NHYTQKNVSHSPGK	Exemplary variant equine IgG5 Fc C1q – Protein A + V(199)L E(200)H
76	GRPSVFIFPPNPKDTLMISRTPEVTCVVVDVS QENPDVKFNWYVDGVEAHTATTKAKEKQDNST YRVVSVLPIQHQDWRRGKEFKCKVNNRALPAP VERTITKAKGELQDPQVYILAPHPDEVTKNTV SVTCLVKDFYPPDINVEWQSNEEPEPEVKYST TPAQLDGDGSYFLYSKLTVETDRWEQGESFTC VVMHEA**LHNH**YRQKSITNFPGK	Exemplary variant equine IgG6 Fc C1q – Protein A + I(199)L R(200)H H(201)N T(202)H
77	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQNNST YRVVSILAIQHKDWLSGKEFKC**S**VNNQALPAP VQKTISKPTGQPREPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDGDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary variant equine IgG7 Fc Protein A + C1q – K(87)S
78	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTC**R**VNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q – K(93)R
79	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKC**R**VNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A – C1q – K(93)R
80	RKTDHPPGPKTGEGPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI	Exemplary wild-type feline IgG1a Fc

	LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Protein A + C1q +
81	RKTDHPPGPKTGEGPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary wild-type feline IgG1b Fc Protein A + C1q +
136	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPS**P**IERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1a Fc Protein A + C1q – P(198)A
82	RKTDHPPGPKTGEGPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPS**P**IERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1a Fc Protein A + C1q – P(198)A
137	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPS**P**IERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1b Fc Protein A + C1q – P(198)A
83	RKTDHPPGPKTGEGPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNSTYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPS**P**IERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary variant feline IgG1b Fc Protein A + C1q – P(198)A
84	PGCGLLGGPSVFIFPPKPKD**T**L**LI**ARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKC**R**VNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc C1q – K(93)R Protein A + I(21)T

		V(23)L T(24)I
85	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGAG	Wild-type GLP1 (7-37)
86	H**S**EGTFTSDVSSYLEGQAAKEFIAWLVKG	GLP1-S8 (7-35)
87	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG	GLP1-G8 (7-35)
88	G	1G extension
89	GG	2G extension
90	GGG	3G extension
91	GGGG	4G extension
92	GGGGG	5G extension
93	GGGGGG	6G extension
94	GGGGGGG	7G extension
95	GGGGGGGG	8G extension
96	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*PKTASTIESKTGEGPKCPVPEIPGAPSV FIFPPKPKDTLSISRTPEVTCLVVDLGPDDSN VQITWFVDNTEMHTAKTRPREEQFNSTYRVVS VLPILHQDWLKGKEFKCKVNSKSLPSAMERTI SKAKGQPHEPQVYVLPPTQEELSENKVSVTCL IKGFHPPDIAVEWEITGQPEPENNYQTTPPQL DSDGTYFLYSRLSVDRSHWQRGNTYTCSVSHE ALHSHHTQKSLTQSPGK	ssGLP1-G8_I_WTfeIgG2
97	*MAVLGLLFCLVTFPSCVLS*H**G**EGTFTSDVSSY LEGQAAKEFIAWLVKG*GAGGGGGSGGGSGGGS GGGS*PKTASTIESKTGEGPKCPVPEIPGAPSV FIFPPKPKDTLSISRTPEVTCLVVDLGPDDSN VQITWFVDNTEMHTAKTRPREEQFNSTYRVVS VLPILHQDWLKGKEFKCKVNSKSLPSAMERTI SKAKGQPHEPQVYVLPPTQEELSENKVSVTCL IKGFHPPDIAVEWEITGQPEPENNYQTTPPQL DSDGTYFLYSRLSVDRSHWQRGNTYTCSVSHE ALHSHHTQKSLTQSPGK*GGGGSGGGG*HAEGTF TSDVSSYLEGQAAKEFIAWLVKG*GGG*	ssGLP1-G8/GLP1-3G_III_ WTfeIgG2
98	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGA	Variant GLP1 (7-36)
99	HAEGTFTSDVSSYLEGQAAKEFIAWLVKG	Variant GLP1 (7-35)
100	*VPKPQCPPYTHSKFL*GGPSVFIFPPNPKDALM ISRTPVVTCVVVNLSDQYPDVQFSWYVDNTEV HSAITKQREAQFNSTYRVVSVLPIQHQDWLSG KEFKCSVTNVGVPQPISRAISRGKGPSRVPQV YVLPPHPDELAKSKVSVTCLVKDFYPPDISVE WQSNRWPELEGKYSTTPAQLDGDGSYFLYSKL SLETSRWQQVESFTCAVMHEALHNHFTKTDIS ESLGK	Exemplary wild-type equine Fc IgG2 (including equine IgG2 hinge) Protein A – C1q –

101	DMSKCPKCPAPELL	Exemplary wild-type equine IgG1 hinge
102	VPKPQCPPYTHSKFL	Exemplary wild-type equine IgG2 hinge
138	PPCVLSAEGVIPIPSVPKPQCPPYTHSKFL	Exemplary wild-type equine IgG2 hinge
103	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGS*DMSKCPKCPAPELLG GPSVFIFPPNPKD**T**LMISRTPVVTCVVVNLSD QYPDVQFSWYVDNTEVHSAITKQREAQFNSTY RVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPI SRAISRGKGPSRVPQVYVLPPHPDELAKSKVS VTCLVKDFYPPDISVEWQSNRWPELEGKYSTT PAQLDGDGSYFLYSKLSLETSRWQQVESFTCA VMHEALHNH**Y**TKTDISESLGK*GGGGSGGGG*HA EGTFTSDVSSYLEGQAAKEFIAWLVKG*GGG*	GLP1-G8/GLP1-3G_III_ VAReqIgG2
104	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKG*GAG GGGGSGGGSGGGSGGGSS*VPKPQCPPYTHSKF LGGPSVFIFPPNPKD**T**LMISRTPVVTCVVVNL SDQYPDVQFSWYVDNTEVHSAITKQREAQFNS TYRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQ PISRAISRGKGPSRVPQVYVLPPHPDELAKSK VSVTCLVKDFYPPDISVEWQSNRWPELEGKYS TTPAQLDGDGSYFLYSKLSLETSRWQQVESFT CAVMHEALHNH**Y**TKTDISESLGK	GLP1-G8_I_VAReqIgG2
105	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKGGGG SGGGGSGGGGSGGGGSPKESTCKCISPCPVPE SLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVLD LGREDPEVQISWFVDGKEVHTAKTQPREQQFN STYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGLP SPIERTISKARGQAHQPSVYVLPPSPKELSSS DTVTLTCLIKDFFPPEIDVEWQSNGQPEPESK YHTTAPQLDEDGSYFLYSKLSVDKSRWQQGDT FTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSGG GG*HAEGTFTSDVSSYLEGQAAKEFIAWLVKG*G G*	GLP1-G8/GLP1-2G_III_ VARcaIgGD
106	H**G**EGTFTSDVSSYLEGQAAKEFIAWLVKGGGG SGGGGSGGGGSGGGGSPKESTSKCISPCPVPE SLGGPSVFIFPPKPKD**T**L**L**I**A**RTPEITCVVLD LGREDPEVQISWFVDGKEVHTAKTQPREQQFN STYRVVSVLPI**G**HQDWLTGKEFKCRVNHIGLP SPIERTISKARGQAHQPSVYVLPPSPKELSSS DTVTLTCLIKDFFPPEIDVEWQSNGQPEPESK YHTTAPQLDEDGSYFLYSKLSVDKSRWQQGDT FTCAVMHEAL**H**NHYTDLSLSHSPGK*GGGGSGG GG*HAEGTFTSDVSSYLEGQAAKEFIAWLVKG*G G*	GLP1-G8/GLP1-2G_III_ VARcaIgGD
139	PAPE**P**LGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP	Exemplary variant canine IgG-B Fc Protein A + C1q +

	ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	CD16 – M(5)P
140	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLD**R**EDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q + CD16 – P(39)R
141	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDL**G**PEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q + CD16 – D(38)G
142	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN **I**ALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q + CD16 – K(97)I
143	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN K**G**LPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q + CD16 – A(98)G
144	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDL**G**PEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN **IG**LPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q + CD16 – D(38)G K(97)I A(98)G
145	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDL**G**PEDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTC**R**VNN **IG**LPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q – CD16 – D(38)G K(93)R K(97)I A(98)G
146	PAPE**P**LGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLD**R**EDPEVQISWFVDGKQMQTAKTQPRE	Exemplary variant canine IgG-B Fc

	EQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Protein A + C1q + CD16 – M(5)P P(39)R
147	PAPE**P**LGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLD**R**EDPEVQISWFVDGKQMQTAKTQPRE EQFNGTYRVVSVLPIGHQDWLKGKQFTC**R**VNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary variant canine IgG-B Fc Protein A + C1q – CD16 – M(5)P P(39)R K(93)R
148	PGCG**P**LGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – L(5)P
149	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLD**R**ENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – P(39)R
150	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDL**G**PENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – D(38)G
151	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN **I**ALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – K(97)I
152	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN K**G**LPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – A(98)G

153	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKC**R**VNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q – CD16 + K(93)R
154	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDL**G**PENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN **IG**LPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – D(38)G K(97)I A(98)G
155	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDL**G**PENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKC**R**VNN **IG**LPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q – CD16 – D(38)G K(93)R K(97)I A(98)G
156	PGCG**P**LGGPSVFIFPPKPKDILVTARTPTVTC VVVDLD**R**ENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q + CD16 – L(5)P P(39)R
157	PGCG**P**LGGPSVFIFPPKPKDILVTARTPTVTC VVVDLD**R**ENPEVQISWFVDSKQVQTANTQPRE EQSNGTYRVVSVLPIGHQDWLSGKQFKC**R**VNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary variant canine IgG-C Fc Protein A + C1q – CD16 – M(5)P P(39)R K(93)R
158	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQF**X_1**GTYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary aglycosyl variant canine IgG-A Fc N(68)X_1 X_1= any amino acid except N
159	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE	Exemplary aglycosyl variant canine IgG-A Fc

	QQFN**P**TYRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	G(69)P
160	PVPEPLGGPSVLIFPPKPKDILRITRTPEVTC VVLDLGREDPEVQISWFVDGKEVHTAKTQSRE QQFNG**X₂**YRVVSVLPIEHQDWLTGKEFKCRVNH IDLPSPIERTISKARGRAHKPSVYVLPPSPKE LSSSDTVSITCLIKDFYPPDIDVEWQSNGQQE PERKHRMTPPQLDEDGSYFLYSKLSVDKSRWQ QGDPFTCAVMHETLQNHYTDLSLSHSPGK	Exemplary aglycosyl variant canine IgG-A Fc T(70)X_2 X_2 = any amino acid except T or S
161	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQF**X₁**GTYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary aglycosyl variant canine IgG-B Fc N(68)X_1 X_1= any amino acid except N
162	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFN**P**TYRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary aglycosyl variant canine IgG-B Fc G(69)P
163	PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTC VVVDLDPEDPEVQISWFVDGKQMQTAKTQPRE EQFNG**X₂**YRVVSVLPIGHQDWLKGKQFTCKVNN KALPSPIERTISKARGQAHQPSVYVLPPSREE LSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEP ESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Exemplary aglycosyl variant canine IgG-B Fc T(70)X_2 X_2 = any amino acid except T or S
164	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQS**X₁**GTYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary aglycosyl variant canine IgG-C Fc N(68)X_1 X_1= any amino acid except N
165	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSN**P**TYRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	Exemplary aglycosyl variant canine IgG-C Fc G(69)P
166	PGCGLLGGPSVFIFPPKPKDILVTARTPTVTC VVVDLDPENPEVQISWFVDSKQVQTANTQPRE EQSNG**X₂**YRVVSVLPIGHQDWLSGKQFKCKVNN KALPSPIEEIISKTPGQAHQPNVYVLPPSRDE MSKNTVTLTCLVKDFFPPEIDVEWQSNGQQEP	Exemplary aglycosyl variant canine IgG-C Fc T(70)X_2

	ESKYRMTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQISLSHSPGK	X_2 = any amino acid except T or S
167	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQF**X_1**STYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary aglycosyl variant canine IgG-D Fc N(68)X_1 X_1= any amino acid except N
168	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFN**P**TYRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary aglycosyl variant canine IgG-D Fc S(69)P
169	PVPESLGGPSVFIFPPKPKDILRITRTPEITC VVLDLGREDPEVQISWFVDGKEVHTAKTQPRE QQFNS**X_2**YRVVSVLPIEHQDWLTGKEFKCRVNH IGLPSPIERTISKARGQAHQPSVYVLPPSPKE LSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPE PESKYHTTAPQLDEDGSYFLYSKLSVDKSRWQ QGDTFTCAVMHEALQNHYTDLSLSHSPGK	Exemplary aglycosyl variant canine IgG-D Fc T(70)X_2 X_2 = any amino acid except T or S
170	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQF**X_1**STYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG1a Fc N(85)X_1 X_1= any amino acid except N
171	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFN**P**TYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG1a Fc S(86)P
172	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNS**X_2**YRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKAK GQPHEPQVYVLPPAQEELSENKVSVTCLIKSF HPPDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFVYSKLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG1a Fc T(87)X_2 X_2 = any amino acid except T or S
173	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQF**X_1**STYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF	Exemplary aglycosyl variant feline IgG1b Fc N(85)X_1 X_1= any amino acid except N

	YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	
174	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFN**P**TYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG1b Fc S(86)P
175	RKTDHPPGPKPCDCPKCPPPEMLGGPSIFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSDVQIT WFVDNTQVYTAKTSPREEQFNS**X$_2$**YRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSPIERTISKDK GQPHEPQVYVLPPAQEELSENKVSVTCLIEGF YPSDIAVEWEITGQPEPENNYRTTPPQLDSDG TYFLYSRLSVDRSRWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG1b Fc T(87)X_2 X_2 = any amino acid except T or S
176	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQF**X$_1$**STYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG2 Fc N(85)X_1 X_1= any amino acid except N
177	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFN**P**TYRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG2 Fc S(86)P
178	PKTASTIESKTGEGPKCPVPEIPGAPSVFIFP PKPKDTLSISRTPEVTCLVVDLGPDDSNVQIT WFVDNTEMHTAKTRPREEQFNS**X$_2$**YRVVSVLPI LHQDWLKGKEFKCKVNSKSLPSAMERTISKAK GQPHEPQVYVLPPTQEELSENKVSVTCLIKGF HPPDIAVEWEITGQPEPENNYQTTPPQLDSDG TYFLYSRLSVDRSHWQRGNTYTCSVSHEALHS HHTQKSLTQSPGK	Exemplary aglycosyl variant feline IgG2 Fc T(87)X_2 X_2 = any amino acid except T or S
179	GGPSVFLFPPNPKDTLMITRTPEVTCVVVDVS QENPDVKFNWYMDGVEVRTATTRPKEEQF**X$_1$**ST YRVVSVLRIQHQDWLSGKEFKCKVNNQALPQP IERTITKTKGRSQEPQVYVLAPHPDESKKSKV SVTCLVKDFYPPEINIEWQSNGQPELETKYST TQAQQDSDGSYFLYSKLSVDRNRWQQGTTFTC GVMHEALHNHYTQKNVSKNPGK	Exemplary aglycosyl variant equine IgG1 Fc N(62)X_1 X_1= any amino acid except N
180	GGPSVFLFPPNPKDTLMITRTPEVTCVVVDVS QENPDVKFNWYMDGVEVRTATTRPKEEQFN**P**T	Exemplary aglycosyl variant equine IgG1 Fc

	YRVVSVLRIQHQDWLSGKEFKCKVNNQALPQP IERTITKTKGRSQEPQVYVLAPHPDESKKSKV SVTCLVKDFYPPEINIEWQSNGQPELETKYST TQAQQDSDGSYFLYSKLSVDRNRWQQGTTFTC GVMHEALHNHYTQKNVSKNPGK	S(63)P
181	GGPSVFLFPPNPKDTLMITRTPEVTCVVVDVS QENPDVKFNWYMDGVEVRTATTRPKEEQFNS**X₂** YRVVSVLRIQHQDWLSGKEFKCKVNNQALPQP IERTITKTKGRSQEPQVYVLAPHPDESKKSKV SVTCLVKDFYPPEINIEWQSNGQPELETKYST TQAQQDSDGSYFLYSKLSVDRNRWQQGTTFTC GVMHEALHNHYTQKNVSKNPGK	Exemplary aglycosyl variant equine IgG1 Fc T(64)X_2 X_2 = any amino acid except T or S
182	GGPSVFIFPPNPKDALMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQF**X₁**ST YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQVESFTC AVMHEALHNHFTKTDISESLGK	Exemplary aglycosyl variant equine IgG2 Fc N(62)X_1 X_1= any amino acid except N
183	GGPSVFIFPPNPKDALMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQFN**P**T YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQVESFTC AVMHEALHNHFTKTDISESLGK	Exemplary aglycosyl variant equine IgG2 Fc S(63)P
184	GGPSVFIFPPNPKDALMISRTPVVTCVVVNLS DQYPDVQFSWYVDNTEVHSAITKQREAQFNS**X₂** YRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQP ISRAISRGKGPSRVPQVYVLPPHPDELAKSKV SVTCLVKDFYPPDISVEWQSNRWPELEGKYST TPAQLDGDGSYFLYSKLSLETSRWQQVESFTC AVMHEALHNHFTKTDISESLGK	Exemplary aglycosyl variant equine IgG2 Fc T(64)X_2 X_2 = any amino acid except T or S
185	GGPSVFIFPPKPKDVLMITRMPEVTCLVVDVS HDSSDVLFTWYVDGTEVKTAKTMPNEEQN**X₁**ST YRVVSVLRIQHQDWLNGKKFKCKVNNQALPAP VERTISKATGQTRVPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDITVEWQSNEHPEPEGKYRT TEAQKDSDGSYFLYSKLTVEKDRWQQGTTFTC VVMHEALHNHVMQKNISKNPGK	Exemplary aglycosyl variant equine IgG3 Fc N(62)X_1 X_1= any amino acid except N
186	GGPSVFIFPPKPKDVLMITRMPEVTCLVVDVS HDSSDVLFTWYVDGTEVKTAKTMPNEEQNN**P**T YRVVSVLRIQHQDWLNGKKFKCKVNNQALPAP VERTISKATGQTRVPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDITVEWQSNEHPEPEGKYRT TEAQKDSDGSYFLYSKLTVEKDRWQQGTTFTC VVMHEALHNHVMQKNISKNPGK	Exemplary aglycosyl variant equine IgG3 Fc S(63)P
187	GGPSVFIFPPKPKDVLMITRMPEVTCLVVDVS HDSSDVLFTWYVDGTEVKTAKTMPNEEQNNS**X₂** YRVVSVLRIQHQDWLNGKKFKCKVNNQALPAP VERTISKATGQTRVPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDITVEWQSNEHPEPEGKYRT	Exemplary aglycosyl variant equine IgG3 Fc T(64)X_2

	TEAQKDSDGSYFLYSKLTVEKDRWQQGTTFTC VVMHEALHNHVMQKNISKNPGK	X_2 = any amino acid except T or S
188	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQF**X_1**ST YRVVSVLPIQHKDWLSGKEFKCKVNNKALPAP VERTISAPTGQPREPQVYVLAPHRDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDSDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG4 Fc N(62)X_1 X_1= any amino acid except N
189	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQFN**P**T YRVVSVLPIQHKDWLSGKEFKCKVNNKALPAP VERTISAPTGQPREPQVYVLAPHRDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDSDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG4 Fc S(63)P
190	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQFNS**X_2** YRVVSVLPIQHKDWLSGKEFKCKVNNKALPAP VERTISAPTGQPREPQVYVLAPHRDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDSDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG4 Fc T(64)X_2 X_2 = any amino acid except T or S
191	GGPSVFIFPPKPKDVLMISRKPEVTCVVVDLG HDDPDVQFTWFVDGVETHTATTEPKEEQF**X_1**PT YRVVSVLPIQHQDWLSGKEFKCSVTSKALPAP VERTISKAKGQLRVPQVYVLAPHPDELAKNTV SVTCLVKDFYPPEIDVEWQSNEHPEPEGKYST TPAQLNSDGSYFLYSKLSVETSRWKQGESFTC GVMHEAVENHYTQKNVSHSPGK	Exemplary aglycosyl variant equine IgG5 Fc N(62)X_1 X_1= any amino acid except N
192	GGPSVFIFPPKPKDVLMISRKPEVTCVVVDLG HDDPDVQFTWFVDGVETHTATTEPKEEQFN**P**T YRVVSVLPIQHQDWLSGKEFKCSVTSKALPAP VERTISKAKGQLRVPQVYVLAPHPDELAKNTV SVTCLVKDFYPPEIDVEWQSNEHPEPEGKYST TPAQLNSDGSYFLYSKLSVETSRWKQGESFTC GVMHEAVENHYTQKNVSHSPGK	Exemplary aglycosyl variant equine IgG5 Fc S(63)P
193	GGPSVFIFPPKPKDVLMISRKPEVTCVVVDLG HDDPDVQFTWFVDGVETHTATTEPKEEQFNS**X_2** YRVVSVLPIQHQDWLSGKEFKCSVTSKALPAP VERTISKAKGQLRVPQVYVLAPHPDELAKNTV SVTCLVKDFYPPEIDVEWQSNEHPEPEGKYST TPAQLNSDGSYFLYSKLSVETSRWKQGESFTC GVMHEAVENHYTQKNVSHSPGK	Exemplary aglycosyl variant equine IgG5 Fc T(64)X_2 X_2 = any amino acid except T or S
194	GRPSVFIFPPNPKDTLMISRTPEVTCVVVDVS QENPDVKFNWYVDGVEAHTATTKAKEKQD**X_1**ST YRVVSVLPIQHQDWRRGKEFKCKVNNRALPAP VERTITKAKGELQDPQVYILAPHPDEVTKNTV SVTCLVKDFYPPDINVEWQSNEEPEPEVKYST TPAQLDGDGSYFLYSKLTVETDRWEQGESFTC VVMHEAIRHTYRQKSITNFPGK	Exemplary aglycosyl variant equine IgG6 Fc N(62)X_1 X_1= any amino acid except N

195	GRPSVFIFPPNPKDTLMISRTPEVTCVVVDVS QENPDVKFNWYVDGVEAHTATTKAKEKQDN**P**T YRVVSVLPIQHQDWRRGKEFKCKVNNRALPAP VERTITKAKGELQDPQVYILAPHPDEVTKNTV SVTCLVKDFYPPDINVEWQSNEEPEPEVKYST TPAQLDGDGSYFLYSKLTVETDRWEQGESFTC VVMHEAIRHTYRQKSITNFPGK	Exemplary aglycosyl variant equine IgG6 Fc S(63)P
196	GRPSVFIFPPNPKDTLMISRTPEVTCVVVDVS QENPDVKFNWYVDGVEAHTATTKAKEKQDNS**X$_2$** YRVVSVLPIQHQDWRRGKEFKCKVNNRALPAP VERTITKAKGELQDPQVYILAPHPDEVTKNTV SVTCLVKDFYPPDINVEWQSNEEPEPEVKYST TPAQLDGDGSYFLYSKLTVETDRWEQGESFTC VVMHEAIRHTYRQKSITNFPGK	Exemplary aglycosyl variant equine IgG6 Fc T(64)X_2 X_2 = any amino acid except T or S
197	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQN**X$_1$**ST YRVVSILAIQHKDWLSGKEFKCKVNNQALPAP VQKTISKPTGQPREPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDGDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG7 Fc N(62)X_1 X_1= any amino acid except N
198	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQNN**P**T YRVVSILAIQHKDWLSGKEFKCKVNNQALPAP VQKTISKPTGQPREPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDGDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG7 Fc S(63)P
199	VGPSVFIFPPKPKDVLMISRTPTVTCVVVDVG HDFPDVQFNWYVDGVETHTATTEPKQEQNNS**X$_2$** YRVVSILAIQHKDWLSGKEFKCKVNNQALPAP VQKTISKPTGQPREPQVYVLAPHPDELSKNKV SVTCLVKDFYPPDIDIEWKSNGQPEPETKYST TPAQLDGDGSYFLYSKLTVETNRWQQGTTFTC AVMHEALHNHYTEKSVSKSPGK	Exemplary aglycosyl variant equine IgG7 Fc T(64)X_2 X_2 = any amino acid except T or S

DESCRIPTION OF THE EMBODIMENTS

[0015] Variant IgG Fc polypeptides from companion animals, such as canine, equine, and feline, are described. In some embodiments, the variant igG Fc polypeptides have increased binding to Protein A, decreased binding to C1q, decreased binding to CD16, increased stability, increased recombinant production, increased hinge disulfide formation, and/or form heterodimeric polypeptides. In some embodiments, antibodies, antibody fragments, or fusion proteins comprise a variant IgG Fc polypeptide. Methods of producing or purifying variant IgG Fc polypeptides and methods of administering variant IgG Fc polypeptides to companion animals are also provided assay.

[0016] Also provided are various embodiments relating to contiguous polypeptides and heterodimeric polypeptides comprising one or more variant GLP1 polypeptide(s) having improved serum half-life. In some embodiments, the contiguous polypeptides or heterodimeric polypeptides comprise a GLP1 polypeptide and a glucagon polypeptide as a dual GLP1 receptor and glucagon receptor agonist. In some embodiments, such polypeptides may be used to treat, for example, diabetes, obesity, or related indications, in companion animals, such as canines, felines, and equines.

[0017] For the convenience of the reader, the following definitions of terms used herein are provided.

[0018] As used herein, numerical terms such as K_D are calculated based upon scientific measurements and, thus, are subject to appropriate measurement error. In some instances, a numerical term may include numerical values that are rounded to the nearest significant figure.

[0019] As used herein, "a" or "an" means "at least one" or "one or more" unless otherwise specified. As used herein, the term "or" means "and/or" unless specified otherwise. In the context of a multiple dependent claim, the use of "or" when referring back to other claims refers to those claims in the alternative only.

Exemplary Variant IgG Fc Polypeptides

[0020] Novel variant IgG Fc polypeptides are provided, for example, variant IgG Fc polypeptides for increased binding to Protein A, for decreased binding to C1q, for decreased binding to CD16, for increased stability, for increased recombinant production, for increased hinge disulfide formation, and/or for forming heterodimeric proteins assay.

[0021] "Amino acid sequence," means a sequence of amino acids residues in a peptide or protein. The terms "polypeptide" and "protein" are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Such polymers of amino acid residues may contain natural or unnatural amino acid residues, and include, but are not limited to, peptides, oligopeptides, dimers, trimers, and multimers of amino acid residues. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. Furthermore, for purposes of the present disclosure, a "polypeptide" refers to a protein which includes modifications, such as deletions, additions, and substitutions (generally conservative in nature), to the native sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

[0022] A "fragment crystallizable polypeptide" or "Fc polypeptide" is the portion of an antibody molecule that interacts with effector molecules and cells. It comprises the C-terminal portions of the immunoglobulin heavy chains. As used herein, an Fc polypeptide includes fragments of the Fc domain having one or more biological activities of an entire Fc polypeptide. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind FcRn. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind C1q. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind CD16. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind protein A. An "effector function" of the Fc polypeptide is an action or activity performed in whole or in part by any antibody in response to a stimulus and may include complement fixation and/or ADCC (antibody-dependent cellular cytotoxicity) induction.

[0023] "IgX Fc" refers to an Fc polypeptide derived from a particular antibody isotype (e.g., IgG, IgA, IgD, IgE, IgM, etc.), where "X" denotes the antibody isotype. Thus, "IgG Fc" denotes that the Fc polypeptide is derived from a γ chain, "IgA Fc" denotes that the Fc polypeptide is derived from an α chain, "IgD Fc" denotes that the Fc polypeptide is derived from a δ chain, "IgE Fc" denotes that the Fc polypeptide is derived from a ε chain, "IgM Fc" denotes that the Fc polypeptide is derived from a μ chain, etc. In some embodiments, the IgG Fc polypeptide comprises the hinge, CH2, and CH3, but does not comprise CH1 or CL. In some embodiments, the IgG Fc polypeptide comprises CH2 and CH3, but does not comprise CH1, the hinge, or CL. In some embodiments, the IgG Fc polypeptide comprises CH1, hinge, CH2, CH3, with or without CL. "IgX-N Fc" or "IgGXN Fc" denotes that the Fc polypeptide is derived from a particular subclass of antibody isotype (such as canine IgG subclass IgG-A, IgG-B, IgG-C, or IgG-D; feline IgG subclass IgG1a, IgG1b, or IgG2; or equine IgG subclass IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, or IgG7, etc.), where "N" denotes the subclass.

[0024] "Hinge" refers to any portion of an Fc polypeptide or variant Fc polypeptide that is proline-rich and comprises at least one cysteine residue located between CH1 and CH2 of a full-length heavy chain constant region.

[0025] In some embodiments, a hinge is capable of forming a disulfide linkage within the same hinge region, within the same Fc polypeptide, with a hinge region of a separate Fc polypeptide, or with a separate Fc polypeptide. In some embodiments, a hinge comprises at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten proline residues.

[0026] The term "companion animal species" refers to an animal suitable to be a companion to humans. In some embodiments, a companion animal species is a canine (or dog), a

feline (or cat), or an equine (or horse). In some embodiments, a companion animal species is a small mammal, such as a canine, feline, dog, cat, rabbit, ferret, guinea pig, rodent, etc. In some embodiments, a companion animal species is a farm animal, such as a horse, cow, pig, etc.

[0027] In some embodiments, an IgX Fc polypeptide or an IgX-N Fc polypeptide is derived from a companion animal, such as a dog, a cat, or a horse. In some embodiments, IgG Fc polypeptides are isolated from canine γ heavy chains, such as IgG-A, IgG-B, IgG-C, or IgG-D. In some instances, IgG Fc polypeptides are isolated from feline γ heavy chains, such as IgG1a, IgG1b, or IgG2. In other instances, IgG Fc polypeptides are isolated from equine γ heavy chains, such as IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, or IgG7.

[0028] The terms "IgX Fc" and "IgX Fc polypeptide" include wild-type IgX Fc polypeptides and variant IgX Fc polypeptides, unless indicated otherwise.

[0029] "Wild-type" refers to a non-mutated version of a polypeptide that occurs in nature, or a fragment thereof. A wild-type polypeptide may be produced recombinantly.

[0030] In some embodiments, a wild-type IgG Fc polypeptide comprises the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 16, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 100, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 117, SEQ ID NO: 118.

[0031] A "variant" is a polypeptide that differs from a reference polypeptide by single or multiple non-native amino acid substitutions, deletions, and/or additions. In some embodiments, a variant retains at least one biological activity of the reference polypeptide. In some embodiments, a variant (e.g., a variant canine IgG-A Fc, a variant canine IgG-C Fc, a variant canine IgG-D Fc, variant equine IgG2 Fc, variant equine IgG5 Fc, or variant equine IgG6 Fc) has an activity that the reference polypeptide substantially lacks. For example, in some embodiments, a variant canine IgG-A Fc, a variant canine IgG-C Fc, a variant canine IgG-D Fc, variant equine IgG2 Fc, variant equine IgG5 Fc, or variant equine IgG6 Fc binds Protein A.

[0032] As used herein, "percent (%) amino acid sequence identity" and "homology" with respect to a nucleic acid molecule or polypeptide sequence are defined as the percentage of nucleotide or amino acid residues in a reference sequence that are identical with the nucleotide or amino acid residues in the specific nucleic acid molecule or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent 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

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

[0033] In some embodiments, a variant has at least about 50% sequence identity with the reference nucleic acid molecule or polypeptide after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Such variants include, for instance, polypeptides wherein one or more amino acid residues are added, deleted, at the N- or C-terminus of the polypeptide. In some embodiments, a variant has at least about 50% sequence identity, at least about 60% sequence identity, at least about 65% sequence identity, at least about 70% sequence identity, at least about 75% sequence identity, at least about 80% sequence identity, at least about 85% sequence identity, at least about 90% sequence identity, at least about 95% sequence identity, at least about 97% sequence identity, at least about 98% sequence identity, or at least about 99% sequence identity with the sequence of the reference nucleic acid or polypeptide.

[0034] A "point mutation" is a mutation that involves a single amino acid residue. The mutation may be the loss of an amino acid, substitution of one amino acid residue for another, or the insertion of an additional amino acid residue.

[0035] An "amino acid substitution" refers to the replacement of one amino acid in a polypeptide with another amino acid. In some embodiments, an amino acid substitution is a conservative substitution. Nonlimiting exemplary conservative amino acid substitutions are shown in Table 2. Amino acid substitutions may be introduced into a molecule of interest and the products screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC or enhanced pharmacokinetics.

[0036] Table 2.

Original Residue	Exemplary Substitutions
Ala (A)	Val; Leu; Ile
Arg (R)	Lys; Gln; Asn
Asn (N)	Gln; His; Asp; Lys; Arg
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn; Glu
Glu (E)	Asp; Gln

Gly (G)	Ala
His (H)	Asn; Gln; Lys; Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg; Gln; Asn
Met (M)	Leu; Phe; Ile
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Val; Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe; Thr; Ser
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine

[0037] Amino acids may be grouped according to common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

[0038] Non-conservative substitutions entail exchanging a member of one of these classes with another class.

[0039] A "variant IgG Fc" as used herein is an IgG Fc polypeptide that differs from a reference IgG Fc polypeptide by single or multiple amino acid substitutions, deletions, and/or additions and substantially retains at least one biological activity of the reference IgG Fc polypeptide.

[0040] An "amino acid derivative," as used herein, refers to any amino acid, modified amino acid, and/or amino acid analogue, that is not one of the 20 common natural amino acids found in humans. Exemplary amino acid derivatives include natural amino acids not found in humans (e.g., seleno cysteine and pyrrolysine, which may be found in some microorganisms) and

unnatural amino acids. Exemplary amino acid derivatives, include, but are not limited to, amino acid derivatives commercially available through chemical product manufacturers (e.g., sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16274965, accessed on May 6, 2017, which is incorporated herein by reference). One or more amino acid derivatives may be incorporated into a polypeptide at a specific location using a translation system that utilizes host cells, orthogonal aminoacyl-tRNA synthetases derived from eubacterial synthetases, orthogonal tRNAs, and an amino acid derivative. For further descriptions, see, e.g., U.S. Patent No. 9,624,485.

[0041] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution with an amino acid derivative. In some embodiments, the amino acid derivative is an alanine derivative, a cysteine derivative, an aspartic acid derivative, a glutamic acid derivative, a phenylalanine derivative, a glycine derivative, a histidine derivative, an isoleucine derivative, a lysine derivative, a leucine derivative, a methionine derivative, an asparagine derivative, a proline derivative, a glutamine derivative, an arginine derivative, a serine derivative, a threonine derivative, a valine derivative, a tryptophan derivative, or a tyrosine derivative.

[0042] In some embodiments, a variant IgG Fc polypeptide comprises a variant IgG Fc polypeptide of a companion animal species. In some embodiments, a variant IgG Fc polypeptide comprises a variant canine IgG Fc polypeptide, a variant equine IgG Fc polypeptide, or a feline IgG Fc polypeptide.

Exemplary Variant IgG Fc Polypeptides with Modified Protein A Binding

[0043] In some embodiments, a variant IgG Fc polypeptide has modified Protein A binding affinity. In some embodiments, a variant IgG Fc polypeptide has increased binding affinity to Protein A. In some embodiments, a variant IgG Fc polypeptide may be purified using Protein A column chromatography.

[0044] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 21, position 23, position 25, position 80, position 205, and/or position 207 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 21, position 23, and/or position 24 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 21, position 23, position 25, position 80, and/or position 207 of SEQ ID NO: 4.

[0045] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 15, and/or position 203 of SEQ ID NO: 64. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a

position corresponding to position 199 and/or position 200 of SEQ ID NO: 67. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 199, position 200, position 201, and/or 202 of SEQ ID NO: 68.

[0046] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 21, position 23, position 25, position 80, position 205, and/or position 207 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 21, position 23, and/or position 24 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 21, position 23, position 25, position 80, and/or position 207 of SEQ ID NO: 3.

[0047] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 15 and/or position 203 of SEQ ID NO: 64. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 199 and/or position 200 of SEQ ID NO: 67. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 199, position 200, position 201, and/or position 202 of SEQ ID NO: 68.

[0048] In some embodiments, a variant IgG Fc polypeptide comprises a threonine at a position corresponding to position 21 of SEQ ID NO: 1, a leucine at a position corresponding to position 23 of SEQ ID NO: 1, an alanine at a position corresponding to position 25 of SEQ ID NO: 1, a glycine at a position corresponding to position 80 of SEQ ID NO: 1, an alanine at a position corresponding to position 205 of SEQ ID NO: 1, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises a threonine at a position corresponding to position 21 of SEQ ID NO: 3, a leucine at a position corresponding to position 23 of SEQ ID NO: 3, and/or an isoleucine at a position corresponding to position 24 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a threonine at a position corresponding to position 21 of SEQ ID NO: 4, a leucine at a position corresponding to position 23 of SEQ ID NO: 4, an alanine at a position corresponding to position 25 of SEQ ID NO: 4, a glycine at a position corresponding to position 80 of SEQ ID NO: 3, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 4.

[0049] In some embodiments, a variant IgG Fc polypeptide comprises a threonine or a valine at a position corresponding to position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at a position corresponding to position 203 of SEQ ID NO: 64. In some embodiments, a variant IgG Fc polypeptide comprises a leucine at a position corresponding to position 199 of SEQ ID NO: 67, and/or a histidine at a position corresponding to position 200 of SEQ ID NO: 67. In some embodiments, a variant IgG Fc polypeptide comprises an isoleucine at a position corresponding

to position 199 of SEQ ID NO: 68, a histidine at a position corresponding to position 200 of SEQ ID NO: 68, an asparagine at a position corresponding to position 201 of SEQ ID NO: 68, and/or a histidine at a position corresponding to position 202 of SEQ ID NO: 68.

[0050] In some embodiments, a variant IgG Fc polypeptide comprises a threonine at position 21 of SEQ ID NO: 1, a leucine at position 23 of SEQ ID NO: 1, an alanine at position 25 of SEQ ID NO: 1, a glycine at position 80 of SEQ ID NO: 1, an alanine at position 205 of SEQ ID NO: 1, and/or a histidine at position 207 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises a threonine at position 21 of SEQ ID NO: 3, a leucine at position 23 of SEQ ID NO: 3, and/or an isoleucine at position 24 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprise a threonine at a position 21 of SEQ ID NO: 4, a leucine at position 23 of SEQ ID NO: 4, an alanine at position 25 of SEQ ID NO: 4, a glycine at position 80 of SEQ ID NO: 4, and/or a histidine at position 207 of SEQ ID NO: 4.

[0051] In some embodiments, a variant IgG Fc polypeptide comprises a threonine or a valine at position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at position 203 of SEQ ID NO: 64. In some embodiments, a variant IgG Fc polypeptide comprises a leucine at position 199 of SEQ ID NO: 67, and/or a histidine at position 200 of SEQ ID NO: 67. In some embodiments, a variant IgG Fc polypeptide comprises an isoleucine at position 199 of SEQ ID NO: 68, a histidine at position 200 of SEQ ID NO: 68, an asparagine at position 201 of SEQ ID NO: 68, and/or a histidine at position 202 of SEQ ID NO: 68.

[0052] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, or SEQ ID NO: 84. In some embodiments, a variant IgG Fc polypeptide comprises SEQ ID NO: 19, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 75, or SEQ ID NO: 76.

Exemplary Variant IgG Fc Polypeptides with Modified CD16 Binding

[0053] In some embodiments, a variant IgG Fc polypeptide has modified CD16 binding affinity. In some embodiments, a variant IgG Fc polypeptide has decreased binding affinity to CD16.. In some embodiments, a vaiant IgG Fc may have a reduced ADCC immune response.

[0054] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 5, position 38, position 39, position 97, and/or position 98 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 5, position 38, position 39, position 97, and/or position 98 of SEQ ID NO: 3.

[0055] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 5, position 38, position 39, position 97, and/or position 98 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 5, position 38, position 39, position 97, and/or position 98 of SEQ ID NO: 3.

[0056] In some embodiments, a variant IgG Fc polypeptide comprises a proline at a position corresponding to position 5, a glycine at a position corresponding to position 38, an arginine at a position corresponding to position 39, a isoleucine at a position corresponding to position 97, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a proline at a position corresponding to position 5, a glycine at a position corresponding to position 38, an arginine at a position corresponding to position 39, a isoleucine at a position corresponding to position 97, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 3.

[0057] In some embodiments, a variant IgG Fc polypeptide comprises a proline at position 5, a glycine at position 38, an arginine at position 39, a isoleucine at position 97, and/or a glycine at position 98 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a proline at position 5, a glycine at position 38, an arginine at position 39, a isoleucine at position 97, and/or a glycine at position 98 of SEQ ID NO: 3.

[0058] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID N: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

Exemplary Variant IgG Fc Polypeptides with Modified C1q Binding

[0059] In some embodiments, a variant IgG Fc polypeptide has modified C1q binding affinity. In some embodiments, a variant IgG Fc polypeptide has reduced binding affinity to C1q. In some embodiments, a variant IgG Fc polypeptide may have reduced complement fixation. In some embodiments, a vaiant IgG Fc may have a reduced complement-mediated immune response.

[0060] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 63. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 65. In some embodiments, a variant IgG Fc

polypeptide comprises an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 66. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 80. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 81.

[0061] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 93 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 93 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 87 of SEQ ID NO: 63. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 87 of SEQ ID NO: 65. In some embodiments, a variant IgG Fc polypeptide comprises or an amino acid substitution at position 87 of SEQ ID NO: 66. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 198 of SEQ ID NO: 80. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 198 of SEQ ID NO: 81.

[0062] In some embodiments, a variant IgG Fc polypeptide comprises an arginine at a position corresponding to position 93 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an arginine at a position corresponding to position 93 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 87 of SEQ ID NO: 63. In some embodiments, a variant IgG Fc polypeptide comprises a serine substitution at a position corresponding to position 87 of SEQ ID NO: 65. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 87 of SEQ ID NO: 66. In some embodiments, a variant IgG Fc polypeptide comprises an alanine at a position corresponding to position 198 of SEQ ID NO: 80. In some embodiments, a variant IgG Fc polypeptide comprises an alanine at a position corresponding to position 198 of SEQ ID NO: 81.

[0063] In some embodiments, a variant IgG Fc polypeptide comprises an arginine at position 93 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 93 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 87 of SEQ ID NO: 63. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 87 of SEQ ID NO: 65. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 87 of SEQ ID NO: 66. In some embodiments, a variant IgG Fc polypeptide comprises an alanine at position 198 of SEQ ID

NO: 80. In some embodiments, a variant IgG Fc polypeptide comprises an alanine at position 198 of SEQ ID NO: 81.

[0064] In some embodiments, a variant IgG Fc polypeptide comprises the amino acid sequence of SEQ ID NO: 78, SEQ ID NO: 79, or SEQ ID NO: 84. In some embodiments, a variant IgG Fc polypeptide comprises the amino acid sequence of SEQ ID NO: 70, SEQ ID NO: 73, SEQ ID NO: 74, or SEQ ID NO: 77. In some embodiments, a variant IgG Fc polypeptide comprises the amino acid sequence of SEQ ID NO: 82 or SEQ ID NO: 83.

Exemplary Variant IgG Fc Polypeptides with a Modified Inter-Chain Disulfide Linkage

[0065] In some embodiments, a variant feline IgG Fc polypeptide has at least one additional inter-chain disulfide linkage relative to the wild-type feline IgG Fc polypeptide. In some embodiments, a variant feline IgG Fc polypeptide has at least one additional inter-chain disulfide linkage in the hinge region. In some embodiments, a variant feline IgG2 Fc polypeptide with at least one additional inter-chain disulfide linkage has increased inter-chain stability relative to the wild-type feline IgG Fc polypeptide. In some embodiments, a variant IgG polypeptide has at least one amino acid modification to a hinge region relative to a wild-type IgG Fc polypeptide. In some embodiments, the wild-type IgG Fc polypeptide is a wild-type feline or equine IgG Fc polypeptide. In some embodiments, the variant IgG Fc polypeptide comprises a hinge region or a portion of a hinge region from an IgG Fc polypeptide of a different isotype. In some embodiments, the variant IgG Fc polypeptide comprises a hinge region from a wild-type feline IgG-1a Fc polypeptide, from a wild-type feline IgG-1b Fc polypeptide, or from a wild-type equine IgG1 Fc polypeptide. In some embodiments, a variant IgG2 Fc polypeptide has increased recombinant production and/or increased hinge disulfide formation relative to the wild-type IgG Fc polypeptide. In some embodiments, the increased recombinant production and/or increased hinge disulfide formation can be determined by SDS-PAGE analysis under reducing and/or non-reducing conditions.

[0066] In some embodiments, a variant IgG Fc polypeptide comprises a cysteine at a position corresponding to position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, or position 16 of SEQ ID NO: 16. In some embodiments, a variant IgG Fc polypeptide comprises a cysteine at position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, or position 16 of SEQ ID NO: 16. In some embodiments, a variant IgG Fc polypeptide comprises SEQ ID NO: 17.

[0067] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118. In some embodiments, a variant IgG Fc

polypeptide comprises an amino acid substitution at a position corresponding to position 3 and/or at a position corresponding to position 20 of SEQ ID NO: 129.

[0068] In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118. In some embodiments, a variant IgG Fc polypeptide comprises an amino acid substitution at position 3 and/or at a position corresponding to position 20 of SEQ ID NO: 129.

[0069] In some embodiments, a variant IgG Fc polypeptide comprises a proline at a position corresponding to position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 3 and/or a proline at a position corresponding to position 20 of SEQ ID NO: 129.

[0070] In some embodiments, a variant IgG Fc polypeptide comprises a proline at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 3 and/or a proline at position 20 of SEQ ID NO: 129.

[0071] In some embodiments, the variant IgG Fc polypeptide comprises SEQ ID NO: 19, SEQ ID NO: 125 or SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID N: 134, SEQ ID NO: 135.

Exemplary Variant IgG Fc Polypeptides for Heterodimeric Polypeptides

[0072] In certain embodiments, a heterodimeric polypeptide provided herein is a a bispecific antibody. A bispecific antibody has a binding specificity for two different epitopes or target molecules. In some embodiments, a bispecific antibody binds to two different epitopes of the same target molecule. Bispecific antibodies may be full length antibodies or antibody fragments.

[0073] In some embodiments, the heterodimeric polypeptide comprises a first variant IgG Fc polypeptide comprising a "knob" mutation and a second variant IgG Fc polypeptide comprising a "hole" mutation. Nonlimiting exemplary knob and hole mutations are described, for example, in Merchant, A. M. *et al.* An efficient route to human bispecific IgG. *Nat Biotechnol*, 16(7):677-81 (1998).

[0074] In some embodiments, a variant canine or variant feline IgG Fc polypeptide comprises a knob mutation. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 1. In some

embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at a position corresponding to position 137 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at a position corresponding to position 137 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 4. In some embodiments, a variant IgG Fc polypeptide comprises a tryptophan at a position corresponding to position 154 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118.

[0075] In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at position 138 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at position 137 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at position 137 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a tyrosine or a tryptophan at position 138 of SEQ ID NO: 4. In some embodiments, a variant IgG Fc polypeptide comprises a tryptophan at position 154 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118.

[0076] In some embodiments, a variant IgG Fc polypeptide comprising a knob mutation comprises an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

[0077] In some embodiments, a variant canine or a variant feline IgG Fc polypeptide comprises a hole mutation. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 4. In some embodiments, a variant IgG Fc polypeptide comprises a serine at a position corresponding to position 154, an alanine at a position corresponding to position 156, and/or a threonine at a

position corresponding to position 197 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118.

[0078] In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 138, an alanine at position 140, and/or a threonine at position 181 of SEQ ID NO: 1. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 137, an alanine at position 139, and/or a threonine at position 181 of SEQ ID NO: 2. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 137, an alanine at position 139, and/or a threonine at position 181 of SEQ ID NO: 3. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 138, an alanine at position 140, and/or a threonine at position 181 of SEQ ID NO: 4. In some embodiments, a variant IgG Fc polypeptide comprises a serine at position 154, an alanine at position 156, and/or a threonine at position 197 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118.

[0079] In some embodiments, a variant IgG Fc polypeptide comprising a hole mutation comprises an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 124.

[0080] In some embodiments, a contiguous polypeptide comprises a GLP1 polypeptide and a variant canine or feline IgG Fc polypeptide comprising a knob mutation. In some embodiments, a contiguous polypeptide comprises a glucagon polypeptide and a variant canine or feline IgG Fc polypeptide comprising a knob mutation. In some embodiments, a contiguous polypeptide comprises a GLP1 polypeptide and a variant canine or feline IgG Fc polypeptide comprising a hole mutation. In some embodiments, a contiguous polypeptide comprises a glucagon polypeptide and a variant canine or feline IgG Fc polypeptide comprising a hole mutation.

[0081] In some embodiments, the heterodimeric polypeptide comprises a first contiguous polypeptide comprises a GLP1 polypeptide and a variant canine or feline IgG Fc polypeptide comprising a knob mutation, and a second contiguous polypeptide comprises a glucagon polypeptide and a variant canine or feline IgG Fc polypeptide comprising a hole mutation. In some embodiments, the heterodimeric polypeptide comprises a first contiguous polypeptide comprises a glucagon polypeptide and a variant canine or feline IgG Fc polypeptide comprising a knob mutation, and a second contiguous polypeptide comprises a GLP1 polypeptide and a variant canine or feline IgG Fc polypeptide comprising a hole mutation.

Exemplary GLP1 Polypeptides and Glucagon Polypeptides

[0082] "GLP1" or a "GLP1 polypeptide," as used herein, is a polypeptide comprising the entirety or a fragment of glucagon-like peptide-1 that binds to a glucagon-like peptide 1 receptor (GLP1R).

[0083] For example, "GLP1" refers to a GLP1 polypeptide from any vertebrate source, including mammals such as primates (e.g., humans and cynomolgus monkeys), rodents (e.g., mice and rats), and companion animals (e.g., dogs, cats, and equine), unless otherwise indicated. In some embodiments, a GLP1 polypeptide is a wild-type GLP1 polypeptide, such as GLP1 (7-37) (SEQ ID N: 85). In some embodiments, a GLP1 polypeptide is a variant GLP1 polypeptide, such as GLP1 (7-36) (SEQ ID NO: 98), GLP1 (7-35) (SEQ ID NO: 99), GLP1-S8 (7-35) (SEQ ID NO: 86), or GLP1-G8 (7-35) (SEQ ID NO: 87). In some embodiments, GLP1 comprises the amino acid sequence of SEQ ID NO: 20.

[0084] "GLP1R," as used herein, is a polypeptide comprising the entirety or a fragment of a glucagon-like peptide 1 receptor that is capable of binding to a wild-type GLP1.

[0085] For example, "GLP1R" refers to a GLP1R polypeptide from any vertebrate source, including mammals such as primates (e.g., humans and cynomolgus monkeys), rodents (e.g., mice and rats), and companion animals (e.g., dogs, cats, and equine), unless otherwise indicated. In some embodiments, GLP1R is an extracellular domain fragment that binds a wild-type GLP1 polypeptide. In some embodiments, a feline GLP1R comprises the amino acid sequence of SEQ ID NO: 49. In some embodiments, a feline GLP1R comprises the amino acid sequence of SEQ ID NO: 48.

[0086] An "extracellular domain" ("ECD") is the portion of a polypeptide that extends beyond the transmembrane domain into the extracellular space. The term "extracellular domain," as used herein, may comprise a complete extracellular domain or may comprise a truncated extracellular domain missing one or more amino acids, that binds to its ligand. The composition of the extracellular domain may depend on the algorithm used to determine which amino acids are in the membrane. Different algorithms may predict, and different systems may express, different extracellular domains for a given protein.

[0087] "Glucagon" or a "glucagon polypeptide," as used herein, is a polypeptide comprising the entirety or a fragment of glucagon that binds to a glucagon receptor.

[0088] For example, "glucagon" refers to a glucagon polypeptide from any vertebrate source, including mammals such as primates (e.g., humans and cynomolgus monkeys), rodents (e.g., mice and rats), and companion animals (e.g., dogs, cats, and equine), unless otherwise

indicated. In some embodiments, a glucagon polypeptide is a wild-type glucagon polypeptide, such as SEQ ID NO: 21.

Exemplary Variant IgG Fc Polypeptides and Fusion Molecules

[0089] Polypeptides and other molecules may comprise a variant IgG Fc polypeptide. In some embodiments, a fusion molecule comprises a variant IgG Fc polypeptide, such as the variant IgG Fc polypeptides described herein. In some embodiments, an antibody or an antibody fragment comprises a variant IgG Fc polypeptide, such as the variant IgG Fc polypeptides described herein.

[0090] A "fusion molecule," as used herein, refers to a molecule comprising one or more "fusion partners." In some embodiments, the fusion partners are covalently linked ("fused"). If two fusion partners are both polypeptides, the fusion partner polypeptides may be part of a contiguous amino acid sequence (i.e., a contiguous polypeptide). A first fusion partner polypeptide may be linked to either the N-terminus or the C-terminus of a second fusion partner. In some embodiments, the fusion partners are translated as a single polypeptide from a coding sequence that encodes both fusion partners. Fusion partners may be covalently linked through other means, such as, for example, a chemical linkage other than a peptide bond. Many known methods of covalently linking polypeptides to other molecules (for example, fusion partners) may be used. In other embodiments, the fusion partners are fused through a "linker," which is comprised of at least one amino acid or chemical moiety. In some embodiments, fusion partners are noncovalently linked. In some such embodiments, they may be linked, for example, using binding pairs. Exemplary binding pairs include, but are not limited to, biotin and avidin or streptavidin, an antibody and its antigen, etc.

[0091] In some embodiments, the fusion partners include an IgG Fc polypeptide and at least one GLP1 polypeptide. In some embodiments, the fusion partners include an IgG Fc polypeptide, a GLP1 polypeptide, and a glucagon polypeptide. In some embodiments, a GLP1 polypeptide may be linked to either the N-terminus or the C-terminus of an IgG Fc polypeptide. In some embodiments, a glucagon polypeptide may be linked to either the N-terminus or the C terminus of an IgG Fc polypeptide.

[0092] The term "contiguous polypeptide" herein is used to mean an uninterrupted sequence of amino acids. A contiguous polypeptide is typically translated from a single continuous DNA sequence. It can be made by genetic engineering, for example, by removing the stop codon from the DNA sequence of the first protein, then appending the DNA sequence of the second protein in frame, so that the DNA sequence is expressed as a single protein. Typically, this is accomplished by cloning a cDNA into an expression vector in frame with an existing gene.

[0093] A "linker" refers to one or more amino acid residues that connects a first polypeptide with a second polypeptide.

[0094] In some embodiments, the linker is a flexible, non-structural linker. In some embodiments, the linker is a glycine-rich, serine-rich, or glycine- and serine-rich linker. In some embodiments, a linker comprises 100%, at least 95%, at least 90%, or at least 85% serine and/or glycine amino acid residues.

[0095] An "extension," as used herein, refers to one or more amino acid residues that are connected to a polypeptide at its C-terminus or at its N-terminus.

[0096] In some embodiments, an extension is flexible. In some embodiments, the extension adds flexibility to the polypeptide without interfering with the biological activity of the polypeptide. In some embodiments, the extension increases solubility of the polypeptide. In some embodiments, the extension comprises one or more glycine residues. In some embodiments, the extension comprises a glycine residue (SEQ ID NO: 88), two glycine residues (SEQ ID NO: 89), a three glycine residues (SEQ ID NO: 90), four glycine residues (SEQ ID NO: 91), five glycine residues (SEQ ID NO: 92), six glycine residues (SEQ ID NO: 93), seven glycine residues (SEQ ID NO: 94), eight glycine residues (SEQ ID NO: 95), or more glycine residues.

[0097] In some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a GLP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 85. In some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a GLP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 86. In

some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a GLP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 87. In some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a GLP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 98. In some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a GLP1 polypeptide comprising an amino acid sequence of SEQ ID NO: 99.

[0098] In some embodiments, the contiguous polypeptide comprises an IgG Fc polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 100, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 167, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175,

176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, or 199 and a glucagon polypeptide comprising an amino acid sequence of SEQ ID NO: 21.

[0099] In some embodiments, a contiguous polypeptide comprises a first GLP1 polypeptide (GLP1A), a first linker (L1), an Fc polypeptide of a companion animal species, optionally a second linker (L2), and optionally a second GLP1 polypeptide (GLP1B). In some embodiments, the contiguous polypeptide comprises:

Formula (I): GLP1A—L1—Fc;

Formula (II): Fc—L1—GLP1A; or

Formula (III): GLP1A—L1—Fc—L2—GLP1B.

[00100] In some embodiments, a contiguous polypeptide comprises a GLP1 polypeptide, a first linker (L1), an Fc polypeptide, a second linker (L2), and a glucagon polypeptide (Gluc). In some embodiments, the contiguous polypeptide comprises:

Formula (IV): GLP1—L1—Fc—L2—Gluc; or

Formula (V): Gluc—L1—Fc—L2—GLP1.

[00101] In some embodiments, the GLP1 fusion molecule has an increased serum half-life compared to a wild-type GLP1 polypeptide. The increased half-life of the GLP1 fusion molecules described herein may require lower doses and less-frequent dosing regimen than wild-type GLP1 polypeptides.

[00102] In some embodiments, GLP1B, if present, comprises the same amino acid sequence as GLP1A.

[00103] In some embodiments, GLP1, GLP1A, or GLP1B, if present, comprises a wild-type GLP1 polypeptide. In some embodiments, GLP1, GLP1A, or GLP1B, if present, comprises a variant GLP1 polypeptide. In some embodiments, GLP1, GLP1A, or GLP1B, if present, comprises an amino acid sequence of SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 98, or SEQ ID NO: 99.

[00104] In some embodiments, the glucagon polypeptide comprises a wild-type glucagon polypeptide. In some embodiments, the glucagon polypeptide comprises an amino acid sequence of SEQ ID NO: 21. In some embodiments, the glucagon polypeptide comprises a variant glucagon polypeptide.

[00105] In some embodiments, the Fc polypeptide is a human IgG Fc. In some embodiments, the Fc polypeptide is a human IgG1 Fc, a human IgG2 Fc, a human IgG3 Fc, or a human IgG4 Fc. In some embodiments, the Fc polypeptide is a variant human IgG Fc.

[00106] In some embodiments, the Fc polypeptide is an IgG Fc from a companion animal. In some embodiments, the Fc polypeptide is a canine IgG-A Fc, a canine IgG-B Fc, a canine IgG-C Fc, a canine IgG-D Fc. In some embodiments, the Fc is an equine IgG1 Fc, an equine IgG2 Fc, an equine IgG3 Fc, an equine IgG4 Fc, an equine IgG5 Fc, an equine IgG6 Fc, or an equine IgG7 Fc. In some embodiments, the Fc is a feline IgG1a Fc, a feline IgG1b Fc, or a feline IgG2 Fc.

[00107] In some embodiments, the Fc polypeptide is a variant IgG Fc. In some embodiments, the FC polypeptide is a variant canine IgG-A Fc, a variant canine IgG-B Fc, a variant canine IgG-C Fc, a variant canine IgG-D Fc. In some embodiments, the Fc is a variant equine IgG1 Fc, a variant equine IgG2 Fc, a variant equine IgG3 Fc, a variant equine IgG4 Fc, a variant equine IgG5 Fc, a variant equine IgG6 Fc, or a variant equine IgG7 Fc. In some embodiments, the Fc is a variant feline IgG1a Fc, a variant feline IgG1b Fc, or a variant feline IgG2 Fc.

[00108] In some embodiments, L1 and L2, if present, each independently is a flexible linker. In some embodiments, the amino acid sequence of L1 and L2, if present, each independently comprises 100%, at least 95%, at least 90%, at least 85% serine and/or glycine amino acid residues.

[00109] In some embodiments, the contiguous polypeptide comprises an extension at its C-terminus. In some embodiments, the contiguous polypeptide comprises a glycine residue, two glycine residues, three glycine residues, four glycine residues, five glycine residues, six glycine residues, seven glycine residues, eight glycine residues, or greater than eight glycine residues at its C-terminus. In some embodiments, the contiguous polypeptide comprises an amino acid sequence of SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, or SEQ ID NO: 95 at its C-terminus.

[00110] In some embodiments, the contiguous polypeptide comprises the amino acid sequence of SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 46; SEQ ID NO: 47, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 103; SEQ ID NO: 104; SEQ ID NO: 105; or SEQ ID NO: 106.

[00111] A nucleotide sequence encoding a polypeptide of interest, such as a variant IgG Fc polypeptide or other polypeptide described herein, can be inserted into an expression vector

suitable for expression in a selected host cell. A variant IgG Fc polypeptide or other polypeptide described herein may be expressed by culturing a host cell transfected with an expression vector comprising the nucleotide sequence.

[00112] A "vector" is a plasmid that can be used to transfer DNA sequences from one organism to another or to express a gene of interest. A vector typically includes an origin of replication and regulatory sequences which regulate the expression of the gene of interest, and may or may not carry a selective marker gene, such as an antibiotic resistance gene. A vector is suitable for the host cell in which it is to be expressed. A vector may be termed a "recombinant vector" when the gene of interest is present in the vector.

[00113] A "host cell" refers to a cell that may be or has been a recipient of a vector or isolated polynucleotide. Host cells may be prokaryotic cells or eukaryotic cells. Exemplary eukaryotic cells include mammalian cells, such as primate or non-primate animal cells; fungal cells, such as yeast; plant cells; and insect cells. Nonlimiting exemplary mammalian cells include, but are not limited to, NS0 cells, PER.C6® cells (Crucell), 293 cells, and CHO cells, and their derivatives, such as 293-6E, DG44, CHO-S, and CHO-K cells. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) encoding an amino acid sequence(s) provided herein.

[00114] The term "isolated" as used herein refers to a molecule that has been separated from at least some of the components with which it is typically found in nature or produced. For example, a polypeptide is referred to as "isolated" when it is separated from at least some of the components of the cell in which it was produced. Where a polypeptide is secreted by a cell after expression, physically separating the supernatant containing the polypeptide from the cell that produced it is considered to be "isolating" the polypeptide. Similarly, a polynucleotide is referred to as "isolated" when it is not part of the larger polynucleotide (such as, for example, genomic DNA or mitochondrial DNA, in the case of a DNA polynucleotide) in which it is typically found in nature, or is separated from at least some of the components of the cell in which it was produced, for example, in the case of an RNA polynucleotide. Thus, a DNA polynucleotide that is contained in a vector inside a host cell may be referred to as "isolated."

[00115] A "signal sequence" refers to a sequence of amino acid residues or polynucleotides encoding such, which facilitates secretion of a polypeptide of interest and is typically cleaved upon export of the polypeptide to the outside of the cell surface membrane.

[00116] In some embodiments, a variant IgG Fc polypeptide or a contiguous polypeptide comprising a variant Fc polypeptide is isolated using chromatography, such as size exclusion chromatography, ion exchange chromatography, protein A column chromatography, hydrophobic interaction chromatography, and CHT chromatography.

[00117] A label can be attached to a variant IgG Fc polypeptides or a contiguous polypeptide comprising a variant Fc polypeptide. A "label" means a moiety attached to a molecule to render it detectable. In some embodiments, a variant IgG Fc polypeptide or a contiguous polypeptide comprising a variant Fc polypeptide is labeled with a detectable moiety including but not limited to radioisotopes, fluorescent labels, and various enzyme-substrate labels known in the art. In some embodiments, the label is a detectable marker that can produce a signal that is detectable by visual or instrumental means, for example, incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (for example, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (for example, ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, or ^{153}Sm); chromogens, fluorescent labels (for example, FITC, rhodamine, lanthanide phosphors), enzymatic labels (for example, p-galactosidase, horseradish peroxidase, luciferase, alkaline phosphatase); chemiluminescent markers; biotinyl groups; predetermined polypeptide epitopes recognized by a secondary reporter (for example, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags); and magnetic agents, such as gadolinium chelates. Representative examples of labels commonly employed for immunoassays include moieties that produce light, for example, acridinium compounds, and moieties that produce fluorescence, for example, fluorescein. In this regard, the moiety itself may not be detectably labeled but may become detectable upon reaction with yet another moiety. General techniques to be used in performing the various immunoassays noted above are known to those of ordinary skill in the art.

Exemplary Variant IgG Fc Polypeptide Affinity to Protein A and/or C1q and/or CD16

[00118] The variant IgG Fc polypeptides described herein may have altered binding affinity to Protein A and/or C1q and/or CD16. In some embodiments, a variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide. Such variant IgG Fc polypeptides may be purified by Protein A column chromatography. In some embodiments, a variant IgG Fc polypeptide has reduced binding affinity to C1q relative to the wild-type IgG Fc polypeptide. Such variant IgG Fc polypeptides may have reduced complement-mediated immune responses. In some embodiments, a variant IgG Fc polypeptide has reduced

binding affinity to CD16 relative to the wild-type IgG Fc polypeptide. Such variant IgG Fc polypeptides may have reduced ADCC immune responses. In some embodiments, a variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide and/or has reduced binding affinity to C1q relative to the wild-type IgG Fc polypeptide and/or has reduced binding affinity to CD16 relative to the wild-type IgG Fc polypeptide.

[00119] "Protein A," as used herein, is a polypeptide comprising the entirety or a portion of Protein A that is capable of binding a wild-type canine IgG-B Fc, a wild-type equine IgG1 Fc, a wild-type equine IgG3 Fc, a wild-type equine IgG4 Fc, a wild-type equine IgG7 Fc, a wild-type feline IgG1a Fc, a wild-type feline IgG1b Fc, or a wild-type feline IgG2 Fc.

[00120] "C1q" or "C1q complex" is used interchangeably to refer to a protein complex involved in the complement system, or a portion thereof, that can bind a wild-type canine IgG-B Fc, a wild-type canine IgG-C Fc, a wild-type equine IgG1 Fc, a wild-type equine IgG3 Fc, a wild-type equine IgG4 Fc, a wild-type equine IgG7 Fc, a wild-type feline IgG1a Fc, or a wild-type feline IgG1b Fc.

[00121] "CD16," as used herein, is a polypeptide comprising the entirety or a portion of CD16 that is capable of binding a wild-type canine IgG-A Fc or a wild-type canine IgG-D Fc. The term "binds" to a substance is a term that is well understood in the art, and methods to determine such binding are also well known in the art. A molecule is said to exhibit "binding" if it reacts, associates with, or has affinity for a particular cell or substance and the reaction, association, or affinity is detectable by one or more methods known in the art, such as, for example, immunoblot, ELISA, KinEx A, biolayer interferometry (BLI), surface plasmon resonance devices, or etc.

[00122] "Protein A +," as used herein, means that the Fc polypeptide has Protein A binding affinity. In some embodiments, a Protein A+ Fc polypeptide comprises at least one an amino acid modification that increases Protein A binding affinity.

[00123] "Protein A –," as used herein, means that the Fc polypeptide has low or no Protein A binding affinity.

[00124] "C1q +," as used herein, means that the Fc polypeptide has C1q binding affinity.

[00125] "C1q –," as used herein, means that the Fc polypeptide has low or no C1q binding affinity. In some embodiments, a C1q– Fc polypeptide has at least one an amino acid modification that reduces C1q binding affinity.

[00126] "CD16 +," as used herein, means that the Fc polypeptide has CD16 binding affinity.

[00127] "CD16 –," as used herein, means that the Fc polypeptide has low or no CD16 binding affinity. In some embodiments, a CD16– Fc polypeptide has at least one an amino acid modification that reduces CD16 binding affinity.

[00128] The term "affinity" means the strength of the sum total of noncovalent interactions between a single binding site of a molecule (for example, a receptor) and its binding partner (for example, a ligand). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, such as, for example, immunoblot, ELISA, KinEx A, biolayer interferometry (BLI), or surface plasmon resonance devices.

[00129] "Surface plasmon resonance" denotes an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (BIAcore International AB, a GE Healthcare company, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson et al. (1993) *Ann. Biol. Clin.* 51: 19-26.

[00130] "Biolayer interferometry" refers to an optical analytical technique that analyzes the interference pattern of light reflected from a layer of immobilized protein on a biosensor tip and an internal reference layer. Changes in the number of molecules bound to the biosensor tip cause shifts in the interference pattern that can be measured in real-time. A nonlimiting exemplary device for biolayer interferometry is an Octet® system (Pall ForteBio LLC). See, e.g., Abdiche et al., 2008, *Anal. Biochem.* 377: 209-277.

[00131] The terms "K_D," "K_d," "Kd" or "Kd value" as used interchangeably to refer to the equilibrium dissociation constant of a receptor - ligand interaction or antibody-antigen interaction.

[00132] In some embodiments, a variant IgG Fc polypeptide binds to Protein A with a dissociation constant (K_D) of less than 5×10^{-6} M, less than 1×10^{-6} M, less than 5×10^{-7} M, less than 1×10^{-7} M, less than 5×10^{-8} M, less than 1×10^{-8} M, less than 5×10^{-9} M, less than 1×10^{-9} M, less than 5×10^{-10} M, less than 1×10^{-10} M, less than 5×10^{-11} M, less than 1×10^{-11} M, less than 5×10^{-12} M, or less than 1×10^{-12} M, as measured by biolayer interferometry.

[00133] In some embodiments, a variant IgG Fc polypeptide binds to C1q or CD16 with a dissociation constant (K_D) of greater than 5×10^{-6} M, greater than 1×10^{-5} M, greater than 5×10^{-5} M, greater than 1×10^{-4} M, greater than 5×10^{-4} M, or greater than 1×10^{-3} M, as measured by biolayer interferometry.

[00134] In some embodiments, the K_D of an IgG Fc polypeptide, such as a variant IgG Fc polypeptide, to Protein A or to C1q or to CD16 is measured by using biolayer interferometry assays using a biosensor, such as an Octet® System (Pall ForteBio LLC, Fremont, CA) according

to the supplier's instructions. In brief, biotinylated Protein A or C1q or CD16 is bound to the sensor tip and the association of IgG Fc polypeptide is monitored for a specified time or until steady state is reached. Dissociation may be monitored for a specified time or until steady state is reached. A buffer only blank curve is subtracted to correct for any drift. The data are fit to a 2:1 binding model using ForteBio data analysis software to determine association rate constant (k_{on}), dissociation rate constant (k_{off}), and the K_d. The equilibrium dissociation constant (K_D) is calculated as the ratio of k_{off}/k_{on}. The term "k_{on}" refers to the rate constant for association of a molecule X to its partner Y and the term "k_{off}" refers to the rate constant for dissociation of a molecule X or partner Y from the molecule X / partner Y complex.

[00135] To "increase" or "stimulate" means to increase, improve, or augment an activity, function, or amount as compared to a reference. In some embodiments, by "increase" or "stimulate" is meant the ability to cause an overall increase of about 5% or greater, of about 10% or greater, of about 20% or greater, of about 30% or greater, of about 40% or greater, of about 50% or greater, of about 60% or greater, of about 70% or greater, of about 80% or greater, of about 90% or greater, of about 100% or greater, of about 125% or greater, of about 200% or greater relative to a reference value. In some embodiments, by "increase" or "stimulate" is meant the ability to cause an overall increase of about 5% to about 50%, of about 10% to about 20%, of about 50% to about 100%, of about 25% to about 70% relative to a reference value. In some embodiments, by "increase" or "stimulate" is meant the ability to cause an overall increase of 50% or greater. In some embodiments, by "increase" or "stimulate" is meant the ability to cause an overall increase of 75%, 85%, 90%, 95%, or greater. In some embodiments, the amount noted above is stimulated or increased over a period of time, relative to a control dose (such as a placebo) over the same period of time.

[00136] In some embodiments, a variant IgG Fc polypeptide is capable of binding to Protein A with an increased affinity of about 5% or greater, of about 10% or greater, of about 20% or greater, of about 30% or greater, of about 40% or greater, of about 50% or greater, of about 60% or greater, of about 70% or greater, of about 80% or greater, of about 90% or greater, of about 100% or greater, of about 125% or greater, of about 150% or greater, of about 200% or greater relative to a reference IgG Fc polypeptide. In some embodiments, a variant IgG Fc polypeptide is capable of binding to Protein A with an increased affinity of about 5% to about 50%, of about 10% to about 20%, of about 50% to about 100%, of about 25% to about 70% relative to a reference IgG Fc polypeptide. In some embodiments, the reference IgG Fc polypeptide is a wild-type IgG Fc polypeptide. In some embodiments, the reference IgG Fc polypeptide is a different variant IgG Fc polypeptide.

[00137] To "reduce" or "inhibit" means to decrease, reduce, or arrest an activity, function, or amount as compared to a reference. In some embodiments, by "reduce" or "inhibit" is meant the ability to cause an overall decrease of about 5% or greater, of about 10% or greater, of about 20% or greater, of about 30% or greater, of about 40% or greater, of about 50% or greater, of about 60% or greater, of about 70% or greater, of about 80% or greater, or of about 90% or greater relative to a reference IgG Fc polypeptide. In some embodiments, by "reduce" or "inhibit" is meant the ability to cause an overall decrease of about 5% to about 50%, of about 10% to about 20%, of about 50% to about 100%, of about 25% to about 70% relative to a reference value. In some embodiments, by "reduce" or "inhibit" is meant the ability to cause an overall decrease of 50% or greater. In some embodiments, by "reduce" or "inhibit" is meant the ability to cause an overall decrease of 75%, 85%, 90%, 95%, or greater. In some embodiments, the amount noted above is inhibited or decreased over a period of time, relative to a control dose (such as a placebo) over the same period of time.

[00138] In some embodiments, a variant IgG Fc polypeptide is capable of binding to C1q or CD16 with a decreased affinity of about 5% or greater, of about 10% or greater, of about 20% or greater, of about 30% or greater, of about 40% or greater, of about 50% or greater, of about 60% or greater, of about 70% or greater, of about 80% or greater, of about 90% or greater relative to a reference IgG Fc polypeptide. In some embodiments, a variant IgG Fc polypeptide is capable of binding to C1q or CD16 with a decreased affinity of about 5% to about 50%, of about 10% to about 20%, of about 50% to about 100%, of about 25% to about 70% relative to a reference IgG Fc polypeptide. In some embodiments, the reference IgG Fc polypeptide is a wild-type IgG Fc polypeptide. In some embodiments, the reference IgG Fc polypeptide is a different variant IgG Fc polypeptide.

[00139] A "reference" as used herein, refers to any sample, standard, or level that is used for comparison purposes. A reference may be a wild-type reference or a variant reference. A reference may be obtained from a healthy or non-diseased sample. In some examples, a reference is obtained from a non-diseased or non-treated sample of a companion animal. In some examples, a reference is obtained from one or more healthy animals of a particular species, which are not the animal being tested or treated.

Exemplary Biological Activity of Variant GLP1 Fusion Molecules

[00140] In some embodiments, a GLP1 fusion molecule binds to GLP1R and activates cAMP production. In some embodiments, a GLP1 fusion polypeptide increases production of cAMP in a cell by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least

35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% compared to signaling function in the absence of the GLP1 fusion polypeptide.

Exemplary Pharmaceutical Compositions

[00141] The terms "pharmaceutical formulation" and "pharmaceutical composition" refer to a preparation which is in such form as to permit the biological activity of the active ingredient(s) to be effective, and which contains no additional components that are unacceptably toxic to a subject to which the formulation would be administered.

[00142] A "pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid, or liquid filler, diluent, encapsulating material, formulation auxiliary, or carrier conventional in the art for use with a therapeutic agent that together comprise a "pharmaceutical composition" for administration to a subject. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. The pharmaceutically acceptable carrier is appropriate for the formulation employed. Examples of pharmaceutically acceptable carriers include alumina; aluminum stearate; lecithin; serum proteins, such as human serum albumin, canine or other animal albumin; buffers such as phosphate, citrate, tromethamine or HEPES buffers; glycine; sorbic acid; potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; water; salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, or magnesium trisilicate; polyvinyl pyrrolidone, cellulose-based substances; polyethylene glycol; sucrose; mannitol; or amino acids including, but not limited to, arginine.

[00143] The pharmaceutical composition can be stored in lyophilized form. Thus, in some embodiments, the preparation process includes a lyophilization step. The lyophilized composition may then be reformulated, typically as an aqueous composition suitable for parenteral administration, prior to administration to the dog, cat, or horse. In other embodiments, particularly where a variant IgG Fc polypeptide or other polypeptide described herein is highly stable to thermal and oxidative denaturation, the pharmaceutical composition can be stored as a liquid, i.e., as an aqueous composition, which may be administered directly, or with appropriate dilution, to the dog, cat, or horse. A lyophilized composition can be reconstituted with sterile Water for Injection (WFI). Bacteriostatic reagents, such benzyl alcohol, may be included. Thus, the invention provides pharmaceutical compositions in solid or liquid form.

[00144] The pH of the pharmaceutical compositions may be in the range of from about pH 5 to about pH 8, when administered. The compositions of the invention are sterile if they are to be used for therapeutic purposes. Sterility can be achieved by any of several means known in the

art, including by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Sterility may be maintained with or without anti-bacterial agents.

Certain Uses of Fc Polypeptides and Pharmaceutical Compositions

[00145] A polypeptide comprising a variant Fc polypeptide, such as a variant IgG Fc polypeptide, of the invention or pharmaceutical compositions comprising a variant Fc polypeptide of the invention may be useful for extending product half-life *in vivo* in a companion animal, including, but not limited to, canine, feline, or equine.

[00146] As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. "Treatment" as used herein, covers any administration or application of a therapeutic for disease in a mammal, including a companion animal. For purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, any one or more of: alleviation of one or more symptoms, diminishment of extent of disease, preventing or delaying spread of disease, preventing or delaying recurrence of disease, delay or slowing of disease progression, amelioration of the disease state, inhibiting the disease or progression of the disease, inhibiting or slowing the disease or its progression, arresting its development, and remission (whether partial or total). Also encompassed by "treatment" is a reduction of pathological consequence of a proliferative disease. The methods provided herein contemplate any one or more of these aspects of treatment. In-line with the above, the term treatment does not require one-hundred percent removal of all aspects of the disorder.

[00147] A "therapeutically effective amount" of a substance/molecule, agonist or antagonist may vary according to factors such as the type of disease to be treated, the disease state, the severity and course of the disease, the type of therapeutic purpose, any previous therapy, the clinical history, the response to prior treatment, the discretion of the attending veterinarian, age, sex, and weight of the animal, and the ability of the substance/molecule, agonist or antagonist to elicit a desired response in the animal. A therapeutically effective amount is also one in which any toxic or detrimental effects of the substance/molecule, agonist or antagonist are outweighed by the therapeutically beneficial effects. A therapeutically effective amount may be delivered in one or more administrations. A therapeutically effective amount refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[00148] In some embodiments, a variant IgG Fc polypeptide or other polypeptide described herein, or a pharmaceutical composition comprising such is administered parenterally, by subcutaneous administration, intravenous infusion, or intramuscular injection. In some embodiments, a variant IgG Fc polypeptide or other polypeptide described herein, or a pharmaceutical composition comprising such is administered as a bolus injection or by continuous

infusion over a period of time. In some embodiments, a variant IgG Fc polypeptide or other polypeptide described herein, or a pharmaceutical composition comprising such is administered by an intramuscular, an intraperitoneal, an intracerebrospinal, a subcutaneous, an intra-arterial, an intrasynovial, an intrathecal, or an inhalation route.

[00149] In some embodiments, a GLP1 fusion polypeptide or pharmaceutical compositions comprising it can be utilized in accordance with the methods herein to treat high blood glucose-related conditions. In some embodiments, an GLP1 fusion polypeptide or pharmaceutical compositions is administered to a companion animal, such as a canine, a feline, or equine, to treat high blood glucose-related condition.

[00150] In some embodiments, a variant IgG Fc polypeptide or other polypeptide described herein, or a pharmaceutical composition comprising such is administered in an amount in the range of 0.0001 mg/kg body weight to 100 mg/kg body weight per dose. In some embodiments, GLP1 analog may be administered in an amount in the range of 0.005 mg/kg body weight to 20 mg/kg body weight per dose. In some embodiments, GLP1 analog may be administered in an amount in the range of 1 mg/kg body weight to 10 mg/kg body weight per dose. In some embodiments, GLP1 analog may be administered in an amount in the range of 0.5 mg/kg body weight to 100 mg/kg body, in the range of 1 mg/kg body weight to 100 mg/kg body weight, in the range of 5 mg/kg body weight to 100 mg/kg body weight, in the range of 10 mg/kg body weight to 100 mg/kg body weight, in the range of 20 mg/kg body weight to 100 mg/kg body weight, in the range of 50 mg/kg body weight to 100 mg/kg body weight, in the range of 1 mg/kg body weight to 10 mg/kg body weight, in the range of 5 mg/kg body weight to 10 mg/kg body weight, in the range of 0.5 mg/kg body weight to 10 mg/kg body weight, or in the range of 5 mg/kg body weight to 50 mg/kg body weight.

[00151] In some embodiments, a variant IgG Fc polypeptide or other polypeptide described herein, or a pharmaceutical composition comprising such is administered to a companion animal at one time or over a series of treatments. In some embodiments, the dose is administered once per week for at least two or three consecutive weeks, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more weeks of no treatment. In other embodiments, the therapeutically effective dose is administered once per day for two to five consecutive days, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more days or weeks of no treatment.

[00152] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive or sequential administration in any order. The term "concurrently" is used herein to refer to administration of two or more therapeutic agents,

where at least part of the administration overlaps in time or where the administration of one therapeutic agent falls within a short period of time relative to administration of the other therapeutic agent. For example, the two or more therapeutic agents are administered with a time separation of no more than about a specified number of minutes. The term "sequentially" is used herein to refer to administration of two or more therapeutic agents where the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s), or wherein administration of one or more agent(s) begins before the administration of one or more other agent(s). For example, administration of the two or more therapeutic agents are administered with a time separation of more than about a specified number of minutes. As used herein, "in conjunction with" refers to administration of one treatment modality in addition to another treatment modality. As such, "in conjunction with" refers to administration of one treatment modality before, during or after administration of the other treatment modality to the animal.

[00153] In some embodiments, the dose is administered once per week for at least two or three consecutive weeks, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more weeks of no treatment. In other embodiments, the therapeutically effective dose is administered once per day for two to five consecutive days, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more days or weeks of no treatment.

[00154] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive or sequential administration in any order. The term "concurrently" is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time or where the administration of one therapeutic agent falls within a short period of time relative to administration of the other therapeutic agent. For example, the two or more therapeutic agents are administered with a time separation of no more than about a specified number of minutes. The term "sequentially" is used herein to refer to administration of two or more therapeutic agents where the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s), or wherein administration of one or more agent(s) begins before the administration of one or more other agent(s). For example, administration of the two or more therapeutic agents are administered with a time separation of more than about a specified number of minutes. As used herein, "in conjunction with" refers to administration of one treatment modality in addition to another treatment modality. As such, "in conjunction with" refers to administration of one

treatment modality before, during or after administration of the other treatment modality to the animal.

[00155] In some embodiments, the method comprises administering in combination with a GLP1 fusion polypeptide insulin, a DPP4 inhibitor, a SGLT2 inhibitor, a biguanides sulfonylurea, a meglitinide derivative, an alpha-glucosidase inhibitor, a thiazolidinedione (TZD), an amylinomimetic, a bile acid sequestrant, a dopamine agonist.

[00156] The following examples illustrate particular aspects of the disclosure and are not intended in any way to limit the disclosure.

EXAMPLES

Example 1

Variant canine IgG Fc polypeptides for increased Protein A binding and/or decreased complement binding and/or decreased CD16 binding

[00157] Purification of antibodies using Protein A affinity is a well-developed process. However, among four subtypes of canine IgG, only IgG-B Fc (e.g., SEQ ID NO: 2 or SEQ ID NO: 107) has Protein A binding affinity. Canine IgG-A Fc (e.g., SEQ ID NO: 1), IgG-C Fc (e.g., SEQ ID NO: 3 or SEQ ID NO: 108), and IgG-D Fc (e.g., SEQ ID NO: 4) have weak or no measurable Protein A binding affinity. Variant canine IgG-A Fc, IgG-C Fc, and IgG-D Fc polypeptides were designed for altered Protein A binding.

[00158] In addition, canine IgG-B Fc and IgG-C Fc have complement activity and bind to C1q, while canine IgG-A Fc and IgG-D Fc have weak or no measurable binding affinity to C1q. To potentially reduce the C1q binding and/or potentially reduce complement-mediated immune responses, variant canine IgG-B Fc and IgG-C Fc polypeptides were designed.

[00159] Furthermore, canine IgG-B Fc and IgG-C Fc have CD16 binding activity. To potentially reduce the binding of CD16 to IgG-B Fc and IgG-C Fc, and/or potentially reduce ADCC, variant canine IgG-B Fc and IgG-C Fc polypeptides were designed.

[00160] Table 3, below summarizes the Protein A and C1q binding characteristics of canine IgG Fc subtypes. Notably, none of the wild-type canine IgG Fc subtypes lacks C1q binding and binds Protein A.

[00161] Table 3.

Wild-type Canine IgG Fc	Protein A Binding	C1q Binding	CD16 Binding
IgG-A Fc	–	–	–
IgG-B Fc	+	+	+

IgG-C Fc	–	+	+
IgG-D Fc	–	–	–

(–) denotes low or no measurable binding activity.

[00162] Using three-dimensional protein modeling and protein sequence analysis, the sequences of canine IgG-B Fc that are likely in contact with Protein A were identified. Figure 1 shows an alignment of canine IgG-A, B, C, and D Fc sequences. The boxes indicate the regions likely in contact with Protein A.

[00163] Two approaches were used to design variant canine IgG-A, IgG-C, and IgG-D Fc polypeptides for increased Protein A binding. For the first approach, variant canine IgG-A, IgG-C, and IgG-D Fc polypeptides were designed to have the same Protein A binding motif sequences as canine IgG-B Fc (e.g., SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, respectively). For the second approach, variant canine IgG-A Fc I(21)T/Q(207)H (SEQ ID NO: 60), variant canine IgG-C Fc I(21)T (SEQ ID NO: 61), and variant canine IgG-D Fc I(21)T/Q(207)H (SEQ ID NO: 62) were designed with one or two amino acid substitutions in the Protein A binding region to correspond with the canine IgG-B Fc sequence.

[00164] In addition, variant canine IgG-A Fc, IgG-C Fc, and IgG-D Fc polypeptides with increased Protein A binding may be prepared having one or more of the amino acid substitutions listed in Table 4.

[00165] Table 4.

Variant Canine IgG Fc Amino Acid Substitutions* (Protein A +)		
Canine IgG-A Fc (SEQ ID NO: 1)	Canine IgG-C Fc (SEQ ID NO: 3)	Canine IgG-D Fc (SEQ ID NO: 4)
Ile (21) Thr	Ile (21) Thr	Ile (23) Thr
Arg (23) Leu	Val (23) Leu	Arg (23) Leu
Thr (25) Ala	Thr (24) Ile	Thr (25) Ala
Glu (80) Gly		Glu (80) Gly
Thr (205) Ala		Gln (207) His
Gln (207) His		

* The amino acid positions listed are relative to the SEQ ID NO. indicated.

[00166] To potentially reduce the binding of C1q to canine IgG-B Fc and IgG-C Fc, and/or potentially reduce complement-mediated immune responses, variant canine IgG-B Fc and IgG-C Fc polypeptides may be prepared having an amino acid substitution of Lys with any amino acid except Lys at an amino acid position corresponding to position 93 of SEQ ID NO: 2 or of SEQ ID NO: 3, respectively. These amino acid substitutions were identified after analysis of the protein sequence and 3-D structure modeling of canine IgG-B Fc and IgG-C Fc compared to canine IgG-

A Fc and IgG-D Fc, which are understood to not exhibit complement activity. For example, variant canine IgG-B Fc K(93)R (SEQ ID NO: 78) and variant canine IgG-C Fc K(93)R (SEQ ID NO: 79) may be prepared. Reduced binding between human C1q and a fusion protein comprising variant canine IgG-B Fc K(93)R was observed when compared to a fusion protein comprising wild-type canine IgG-B Fc.

[00167] To potentially reduce the binding of CD16 to IgG-B Fc and IgG-C Fc, and/or potentially reduce ADCC, variant canine IgG-B Fc and IgG-C Fc polypeptides may be prepared having one or more of the amino acid substitutions listed in Table 5. The amino acid substitution(s) were identified after analysis of the protein sequence and 3-D structure modeling of canine IgG-B and IgG-C compared to IgG-A and IgG-D, which are understood to not exhibit ADCC activity.

[00168] Table 5.

Original residue position*		Substitution(s)
Canine IgG-B Fc (SEQ ID NO: 2)	Canine IgG-C Fc (SEQ ID NO: 3)	
Met (5)	Leu (5)	Any amino acid except original residue, such as Pro
Asp (38)	Asp (38)	Any amino acid except original residue, such as Gly
Pro (39)	Pro (39)	Any amino acid except original residue, such as Arg
Lys (97)	Lys (97)	Any amino acid except original residue, such as Ile
Ala (98)	Ala (98)	Any amino acid except original residue, such as Gly

* The amino acid positions listed are relative to the SEQ ID NO. indicated.

[00169] Since wild-type canine IgG-C Fc lacks Protein A binding and has C1q binding, a double variant canine IgG-C Fc that binds Protein A and has reduced binding to C1q may be prepared by combining one or more of the amino acid substitutions listed in Table 4 with a K(93)R substitution or K(93)X substitution, wherein X is any amino acid except Lys. A double variant canine IgG-B Fc or double variant canine IgG-C Fc with reduced binding to C1q and reduced binding to CD16 may be prepared by combining one or more of the amino acid substitutions listed in Table 5 with a K(93)R substitution or K(93)X substitution, wherein X is any amino acid except

Lys. A triple variant canine-IgG-C Fc that binds Protein A and has reduced binding to C1q and CD16 may be prepared by combining one or more of the amino acid substitutions listed in Table 4 and one or more of the amino acid substitutions listed in Table 5 with a K(93)R substitution or K(93)X substitution, wherein X is any amino acid except Lys.

[00170] The binding of any variant canine IgG Fc to Protein A, CD16, and/or C1q may be determined and compared to the binding of another IgG Fc to Protein A, CD16, and/or C1q (e.g., the corresponding wild-type canine IgG Fc, another wild-type or variant canine IgG Fc, or a wild-type or variant IgG Fc of another companion animal, etc.).

[00171] Binding analysis may be performed using an Octet biosensor. Briefly, the target molecule (e.g., Protein A, C1q, CD16, etc.) may be biotinylated and free unreacted biotin removed (e.g., by dialysis). The biotinylated target molecule is captured on streptavidin sensor tips. Association of the target molecule with various concentrations (e.g., 10 μg/mL) of IgG Fc polypeptide is monitored for a specified time or until steady state is reached. Dissociation is monitored for a specified time or until steady state is reached. A buffer only blank curve may be subtracted to correct for any drift. The data are fit to a 1:1 binding model using ForteBio™ data analysis software to determine the k_{on}, k_{off}, and the K_d.

Example 2

Variant equine IgG Fc polypeptides for increased Protein A binding and/or decreased complement binding

[00172] Of the seven subtypes of equine IgG, IgG1 Fc (e.g., SEQ ID NO: 63), IgG3 Fc (e.g., SEQ ID NO: 65), IgG4 Fc (e.g., SEQ ID NO: 66), IgG7 Fc (e.g., SEQ ID NO: 69) have Protein A binding affinity. Equine IgG2 Fc (e.g., SEQ ID NO: 18, SEQ ID NO: 64), IgG5 Fc (e.g., SEQ ID NO: 67), and IgG6 Fc (e.g., SEQ ID NO: 68) have weak or no measurable Protein A binding affinity. Variant equine IgG2 Fc, IgG5 Fc, and IgG6 Fc polypeptides were designed for altered Protein A binding.

[00173] In addition, equine IgG2 Fc, IgG5 Fc, and IgG6 Fc have weak or no measurable binding affinity to C1q, while equine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc bind to C1q. To potentially reduce the C1q binding and/or potentially reduce complement-mediated immune responses, variant equine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc polypeptides were designed.

[00174] Table 6, below summarizes the Protein A and C1q binding characteristics of equine IgG Fc subtypes. Notably, none of the wild-type equine IgG Fc subtypes lacks C1q binding and binds Protein A.

[00175] Table 6.

Wild-type Equine IgG Fc	Protein A Binding	C1q Binding
IgG1 Fc	+	+
IgG2 Fc	–	–
IgG3 Fc	+	+
IgG4 Fc	+	+
IgG5 Fc	–	–
IgG6 Fc	–	–
IgG7 Fc	+	+

(–) denotes low or no measurable binding activity.

[00176] Using three-dimensional protein modeling and protein sequence analysis, the sequences of equine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc that are likely in contact with Protein A were identified. Variant equine IgG2 Fc, IgG5 Fc, and IgG6 Fc polypeptides with increased Protein A binding may be prepared having one or more of the amino acid substitutions listed in Table 7.

[00177] Table 7.

Variant Equine IgG Fc Amino Acid Substitutions* (Protein A +)		
Equine IgG2 Fc (SEQ ID NO: 64)	Equine IgG5 Fc (SEQ ID NO: 67)	Equine Ig6 Fc (SEQ ID NO: 68)
Ala (15) Thr	Val (199) Leu	Ile (199) Leu
Phe (203) Tyr	Glu (200) Tyr	Arg (200) His
		His (201) Asn
		Thr (202) His

* The amino acid positions listed are relative to the SEQ ID NO. indicated

[00178] For example, variant equine IgG2 Fc, IgG5 Fc, and IgG6 Fc polypeptides were designed with one or multiple amino acid substitutions in the Protein A binding region to correspond with the sequence of wild-type equine IgG Fc, which does bind Protein A. Variant equine IgG2 Fc F(203)Y (SEQ ID NO: 71); variant equine IgG2 Fc A(15)T/F(203)Y (SEQ ID NO: 72); variant equine IgG5 Fc V(199)L/E(200)Y (SEQ ID NO: 75); and variant equine IgG6 Fc I(199)L/R(200)H/H(201)N/T(202)H (SEQ ID NO: 76) with increased Protein A binding may be prepared.

[00179] To potentially reduce the binding of C1q to equine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc, and/or potentially reduce complement-mediated immune responses, variant canine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc polypeptides may be prepared having an amino acid substitution of Lys with any amino acid except Lys at an amino acid position corresponding to

position 87 of SEQ ID NO: 63, of SEQ ID NO: 65, of SEQ ID NO: 66, of SEQ ID NO: 69, respectively. These amino acid substitutions were identified after analysis of the protein sequence and 3-D structure modeling of equine IgG1 Fc, IgG3 Fc, IgG4 Fc, and IgG7 Fc compared to equine IgG2 Fc, IgG5 Fc, and IgG6 Fc, which are understood to not exhibit complement activity. For example, variant equine IgG1 Fc K(87)S (SEQ ID NO: 70), variant equine IgG 3 Fc K(87)S (SEQ ID NO: 73), variant equine IgG4 Fc K(87)S (SEQ ID NO: 74), and variant equine IgG7 Fc K(87)S (SEQ ID NO: 77) may be prepared.

[00180] The binding of any variant equine IgG Fc to Protein A and/or C1q may be determined and compared to the binding of another IgG Fc to Protein A and/or C1q (e.g., the corresponding wild-type equine IgG Fc, another wild-type or variant equine IgG Fc, or a wild-type or variant IgG Fc of another companion animal, etc.). The binding assay described in Example 1 may be used.

Example 3

Variant feline IgG Fc polypeptides for decreased complement binding

[00181] Each of the three subtypes of feline IgG, IgG1a Fc (SEQ ID NO: 80 or SEQ ID NO: 117), IgG1b Fc (SEQ ID NO: 81 or SEQ ID NO: 118), and IgG2 Fc (SEQ ID NO: 16) have Protein A binding affinity. However, only feline IgG2 Fc has weak or no measurable binding affinity to C1q, while feline IgG1a Fc, IgG1b Fc bind to C1q. To potentially reduce the C1q binding and/or potentially reduce complement-mediated immune responses, variant feline IgG1a Fc and IgG1b Fc polypeptides were designed.

[00182] Table 8, below summarizes the Protein A and C1q binding characteristics of feline IgG Fc subtypes. Notably, none of the wild-type equine IgG Fc subtypes lacks C1q binding and binds Protein A.

[00183] Table 8.

Wild-type Feline IgG Fc	Protein A Binding	C1q Binding
IgG1a Fc	+	+
IgG1b Fc	+	+
IgG2 Fc	+	–

(–) denotes low or no measurable binding activity.

[00184] To potentially reduce the binding of C1q to feline IgG1a Fc and IgG1b Fc, and/or potentially reduce complement-mediated immune responses, variant feline IgG1a Fc and IgG1b Fc polypeptides may be prepared having an amino acid substitution of Pro with any amino acid except Pro at an amino acid position corresponding to position 198 of SEQ ID NO: 80 or of SEQ

ID NO: 81, respectively. These amino acid substitutions were identified after analysis of the protein sequence and 3-D structure modeling of feline IgG1a Fc and IgG1b Fc compared to feline IgG2 Fc, which is understood to not exhibit complement activity. For example, variant feline IgG1a Fc P(198)A (SEQ ID NO: 82) and variant feline IgG1b Fc P(198)A (SEQ ID NO: 83) may be prepared.

[00185] The binding of any variant feline IgG Fc to C1q may be determined and compared to the binding of another IgG Fc to C1q (e.g., the corresponding wild-type feline IgG Fc, another wild-type or variant feline IgG Fc, or a wild-type or variant IgG Fc of another companion animal, etc.). The binding assay described in Example 1 may be used.

Example 4

Variant canine and feline IgG Fc polypeptides for heterodimeric proteins

[00186] To enable the preparation of a bispecific canine or feline antibody or a bifunctional canine or feline Fc fusion protein using a knob-in-hole heterodimerization approach, pairing of variant canine IgG Fc polypeptides and variant feline IgG Fc polypeptides was investigated.

[00187] An amino acid substitution of threonine at a position corresponding to position 138 of canine IgG-A (SEQ ID NO: 1), at a position corresponding to position 137 of canine IgG-B Fc (SEQ ID NO: 2), at a position corresponding to position 137 of canine IgG-C Fc (SEQ ID NO: 3), or at a position corresponding to position 138 of canine IgG-D Fc (SEQ ID NO: 4) to tyrosine (T138Y or T137Y) can be introduced to one Fc chain (heterodimer chain 1). Examples of amino acid sequences of variant canine IgG-A Fc, IgG-B Fc, IgG-C Fc, and IgG-D Fc heterodimer chain 1 are SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, and SEQ ID NO: 14, respectively.

[00188] An amino acid substitution of tyrosine at a position corresponding to position 181 of canine IgG-A (SEQ ID NO: 1), at a position corresponding to position 180 of canine IgG-B Fc (SEQ ID NO: 2), at a position corresponding to position 180 of canine IgG-C Fc (SEQ ID NO: 3), or at a position corresponding to position 181 of canine IgG-D Fc (SEQ ID NO: 4) to threonine (Y181T or Y180T) can be introduced to a second Fc chain (heterodimer chain 2). Examples of amino acid sequences of variant canine IgG-A Fc, IgG-B Fc, IgG-C Fc, and IgG-D Fc heterodimer chain 2 are SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, and SEQ ID NO: 15, respectively.

[00189] A second pairing of variant canine IgG Fc heterodimer chains 3 and 4 was also investigated. An amino acid substitution of threonine to tryptophan at a position corresponding to position 138 of canine IgG-A (SEQ ID NO: 1) or of canine IgG-D (SEQ ID NO: 4) (T138W), or at a position corresponding to position 137 of canine IgG-B Fc (SEQ ID NO: 2) or of canine IgG-C Fc (SEQ ID NO: 3) (T137W) can be introduced to one Fc chain (heterodimer chain 3).

Examples of amino acid sequences of variant canine IgG-A Fc, IgG-B Fc, IgG-C Fc, and IgG-D Fc heterodimer chain 3 are SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, and SEQ ID NO: 115.

[00190] An amino acid substitution of threonine to serine at a position corresponding to position 138, of leucine to alanine at a position corresponding to position 140, and of tyrosine to threonine at a position corresponding to position 181 of canine IgG-A (SEQ ID NO: 1) or of IgG-D (SEQ ID NO: 4) (T138S, L140A, Y181T), or of threonine to serine at a position corresponding to position 137, of leucine to alanine at a position corresponding to position 139, and of tyrosine to threonine at a position corresponding to position 180 of canine IgG-B Fc (SEQ ID NO: 2) or of IgG-C (SEQ ID NO: 3) (T137S, L139A, Y180T) can be introduced to a second Fc chain (heterodimer chain 4). Examples of amino acid sequences of variant canine IgG-A Fc, IgG-B Fc, IgG-C Fc, and IgG-D Fc heterodimer chain 4 are SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, and SEQ ID NO: 116.

[00191] An amino acid substitution of threonine to tryptophan at a position corresponding to position 154 of feline IgG2 (SEQ ID NO: 16), of feline IgG1a Fc (SEQ ID NO: 80 or SEQ ID NO: 117), or of feline IgG1b Fc (SEQ ID NO: 81 or SEQ ID NO: 118) (T154W) can be introduced to one Fc chain (heterodimer chain 1). Examples of amino acid sequences of variant feline IgG2 Fc, IgG1a Fc, and IgG1b Fc heterodimer chain 1 are SEQ ID NO: 119, SEQ ID NO: 121, and SEQ ID NO: 123, respectively.

[00192] An amino acid substitution of threonine to serine at a position corresponding to position 154, of leucine to alanine at a position corresponding to position 156, and of tyrosine to threonine at a position corresponding to position 197 of feline IgG2 Fc (SEQ ID NO: 16), of IgG-1a (SEQ ID NO: 80 or SEQ ID NO: 117), or of IgG-1b Fc (SEQ ID NO: 81 or SEQ ID NO: 118) (T154S, L156A, Y197T) can be introduced to a second Fc chain (heterodimer chain 4). Examples of amino acid sequences of variant feline IgG2 Fc, IgG1a Fc, and IgG1b Fc heterodimer chain 4 are SEQ ID NO: 120, SEQ ID NO: 122, and SEQ ID NO: 124.

[00193] The pairing of variant canine IgG Fc heterodimer chains 1 and 2, the pairing of variant canine IgG Fc heterodimer chains 3 and 4, or the pairing of variant feline IgG Fc heterodimer chains 1 and 2 may allow for Fc heterodimerization and prevent or reduce Fc homodimerization. A heterodimer chain 1 of one canine IgG subtype may be combined with a heterodimer chain 2 of the same or a different canine IgG subtype. A heterodimer chain 3 of one canine IgG subtype may be combined with a heterodimer chain 4 of the same or a different canine IgG subtype. A heterodimer chain 1 of one feline IgG subtype may be combined with a heterodimer chain 2 of the same or a different feline IgG subtype. The design can enable

dimerization of bispecific canine or feline antibodies. In addition, two different peptides or proteins or a combination of different proteins can be fused to the heterodimeric Fc chains. For example, a dual GLP1 and glucagon molecule can be created using variant canine IgG Fc heterodimer chains or variant feline IgG Fc heterodimer chains, such as a GLP1 polypeptide (e.g., SEQ ID NO: SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, or SEQ ID NO: 91) fused to a variant canine IgG-D Fc heterodimer chain 1 (e.g., SEQ ID NO: 14) and a glucagon polypeptide (e.g., SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, or SEQ ID NO: 95) fused to a variant canine IgG-D Fc heterodimer chain 2 (e.g., SEQ ID NO: 15).

Example 5

GLP1 fusion proteins

[00194] The amino acid sequence of GLP1 is conserved among human, feline, canine, and equine, among other species. GLP1 proteolytic products (e.g., GLP1 (amino acids 7-37) (SEQ ID NO: 85) are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and are understood to have a short serum half-life of a couple minutes.

[00195] The design of contiguous polypeptides comprising at least one GLP1 polypeptide and feline, canine, or equine IgG Fc polypeptides was investigated to generate long-acting GLP1 fusion proteins. The following constructs were designed:

Formula (I): GLP1A—L1—Fc;

Formula (II): Fc—L1—GLP1A; or

Formula (III): GLP1A—L1—Fc—L2—GLP1B.

wherein GLP1A is a first GLP1 polypeptide, GLP1B is a second GLP1 polypeptide, L1 and L2 are linkers; and Fc is an IgG Fc polypeptide of a companion animal species.

[00196] GLP1 was modified to be DPP-4 resistant by replacing alanine with either glycine or serine at a position corresponding to position 8 of wild-type GLP1 (7-37) (SEQ ID NO: 85). A minimal sequence of wild-type GLP1 (7-37) (SEQ ID NO:87) for binding to the N-terminal domain of mature feline GLP1R (SEQ ID NO: 49) was analyzed by three-dimensional protein modeling of the complex. Based on this modeling, the two C-terminal amino acids were removed from the DPP-4 resistant GLP1 to generate GLP1-S8 (7-35) (SEQ ID NO: 86) and GLP1-G8 (7-35) (SEQ ID NO: 87) polypeptides.

[00197] GLP1 polypeptides when positioned at the C-terminus of a construct, such as in formulas II and III, are not susceptible to DPP-4 degradation. Therefore, the alanine to glycine or serine substitution is not necessary for GLP1 polypeptides positioned at the C-terminus. Accordingly, wild-type GLP1 (7-37) (SEQ ID NO: 85) may be used at the C-terminus.

[00198] The linker may be a flexible, non-structural linker, such as a glycine- and serine-rich linker. A flexible extension may be added to the C-terminus of the contiguous polypeptide. The extension may comprise a glycine residue (SEQ ID NO: 88), two glycine residues (SEQ ID NO: 89), a three glycine residues (SEQ ID NO: 90), four glycine residues (SEQ ID NO: 91), five glycine residues (SEQ ID NO: 92), six glycine residues (SEQ ID NO: 93), seven glycine residues (SEQ ID NO: 94), eight glycine residues (SEQ ID NO: 95), or more glycine residues.

Example 6

GLP1 and feline IgG Fc fusion proteins

[00199] Nucleotide sequences encoding (1) a contiguous polypeptide of Formula I having a signal sequence, GLP1-G8 (7-35) (SEQ ID NO: 87), a flexible linker, and wildtype feline IgG2 Fc (ssGLP1-G8_I_WTfeIgG2; SEQ ID NO: 96); and (2) a contiguous polypeptide of Formula III having a signal sequence, GLP1-G8 (7-35) (SEQ ID NO: 87), GLP1 (7-35) (SEQ ID NO: 89), two flexible linkers, a 2G C-terminal extension, and wildtype feline IgG2 Fc (ssGLP1-G8/GLP1-2G_III_WTfeIgG2; SEQ ID NO: 97) were synthesized and cloned into separate mammalian expression vectors. Wild-type feline IgG2 Fc (SEQ ID NO: 16) was chosen based on its low or no C1Q binding for reduced complement activity and Protein A binding for ease of purification.

[00200] The resulting vectors were separately transfected to CHO cells. The supernatant containing the contiguous polypeptides without the signal peptide (SEQ ID NOs: 24 and 23) was collected and filtered. Both proteins were affinity purified using a Protein A column (CaptivA® Protein A Affinity Resin, Repligen). The proteins were determined to be monomeric as assessed by HPLC gel filtration. However, the SDS-PAGE analysis showed that a percentage of both continuous polypeptides migrated to the same position in the gel in the absence and presence of reducing agent (DTT) (Figure 2A). This result suggests that the hinge of wild-type feline IgG2 Fc, which has only one pair of cysteine residues, may not be enough to form an effective disulfide linkage.

[00201] Three-dimensional protein modeling analysis of several ortholog hinge structures was used to determine the approximate locations for modifying the feline IgG2 hinge to increase disulfide formation. To increase disulfide formation at the feline IgG2 hinge, the hinge sequence may be modified by substituting an amino acid with cysteine. For example, a variant feline IgG2 Fc (SEQ ID NO: 17) having a modified hinge was prepared by substituting Gly with Cys at an amino acid position corresponding to position 14 of SEQ ID NO: 16. The corresponding contiguous polypeptides ssGLP1-G8_I_VARfeIgG2 (SEQ ID NO: 39) and ssGLP1-G8/GLP1-2G _III_WTfeIgG2 (SEQ ID NO: 38) comprising variant feline IgG Fc of SEQ ID NO: 17 were

designed, expressed in CHO cells, and purified by Protein A chromatography. The amino acid sequences of the secreted proteins after cleavage of the signal sequence are SEQ ID NOs 26 and 25, respectively. The SDS-PAGE analysis of the variant feline IgG2 constructs showed a decrease in the amount of protein in the lower molecular weight band in absence of reducing agent compared to the wild-type feline IgG2 constructs (compare Figure 2 B to Figure 2A). These results suggest that the Fc covalent pairing was improved for both variant feline IgG2 constructs.

[00202] Furthermore, differential scanning fluorimetry was used to assess the stability of the contiguous polypeptides at various pH, as reflected by mean melting point temperature (n=3) (Table 9, below). The increased stability of the variant feline IgG2 hinge is most evident at pH 6. For example, the constructs having variant feline IgG2 (SEQ ID NOs: 25 and 26) exhibited a higher Tm at pH 6 (56.9 and 59.7 °C) than the corresponding constructs having wild-type feline IgG2 (SEQ ID NOs: 23 and 24), which had a Tm of 55.2 and 56.9 °C, respectively.

[00203] Table 9.

Construct (10 µg)	**Mean Melting Point Temperature (Tm °C) (n=3)**					
	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8
GLP1-G8/GLP1-2G_III_ WTfeIgG2 (SEQ ID NO:23)	NC	NC	NC	55.2	55.7	54.2
GLP1-G8_I_WTfeIgG2 (SEQ ID NO:24)	NC	NC	48.5	56.9	59.9	59
GLP1-G8/GLP1-2G_III_ WTfeIgG2 (SEQ ID NO:25)	NC	NC	NC	56.9	55	52.5
GLP1-G8_I_VARfeIgG2 (SEQ ID NO:26)	NC	NC	53.1	59.7	59.9	58.2

NC = no curve because no distinct transition point was observed.

[00204] Contiguous polypeptides of Formulas I, II, and III comprising GLP1-S8 (7-35) (SEQ ID NO: 86) instead of GLP1-G8 (7-35) (SEQ ID NO: 87) may be similarly designed and prepared. For example, ssGLP1-S8_I_WTfeIgG2 (SEQ ID NO: 40), GLP1-S8_I_WTfeIgG2 (SEQ ID NO: 28), ssGLP1-S8/GLP1-3G_III_WTfeIgG2 (SEQ ID NO: 37), and GLP1-S8/GLP1-3G_III_WTfeIgG2 (SEQ ID NO: 27) may be prepared. Similar constructs having variant instead of wild-type feline IgG Fc, such as GLP1-S8_I_VARfeIgG2, GLP1-S8_I_ VARfeIgG2, GLP1-S8/GLP1-2G_III_VARfeIgG2, and GLP1-S8/GLP1-3G_III_ VARfeIgG2, may also be prepared.

[00205] While feline IgG2 Fc was used in this example, contiguous polypeptides of Formulas I, II, and III comprising feline IgG1a Fc or IgG1b Fc instead of IgG2 may be designed and prepared. For example, similar contiguous polypeptides having wild-type feline IgG1a Fc, wild-type feline IgG1b Fc, variant feline IgG1a Fc, or variant feline IgG1b Fc (SEQ ID NOs: 80 to 83, respectively), may be designed and prepared.

Example 7

GLP1 and canine IgG Fc fusion proteins

[00206] Various Formula I, II, and III contiguous polypeptides comprising a variant GLP1 and a canine IgG Fc may be designed and prepared. For example, a variant canine IgGD Fc (e.g., SEQ ID NO: 7 or SEQ ID NO: 62) may be chosen based on its low or no C1q binding for reduced complement activity and Protein A binding for ease of purification. In addition, a flexible, non-structural linker, such as a glycine- and/or serine-rich linker, may be used.

[00207] GLP1-G8_I_VARcaIgGD (SEQ ID NO: 30) and GLP1-S8_I_VARcaIgGD (SEQ ID NO: 32) are examples of Formula I contiguous polypeptides comprising (1) either GLP1-G8 (7-35) or GLP1-S8 (7-35), (2) a flexible linker, and (3) a variant canine IgGD Fc (e.g., SEQ ID NO: 7). GLP1-G8/GLP1-3G_III_VARcaIgGD (SEQ ID NO: 29) and GLP1-S8/GLP1-3G_III_VARcaIgGD (SEQ ID NO: 31) are examples of Formula III contiguous polypeptides comprising (1) either GLP1-G8 (SEQ ID NO: 87) or GLP1-S8 (SEQ ID NO: 86), (2) GLP1 (7-35) (SEQ ID NO: 61), (3) two flexible linkers, (4) a 3G C-terminal extension, and (5) a variant canine IgGD Fc.

[00208] The contiguous polypeptides may be designed with a signal sequence, a different GLP1 polypeptide (e.g., SEQ ID NO: 85, 86, 87, 98, or 99), or different modifications to the canine IgG Fc. Examples with such variations include ssGLP1-S8/GLP1-2G_III_VARcaIgGD (SEQ ID NO: 41), ssGLP1-G8/GLP1-2G_III_VARcaIgGD (SEQ ID NO: 42), ssGLP1-S8/GLP1-3G_III_VARcaIgGD (SEQ ID NO: 43), GLP1-S8/GLP1-2G_III_VARcaIgGD (SEQ ID NO: 105), and GLP1-G8/GLP1-2G_III_VARcaIgGD (SEQ ID NO: 106).

[00209] Furthermore, contiguous polypeptides of Formulas I, II, and III may comprise a wild-type canine IgGD, or a wild-type or variant canine IgGA, IgGB, or IgGC, instead of a variant canine IgGD. For example, similar contiguous polypeptides may be designed and prepared having a wild-type canine IgGA Fc, IgGB Fc, IgGC Fc, or IgGD Fc (e.g., SEQ ID NO: 1, 2, 3, or 4, respectively). Additional examples include contiguous polypeptides comprising a variant canine IgGA Fc (e.g., SEQ ID NO: 5 or 60), a variant canine IgGB Fc (e.g., SEQ ID NO: 78), or a variant canine IgGC Fc (e.g., SEQ ID NO: 6, 61, 79, or 84).

[00210] GLP1-G8/GLP1-3G_III_VARcaIgGD (SEQ ID NO: 29) and GLP1-G8_I_VARcaIgGD (SEQ ID NO: 30) were expressed separately in CHO cells and the supernatants containing the proteins collected and filtered. Both contiguous polypeptides were affinity purified by Protein A chromatography. The SDS-PAGE profiles of the two contiguous polypeptides in the absence and presence of reducing agent (DTT) were compared and the results suggested that the Fc disulfide bond was effectively formed for both polypeptides (data not shown).

Example 8

GLP1 and equine IgG Fc fusion proteins

[00211] Various Formula I, II, and III contiguous polypeptides comprising a variant GLP1 and an equine IgG Fc may be designed and prepared. For example, a variant canine IgG2 Fc (e.g., SEQ ID NO: 19, 71, or 72) may be chosen based on its low or no C1q binding for reduced complement activity and Protein A binding for ease of purification. In addition, a flexible, non-structural linker, such as a glycine- and/or serine-rich linker, may be used.

[00212] GLP1-G8_I_VAReqIgG2 (SEQ ID NO: 34) and GLP1-S8_I_VAReqIgG2 (SEQ ID NO: 36) are examples of Formula I contiguous polypeptides comprising (1) either GLP1-G8 or GLP1-S8, (2) a flexible linker, and (3) a variant equine IgG2 Fc (e.g., SEQ ID NO: 19). GLP1-G8/GLP1-3G_III_VAReqIgG2 (SEQ ID NO: 33) and GLP1-S8/GLP1-3G_III_VAReqIgG2 (SEQ ID NO: 35) are examples of Formula III contiguous polypeptides comprising (1) either GLP1-G8 (7-35) (SEQ ID NO: 87) or GLP1-S8 (7-35) (SEQ ID NO: 86), (2) GLP1 (7-35) (SEQ ID NO: 61), (3) two flexible linkers, (4) a 3G C-terminal extension, and (5) a variant equine IgGD Fc.

[00213] The contiguous polypeptides may be designed with a signal sequence, a different GLP1 analog (e.g., SEQ ID NO: 86, 87, 98, or 99), a glycine extension (e.g., SEQ ID NO: 88 to 95) or additional modifications to the equine IgG Fc. Examples with such variations include ssGLP1-G8/GLP1-3G_III_VAReqIgG2 (SEQ ID NO: 44), ssGLP1-G8_I_VAReqIgG2 (SEQ ID NO: 45), ssGLP1-S8/GLP1-3G_III_VAReqIgG2 (SEQ ID NO: 46), and ssGLP1-S8_I_VAReqIgG2 (SEQ ID NO: 47).

[00214] Furthermore, contiguous polypeptides of Formulas I, II, and III may comprise a wild-type equine IgG2, or a wild-type or variant equine IgG1, IgG3, IgG4, IgG5, IgG6, IgG7, instead of a variant equine IgG2. For example, similar contiguous polypeptides may be designed and prepared having a wild-type equine IgG1 Fc (e.g., SEQ ID NO: 63), IgG2 Fc (e.g., SEQ ID NO: 18 or 64), IgG3 Fc (e.g., SEQ ID NO: 65), IgG4 Fc (e.g., SEQ ID NO: 66), IgG5 Fc (e.g., SEQ ID NO: 67), IgG6 Fc (e.g., SEQ ID NO: 68), or IgG7 Fc (e.g., SEQ ID NO: 69). Additional examples include contiguous polypeptides comprising a variant equine IgG1Fc (e.g., SEQ ID NO: 70), a variant equine IgG3 Fc (e.g., SEQ ID NO: 73), a variant equine IgG4 Fc (e.g., SEQ ID NO: 74), a variant equine IgG5 Fc (e.g., SEQ ID NO: 75), a variant equine IgG6 Fc (e.g., SEQ ID NO: 76), or a variant equine IgG7 Gc (e.g., SEQ ID NO: 77).

[00215] The nucleotide sequences encoding ssGLP1-G8/GLP1-3G_III_VAReqIgG2 (SEQ ID NO: 44) and ssGLP1-G8_I_ VAReqIgG2 (SEQ ID NO: 45) were synthesized and cloned into separate mammalian expression vectors. The resulting vectors were separately transfected to CHO

cells. The supernatant containing the contiguous polypeptides following cleavage of the signal peptide (SEQ ID NOs: 103 and 104) was collected and filtered. Both proteins were affinity purified using a Protein A column (CaptivA® Protein A Affinity Resin, Repligen). were expressed separately in CHO cells and the supernatants containing the proteins collected and filtered. Both contiguous polypeptides were affinity purified by Protein A chromatography. The SDS-PAGE profiles of the two contiguous polypeptides in the absence and presence of reducing agent (DTT) were compared and the results suggested that the Fc disulfide bond was effectively formed for both polypeptides (data not shown).

Example 9

Expression and purification of feline GLP1R N-terminal soluble domain

[00216] The N-terminal domain of mature feline GLP1R (SEQ ID NO: 49) responsible for binding GLP1 to GLP1R was identified from the full-length feline GLP1R amino acid sequence (SEQ ID NO: 48). Nucleotide sequences encoding (1) a signal sequence, feline N-terminal GLP1R, human Fc, and a poly-His tag (ssFeGLP1R-N-huFc_PolyHis; SEQ ID NO: 50) and (2) a signal sequence, feline N-terminal GLP1R, and a poly-His tag (ssFeGLP1R-N_polyHis; SEQ ID NO: 51) were synthesized and cloned into separate mammalian expression vectors. The resulting vectors were separately transfected to CHO cells. The supernatant containing the polypeptides was collected and filtered. The proteins were affinity purified using a Ni-Sepharose column or Protein A column (CaptivA® Protein A Affinity Resin, Repligen) for the huFc construct. Both proteins were used for GLP1 functional binding and ELISAs.

Example 10

GLP1 fusion protein binding kinetics

[00217] The binding affinity of GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) to FeGLP1R-N-huFc_PolyHis was assessed using biolayer interferometry (Octet). Briefly, FeGLP1R-N-huFc_PolyHis was biotinylated, the free unreacted biotin was removed, and the biotinylated protein was captured to streptavidin sensor tips. The association of different concentrations GLP1-G8_I_VARfeIgG2 was monitored for ninety seconds. Dissociation was monitored for 600 seconds. A buffer only blank curve was subtracted to correct for any drift. The data were fit to a 1:1 binding model using ForteBio™ data analysis software to determine the k_{on}, k_{off}, and the K_d. The buffer for dilutions and all binding steps was: 20 mM phosphate, 150 mM NaCl, pH 7.2. The K_d between Feline GLP1R N-terminal domain and GLP1-G8_I_VARfeIgG2 was between 8.0×10^{-9} and 16×10^{-9} M.

Example 11

GLP1 fusion protein bioactivity in a cell-based assay

[00218] CHOK-1-GL1R cell line (Discoverx, cat# 95-0062C2), a hamster ovarian cell line which overexpresses Gs-coupled human glucagon ligand peptide-1 receptors (GLP1R) on the cell surface, was used to measure GLP1 cellular activity with a cAMP Hunter Bioassay kit (Discoverx, Cat# 95-0062Y2). Cells were plated in a 96-well plate and incubated at 37°C, 5% CO_2 for 24 hours. Cells were then treated with a control agonist—either GLP1 human (37 a.a.) (Prospec, Cat# HOR-236) or Extendin-4 (Discoverx, Cat# 92-1115)—or a contiguous polypeptide comprising a variant GLP1 at a series of 3-fold dilutions followed by incubation at 37°C for 30 min. The contiguous polypeptides tested were GLP1-G8/GLP1-2G_III_VARfeIgG2 (SEQ ID NO: 25) and GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26).

[00219] Upon GLP1 binding to the Gs-coupled GLP1R receptor, Gs stimulates adenylate cyclase to generate cAMP. At the end of incubation, cAMP Antibody Reagent and cAMP Working Detection Solution, which contains lysis buffer, β-galactosidase (β-gal) small fragment conjugated cAMPs, and substrates, were added to the cells. The cells were incubated in the dark for 1 hour at room temperature to allow the immunocompetition reaction to occur between endogenously generated cAMPs and β-gal small fragment conjugated cAMPs for cAMP antibody binding.

[00220] At the end of the 1 hour incubation, cAMP Solution A containing β-gal large fragments, which can complement with the free (non-antibody binding) β-gal small fragment-cAMPs to form functional enzymes, were added to the cell lysate. The lysate was incubated for 3 to 6 hours in the dark at room temperature to allow the β-gal to hydrolyze the substrate and generate luminescent signals.

[00221] The more unbound free β-gal small fragment-cAMPs that remain, the more functional β-gal enzymes form. Therefore, the amount of signal produced is directly proportional to the amount of cAMP in the cell lysate. At the end of incubation, luminescence was read on a Synergy HT microplate reader (Biotek, Winooski, VT). The EC50s were calculated with a software GraphPad Prism (GraphPad Software, Inc. La Jolla, USA).

[00222] Figure 3 shows a plot of the relative light units (RLU) versus concentration for each sample tested. The EC50s are listed in Table 10, below. Both GLP1-G8/GLP1-2G_III_ VARfeIgG2 (SEQ ID NO: 25) and GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) are more active than GLP1 (7-37) and Extendin-4. GLP1-G8/GLP1-2G_III_ VARfeIgG2 (SEQ ID NO: 25) is more potent than GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26), suggesting that the C-terminal GLP1 may contribute additional activity.

[00223] Table 10.

Sample	EC 50 (nM)
GLP1 (7-37)	0.1449
Extendin-4	0.4596
GLP1-G8/GLP1-2G_III_VARfeIgG2 (SEQ ID NO: 25)	0.01751
GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26)	0.02806

Example 12

GLP1 fusion protein long-term stability

[00224] GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) was stored in PBS, pH7.2 at a concentration of 1.3 mg/mL, placed in 1.5 mL Eppendorf tube, and stored at 2-8 °C for one year (Lot 2-29-2016). GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) was also stored in PBS, pH7.2 at a concentration of 10 mg/mL, placed in 1.5 mL Eppendorf tube, and stored at 2-8 °C for one day (Lot 2-2-2017). To evaluate stability, the stored sample were analyzed by cell-based assay using the same CHOK-1-GL1R cell line (Discoverx, cat # 95-0062C2) described in Example 11, but cellular activity was assessed using a cAMP-Glo™ Max Assay (Promega, Cat# PAV1682).

[00225] CHOK-1-GL1R cells were plated in a 96-well plate (Corning, Cat# 3610) at a density of 20,000 cells per well in F-12K Medium (ATCC, Cat# ATCC® 30-2004) supplemented with 10% Fetal Bovine Serum, heat inactivated (Sigma, Cat#2868) and incubated at 37°C, 5% CO2 for 24 hours. Cells were then stimulated with a control agonist GLP1 human (37 a.a.) (Prospec, Cat# HOR-236), Lot 2-20-2016, or Lot 2-2-2017 at a series of 3-fold dilutions with serum-free medium followed by addition of Complete Induction Buffer which contains $MgCl_2$ to a final concentration 20 mM, isobutyl-1-methylxanthine (IBMX) (Sigma-Aldrich Cat.# I7018) to a final concentration 500 μM and Ro 20-1724 [4-(3-butoxy-4-methoxy-benzyl) imidazolidone] (Sigma Aldrich, Cat.# B8279) to a final concentration 100 μM.

[00226] The cells were incubated at room temperature for 30 minutes. In this process, upon GLP1 binding to the Gs-coupled GLP1R receptor, Gs stimulates adenylate cyclase to generate cAMP. At the end of incubation, cAMP Detection Solution, which contains an inactive protein kinase A holoenzyme, protein kinase A substrate, and lysis buffer, was added to the cells. The plates placed on an orbital shaker for 1–2 minutes and then incubated at room temperature (23°C) for 20 minutes. Cellular cAMP will activate protein kinase A by binding its regulatory-inhibitory subunits and releasing the catalytic subunits. The free catalytic subunits catalyze the transfer of the terminal phosphate of ATP to the protein kinase A substrate, consuming cellular ATP in the process. At the end of incubation, a luciferase-based Kinase-Glo® Reagent was added to the cell

lysates and the plates were shaken on an orbital shaker for 2 min followed by incubation in the dark at room temperature for 10 min.

[00227] Mono-oxygenation of luciferin was catalyzed by luciferase in the presence of Mg^{2+} and ATP that presented in the cell lysate, resulting in a luminescent signal proportional to the amount of ATP in the cells. At the end of 10 min incubation, the plate was read on a Synergy HT microplate reader (Biotek, Winooski, VT). Luminescence is proportional to ATP levels but inversely proportional to cAMP levels. Thus, as cAMP concentration increases, luminescence decreases.

[00228] Figure 4 shows the results of the cell-based assay as a plot of luminescence versus concentration for Lot 2-29-2016 compared to Lot 2-2-2017 and GLP1 (31 a.a.). The GLP1-G8_I_VARfeIgG2 sample maintained cellular activity after storage in PBS at 2-8 °C for one year.

Example 13

GLP1 fusion protein serum stability

[00229] GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) was stored in PBS, pH7.2 with feline serum at 37 °C for 24 hours to test in vitro serum stability. The cell-based assay was performed as described in Example 12 and results suggested that the activity was maintained (data not shown). In addition, no visible degradations were observed by Western blot analysis (Figure 5).

Example 14

GLP1 fusion protein *in vivo* pharmacokinetics

[00230] GLP1-G8_I_VARfeIgG2 (SEQ ID NO: 26) was administered as a single dose (2 mg/kg) by subcutaneous injection to 5 cats. Serum samples were taken before dosing (time 0) and at 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, and 168 hours. The concentration of GLP1-G8_I_VARfeIgG2 in the serum samples was measured by quantitative ELISA. GLP1-G8_I_VARfeIgG2 polypeptide with a detection limit of 4 ng/mL was used as a reference. The serum concentration of GLP1-G8_I_VARfeIgG2 was plotted against time (Figure 6). The mean serum half-life ($t_{½}$) of GLP1-G8_I_VARfeIgG2 was 39 hours. The average T_{max} was 22 hours, the average C_{max} was 12 μg /mL, and the mean area under the curve (AUC) was about 950 μg(h)/mL.

[00231] The quantitative ELISA used an anti-GLP1 antibody (4F3, Novus Biologicals, Catalog No. NBP1-97413) and a goat anti-cat IgG-Fc, HRP conjugated antibody (Bethyl Laboratories, Inc., Catalog No. A20-117P) for quantification of GLP1-G8_I_VARfeIgG2 in feline serum samples from the in vivo pharmacokinetics study. A 96-well plate was coated with anti-GLP1 antibody (5 μg/mL in coating buffer, 100 μl/well). The plate was sealed and incubated

overnight at 4°C. The plate was washed in triplicate with 1X TBST (10X TBST, Teknova, Catalog No. T9511) and blocking buffer was added. After removing the blocking buffer, serial dilutions of reference standard and samples in blocking buffer were added (100 µl/well) and the plate was incubated for 2 hours at room temperature. The plate was washed in triplicate with 1X TBST and goat anti-cat IgG Fc antibody was added (0.1 µg/mL in blocking buffer, 100 µl/well). After incubation for 1 hour at room temperature, the plate was washed 5 times with 1X TBST. TMB substrate (ScyTek, Catalog No. TM1999) was added (100 µl/well) and allowed to incubate at room temperature for 1 minute. The reaction was stopped by the addition of 2M H_2SO_4 (50 µl/well). Absorbance at 450 nm was measured and the concentration of GLP1-G8_I_ VARfeIgG2 in the serum samples calculated.

[00232] Furthermore, GLP1-G8_I_VARfeIgG2 concentration in the same serum samples (no DPP-4 inhibitor added) was assessed using a cell-based activity assay. The same CHOK-1-GL1R cell line (Discoverx, cat # 95-0062C2) and cAMP-Glo™ Max Assay (Promega, Cat# PAV1682) described in Example 12 was used. In this Example, however, the cells were stimulated with a control agonist GLP1 human (37 a.a.) (Prospec, Cat# HOR-236) or samples of cat serum taken before dosing (time 0) and at at 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, and 168 hours diluted in serum-free medium (5%, 0.5%, and 0.05% dilutions). The concentration of GLP1-G8_I_VARfeIgG2 in each sample was calculated using SoftMax pro 7 (Molecular Devices, Sunnyvale, CA). The mean concentration of GLP1-G8_I_VARfeIgG2 for the 5 cats was plotted against time (Figure 7). The mean AUC was about 840 µg(h)/mL and the mean $t_{1/2}$ was 36 hours. The concentrations calculated from the cell-based activity assay are consistent with the concentrations obtained from the ELISA, which suggests that the variant GLP1 detected by ELISA is biologically active.

Example 15

GLP1, glucagon, and IgG Fc fusion proteins

[00233] To investigate a long acting GLP1 receptor and Glucagon receptor dual agonist, contiguous polypeptides comprising a GLP1 polypeptide, a glucagon polypeptide, and an IgG Fc polypeptide having the following constructs were designed:

Formula (IV): GLP1—L1—Fc—L2—Gluc; and

Formula (V): Gluc—L1—Fc—L2—GLP1,

wherein GLP1 is a GLP1 polypeptide, Gluc is a glucagon polypeptide, L1 and L2 are linkers, and Fc is an Fc polypeptide.

[00234] As discussed above, GLP1 was modified to be DPP-4 resistant by replacing alanine with either glycine or serine at a position corresponding to position 8 of wild-type GLP1 (7-37) (SEQ ID NO: 85). In addition, the DPP-4 resistant GLP1 was further modified by removing the two C-terminal amino acids to generate variant GLP1-S8 (7-35) (SEQ ID NO: 86) and variant GLP1-G8 (7-35) (SEQ ID NO: 87) polypeptides.

[00235] GLP1 polypeptides when positioned at the C-terminus of a construct, such as in Formula (V), are not susceptible to DPP-4 degradation. Therefore, the alanine to glycine or serine substitution is not necessary for GLP1 polypeptides positioned at the C-terminus. Accordingly, wild-type GLP1 (7-37) (SEQ ID NO: 85) may be used at the C-terminus.

[00236] The linker may be a flexible, non-structural linker, such as a glycine- and serine-rich linker. A flexible extension may be added to the C-terminus of the contiguous polypeptide. The extension may comprise a glycine residue (SEQ ID NO: 88), two glycine residues (SEQ ID NO: 89), a three glycine residues (SEQ ID NO: 90), four glycine residues (SEQ ID NO: 91), five glycine residues (SEQ ID NO: 92), six glycine residues (SEQ ID NO: 93), seven glycine residues (SEQ ID NO: 94), eight glycine residues (SEQ ID NO: 95), or more glycine residues.

[00237] The contiguous polypeptide may comprise a wildtype glucagon polypeptide (e.g., SEQ ID NO: 21) or a variant glucagon polypeptide.

[00238] The contiguous polypeptide may comprise a human IgG Fc or an IgG Fc of a companion animal species, such as canine, feline, or equine. The subtype of IgG Fc used may be based on having low or no C1q binding activity and/or having Protein A binding capacity. For example, a wild-type or variant human, canine, equine, or feline IgG Fc having low or no C1q binding and/or having Protein A binding capacity may be used (e.g., SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, or 84).

[00239] Exemplary contiguous polypeptides comprising a GLP1 polypeptide, a Glucagon polypeptide, and a feline IgG Fc polypeptide include GLP1-G8/Gluc-3G_IV_WTfeIgG2 (SEQ ID NO: 52) and Gluc/GLP1-2G_V_WTfeIgG2 (SEQ ID NO: 53).

[00240] Exemplary contiguous polypeptides comprising a GLP1 polypeptide, a Glucagon polypeptide, and a canine IgG Fc polypeptide include GLP1-G8/Gluc-4G_IV_VARcaIgGD (SEQ ID NO: 54) and Gluc/GLP1-3G_V_VARcaIgGD (SEQ ID NO: 55).

[00241] Exemplary contiguous polypeptides comprising a GLP1 polypeptide, a Glucagon polypeptide, and an equine IgG Fc polypeptide include GLP1-G8/Gluc-4G_IV_VAReqIgGD (SEQ ID NO: 56) and Gluc/GLP1-3G_V_VAReqIgG2 (SEQ ID NO: 57).

[00242] Exemplary contiguous polypeptides comprising a GLP1 polypeptide, a Glucagon polypeptide, and a human IgG Fc polypeptide include GLP1-G8/Gluc-4G_IV_huIgG4 (SEQ ID NO: 8) and Gluc/GLP1-3G_V_huIgG4 (SEQ ID NO: 59).

Example 16

Variant IgG Fc polypeptides for enhanced hinge disulfide formation

[00243] Additional three-dimensional protein modeling analysis of several ortholog hinge structures was used to modify feline and equine IgG hinges to enhance disulfide formation. To enhance disulfide formation at the feline IgG hinge, the hinge sequence may be modified by substituting lysine with proline at a position corresponding to position 16 of feline IgG2 (SEQ ID NO: 16), of feline IgG1a (SEQ ID NO: 80 or SEQ ID NO: 117), or of feline IgG1b (SEQ ID NO: 81 or SEQ ID NO: 118) (e.g., K16P). Examples of amino acid sequences of variant feline IgG polypeptides having a modified hinge include SEQ ID NO: 125, SEQ ID NO: 126, and SEQ ID NO: 127.

[00244] To enhance disulfide formation at the equine IgG hinge, the hinge sequence may be modified by substitution cysteine with serine at a position corresponding to position 3 of an equine IgG (e.g., IgG2 Fc (SEQ ID NO: 129)) and/or substituting glutamine with proline at a position corresponding to position 20 of an equine IgG (e.g., IgG2 Fc (SEQ ID NO: 129) (e.g., C3S, Q20P). Examples of amino acid sequences of variant equine IgG polypeptides having a modified hinge include SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 134, and SEQ ID NO: 135.

Example 17

Variant IgG Fc polypeptides for enhanced recombinant production and/or enhanced hinge disulfide formation

[00245] Three-dimensional protein modeling was used to design feline and equine variant IgG Fc polypeptides comprising sequences from the hinge region from a different IgG isotype for enhanced recombinant production and improved hinge disulfide formation. Variant feline IgG2 Fc polypeptides may be prepared that comprise sequences from the hinge region of feline IgG1a or IgG1b (e.g., SEQ ID NO: 125). In addition, variant equine IgG2 Fc polypeptides may be prepared that comprise sequences from the hinge region of equine IgG1 (e.g., SEQ ID NO: 19).

[00246] Levels of recombinant production of variant IgG Fc polypeptides and/or levels of hinge disculfide formation may be determined and compared to that of another IgG Fc by SDS-PAGE analysis under reducing and non-reducing conditions (e.g., the corresponding wild-type

IgG Fc of the same or different isotype, or a wild-type or variant IgG Fc of another companion animal, etc.).

CLAIMS

1. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification relative to a wild-type IgG Fc polypeptide of a companion animal species, wherein the variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

2. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification relative to a wild-type IgG Fc polypeptide of a companion animal species, wherein the variant IgG Fc polypeptide has reduced binding affinity to C1q and/or CD16 relative to the wild-type IgG Fc polypeptide.

3. The polypeptide of claim 1 or claim 2, wherein the variant IgG Fc polypeptide binds to C1q and/or CD16 with a dissociation constant (K_d) of greater than 5×10^{-6} M, greater than 1×10^{-5} M, greater than 5×10^{-5} M, greater than 1×10^{-4} M, greater than 5×10^{-4} M, or greater than 1×10^{-3} M, as measured by biolayer interferometry.

4. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

5. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide binds to Protein A with a dissociation constant (K_d) of less than 5×10^{-6} M, less than 1×10^{-6} M, less than 5×10^{-7} M, less than 1×10^{-7} M, less than 5×10^{-8} M, less than 1×10^{-8} M, less than 5×10^{-9} M, less than 1×10^{-9} M, less than 5×10^{-10} M, less than 1×10^{-10} M, less than 5×10^{-11} M, less than 1×10^{-11} M, less than 5×10^{-12} M, or less than 1×10^{-12} M, as measured by biolayer interferometry.

6. The polypeptide of any one of the preceding claims, wherein the companion animal species is canine, feline, or equine.

7. The polypeptide of any one of the preceding claims, wherein the wild-type IgG Fc polypeptide is

a) a canine IgG-A Fc, IgG-B Fc, IgG-C Fc, or IgG-D Fc;
b) an equine IgG1 Fc, IgG2 Fc, IgG3 Fc, IgG4 Fc, IgG5 Fc, IgG6 Fc, or IgG7 Fc; or
c) a feline IgG1a Fc, IgG1b Fc, or IgG2 Fc.

8. A polypeptide comprising a variant IgG Fc polypeptide comprising at least one amino acid modification to a hinge region relative to a wild-type feline or equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide has increased recombinant production and/or increased hinge disulfide formation relative to the wild-type IgG Fc polypeptide, as determined by SDS-PAGE analysis under reducing and/or nonreducing conditions.

9. The polypeptide of any one the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 20 of SEQ ID NO: 129.

10. The polypeptide of any one the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises an amino acid substitution at position 20 of SEQ ID NO: 129.

11. The polypeptide of any one the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a proline at a position corresponding to

position 16 or at position 16 of SEQ ID NO: 16, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 117, or SEQ ID NO: 118;

b) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a serine at a position corresponding to position 3 or at position 3 of SEQ ID NO: 129; and/or

c) at least one amino acid substitution relative to a wild-type equine IgG Fc polypeptide, wherein the variant IgG Fc polypeptide comprises a proline at a position corresponding to position 20 or at position 20 of SEQ ID NO: 129.

12. The polypeptide of any one the preceding claims, wherein the variant IgG Fc polypeptide comprises a hinge region or a portion of a hinge region from an IgG Fc polypeptide of a different isotype.

13. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises a hinge region or a portion of a hinge region from a wild-type feline IgG-1a Fc polypeptide, from a wild-type feline IgG-1b Fc polypeptide, or from a wild-type equine IgG1 Fc polypeptide.

14. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises SEQ ID NO: 19, SEQ ID NO: 125 or SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID N: 134, SEQ ID NO: 135.

15. A polypeptide comprising an amino acid sequence of SEQ ID NO: 19, SEQ ID NO: 125 or SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID N: 134, SEQ ID NO: 135.

16. A polypeptide comprising a variant IgG2 Fc polypeptide comprising at least one amino acid substitution relative to a wild-type feline IgG2 Fc polypeptide, wherein the at least one amino acid substitution is a cysteine, and wherein the variant IgG2 Fc polypeptide is capable of forming at least one additional inter-chain disulfide linkage relative to the wild-type feline IgG2 Fc polypeptide.

17. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises at least one amino acid substitution relative to a wild-type feline IgG Fc polypeptide, wherein the at least one amino acid substitution is a cysteine, and wherein the variant IgG Fc

polypeptide is capable of forming at least one additional inter-chain disulfide linkage relative to the wild-type feline IgG Fc polypeptide.

18. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises a cysteine at a position corresponding to position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, or position 16 of SEQ ID NO: 16.

19. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises a cysteine at a position corresponding to position 14 of SEQ ID NO: 16.

20. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises a cysteine at position 14 of SEQ ID NO: 16.

21. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide is at least 90% identical, at least 95% identical, at least 97% identical, or at least 99% identical to the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 100, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO:122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

22. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises SEQ ID NO: 17.

23. A polypeptide comprising an amino acid sequence of SEQ ID NO: 17.

24. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 205 of SEQ ID NO: 1, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 1;

b) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 24 of SEQ ID NO: 3;

c) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 4, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 4;

d) an amino acid substitution at a position corresponding to position 15 of SEQ ID NO: 64, and/or an amino acid substitution at a position corresponding to position 203 of SEQ ID NO: 64;

e) an amino acid substitution at a position corresponding to position 199 of SEQ ID NO: 67, and/or an amino acid substitution at a position corresponding to position 200 of SEQ ID NO: 67; and/or

f) an amino acid substitution at a position corresponding to position 199 of SEQ ID NO: 68, an amino acid substitution at a position corresponding to position 200 of SEQ ID NO: 68, an amino acid substitution at a position corresponding to position 201 of SEQ ID NO: 68, and/or an amino acid substitution at a position corresponding to position 202 of SEQ ID NO: 68.

25. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 21 of SEQ ID NO: 1, an amino acid substitution at position 23 of SEQ ID NO: 1, an amino acid substitution at position 25 of SEQ ID NO: 1, an amino acid substitution at position 80 of SEQ ID NO: 1, an amino acid substitution at position 205 of SEQ ID NO: 1, and/or an amino acid substitution at position 207 of SEQ ID NO: 1;
b) an amino acid substitution at position 21 of SEQ ID NO: 3, an amino acid substitution at position 23 of SEQ ID NO: 3, and/or an amino acid substitution at position 24 of SEQ ID NO: 3;
c) an amino acid substitution at position 21 of SEQ ID NO: 4, an amino acid substitution at position 23 of SEQ ID NO: 4, an amino acid substitution at position 25 of SEQ ID NO: 4, an amino acid substitution at position 80 of SEQ ID NO: 4, and/or an amino acid substitution at position 207 of SEQ ID NO: 4;
d) an amino acid substitution at position 15 of SEQ ID NO: 64, and/or an amino acid substitution at position 203 of SEQ ID NO: 64;
e) an amino acid substitution at position 199 of SEQ ID NO: 67, and/or an amino acid substitution at position 200 of SEQ ID NO: 67; and/or
f) an amino acid substitution at position 199 of SEQ ID NO: 68, an amino acid substitution at position 200 of SEQ ID NO: 68, an amino acid substitution at position 201 of SEQ ID NO: 68, and/or an amino acid substitution at position 202 of SEQ ID NO: 68.

26. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a threonine at a position corresponding to position 21 of SEQ ID NO: 1, a leucine at a position corresponding to position 23 of SEQ ID NO: 1, an alanine at a position corresponding to position 25 of SEQ ID NO: 1, a glycine at a position corresponding to position 80 of SEQ ID NO: 1, an alanine at a position corresponding to position 205 of SEQ ID NO: 1, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 1;
b) a threonine at a position corresponding to position 21 of SEQ ID NO: 3, a leucine at a position corresponding to position 23 of SEQ ID NO: 3, and/or an isoleucine at a position corresponding to position 24 of SEQ ID NO: 3;

c) a threonine at a position corresponding to position 21 of SEQ ID NO: 4, a leucine at a position corresponding to position 23 of SEQ ID NO: 4, an alanine at a position corresponding to position 25 of SEQ ID NO: 4, a glycine at a position corresponding to position 80 of SEQ ID NO: 4, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 4;

d) a threonine or a valine at a position corresponding to position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at a position corresponding to position 203 of SEQ ID NO: 64;

e) a leucine at a position corresponding to position 199 of SEQ ID NO: 67, and/or a histidine at a position corresponding to position 200 of SEQ ID NO: 67; and/or

f) a leucine at a position corresponding to position 199 of SEQ ID NO: 68, a histidine at a position corresponding to position 200 of SEQ ID NO: 68, an asparagine at a position corresponding to position 201 of SEQ ID NO: 68, and/or a histidine at a position corresponding to position 202 of SEQ ID NO: 68.

27. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a threonine at position 21 of SEQ ID NO: 1, a leucine at position 23 of SEQ ID NO: 1, an alanine at position 25 of SEQ ID NO: 1, a glycine at position 80 of SEQ ID NO: 1, an alanine at position 205 of SEQ ID NO: 1, and/or a histidine at position 207 of SEQ ID NO: 1;

b) a threonine at position 21 of SEQ ID NO: 3, a leucine at position 23 of SEQ ID NO: 3, and/or an isoleucine at position 24 of SEQ ID NO: 3;

c) a threonine at a position 21 of SEQ ID NO: 4, a leucine at position 23 of SEQ ID NO: 4, an alanine at position 25 of SEQ ID NO: 4, a glycine at position 80 of SEQ ID NO: 4, and/or a histidine at position 207 of SEQ ID NO: 4;

d) a threonine or a valine at position 15 of SEQ ID NO: 64, and/or a tyrosine or a valine at position 203 of SEQ ID NO: 64;

e) a leucine at position 199 of SEQ ID NO: 67, and/or a histidine at position 200 of SEQ ID NO: 67; and/or

f) a leucine at position 199 of SEQ ID NO: 68, a histidine at position 200 of SEQ ID NO: 68, an asparagine at position 201 of SEQ ID NO: 68, and/or a histidine at position 202 of SEQ ID NO: 68.

28. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of:

a) SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, or SEQ ID NO: 84; or
b) SEQ ID NO: 19, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 75, or SEQ ID NO: 76.

29. A polypeptide comprising an amino sequence of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 84, SEQ ID NO: 19, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 75, or SEQ ID NO: 76.

30. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 2, or an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 3;
b) an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 63, an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 65, an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 66, or an amino acid substitution at a position corresponding to position 87 of SEQ ID NO: 69; or
c) an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 80, or an amino acid substitution at a position corresponding to position 198 of SEQ ID NO: 81.

31. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 93 of SEQ ID NO: 2, or an amino acid substitution at position 93 of SEQ ID NO: 3;
b) an amino acid substitution at position 87 of SEQ ID NO: 63, an amino acid substitution at position 87 of SEQ ID NO: 65, an amino acid substitution at position 87 of SEQ ID NO: 66, or an amino acid substitution at position 87 of SEQ ID NO: 69; or
c) an amino acid substitution at position 198 of SEQ ID NO: 80, or an amino acid substitution at position 198 of SEQ ID NO: 81.

32. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an arginine at a position corresponding to position 93 of SEQ ID NO: 2, or an arginine at a position corresponding to position 93 of SEQ ID NO: 3;
b) a serine at a position corresponding to position 87 of SEQ ID NO: 63, a serine substitution at a position corresponding to position 87 of SEQ ID NO: 65, a serine at a position corresponding to position 87 of SEQ ID NO: 66, or a serine at a position corresponding to position 87 of SEQ ID NO: 69; or
c) an alanine at a position corresponding to position 198 of SEQ ID NO: 80, or an alanine at a position corresponding to position 198 of SEQ ID NO: 81.

33. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an arginine at position 93 of SEQ ID NO: 2, or an arginine at position 93 of SEQ ID NO: 3;
b) a serine at position 87 of SEQ ID NO: 63, a serine at position 87 of SEQ ID NO: 65, a serine at position 87 of SEQ ID NO: 66, or a serine at position 87 of SEQ ID NO: 69; or
c) an alanine at position 198 of SEQ ID NO: 80, or alanine at position 198 of SEQ ID NO: 81.

34. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises the amino acid sequence of:

a) SEQ ID NO: 78, SEQ ID NO: 79, or SEQ ID NO: 84; or
b) SEQ ID NO: 70, SEQ ID NO: 73, SEQ ID NO: 74, or SEQ ID NO: 77; or
c) SEQ ID NO: 82 or SEQ ID NO: 83.

35. A polypeptide comprising an amino sequence of SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 70, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 82, or SEQ ID NO: 83.

36. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 2, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 3.

37. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 5 of SEQ ID NO: 2, an amino acid substitution at position 38 of SEQ ID NO: 2, an amino acid substitution at position 39 of SEQ ID NO: 2, an amino acid substitution at position 97 of SEQ ID NO: 2, and/or an amino acid substitution at position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at position 5 of SEQ ID NO: 3, an amino acid substitution at position 38 of SEQ ID NO: 3, an amino acid substitution at position 39 of SEQ ID NO: 3, an amino acid substitution at position 97 of SEQ ID NO: 3, and/or an amino acid substitution at position 98 of SEQ ID NO: 3.

38. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a proline at a position corresponding to position 5 of SEQ ID NO: 2, a glycine at a position corresponding to position 38 of SEQ ID NO: 2, an arginine at a position corresponding to position 39 of SEQ ID NO: 2, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 2, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 2; or

b) a proline at a position corresponding to position 5 of SEQ ID NO: 3, a glycine at a position corresponding to position 38 of SEQ ID NO: 3, an arginine at a position corresponding to position 39 of SEQ ID NO: 3, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 3, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 3.

39. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a proline at position 5 of SEQ ID NO: 2, a glycine at position 38 of SEQ ID NO: 2, an arginine at position 39 of SEQ ID NO: 2, an isoleucine at position 97 of SEQ ID NO: 2, and/or a glycine at position 98 of SEQ ID NO: 2; or

b) a proline at position 5 of SEQ ID NO: 3, a glycine at position 38 of SEQ ID NO: 3, an arginine at position 39 of SEQ ID NO: 3, an isoleucine at position 97 of SEQ ID NO: 3, and/or a glycine at position 98 of SEQ ID NO: 3.

40. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of:

a) SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, or SEQ ID NO: 147; or

b) SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

41. A polypeptide comprising an amino sequence of SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, or SEQ ID NO: 157.

42. A polypeptide comprising a variant IgG Fc polypeptide comprising:

a) a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 1, a tyrosine or a tryptophan at aposition corresponding to position 137 of SEQ ID NO: 2, a tyrosine or a tryptophan at a position corresponding to position 137 of SEQ ID NO: 3, or a tyrosine or a tryptophan at a position corresponding to position 138 of SEQ ID NO: 4; or

b) a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 16, a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118.

43. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a tyrosine or a tryptophan at position 138 of SEQ ID NO: 1, a tyrosine or a tryptophan at position 137 of SEQ ID NO: 2, a tyrosine or a tryptophan at position 137 of SEQ ID NO: 3, or a tyrosine or a tryptophan at position 138 of SEQ ID NO: 4; or

b) a tyrosine or a tryptophan at position 154 of SEQ ID NO: 16, a tyrosine or a tryptophan at position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a tyrosine or a tryptophan at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118.

44. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

45. A polypeptide comprising an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

46. A contiguous polypeptide comprising the polypeptide of any one of the preceding claims and a glucagon-like peptide-1 (GLP1) polypeptide.

47. A contiguous polypeptide comprising the polypeptide of any one of the preceding claims and a glucagon polypeptide.

48. A polypeptide comprising a variant IgG Fc polypeptide comprising:

a) a serine at a position corresponding to position 138 of SEQ ID NO: 1, a serine at a position corresponding to position 137 of SEQ ID NO: 2, a serine at a position corresponding to position 137 of SEQ ID NO: 3, a serine at a position corresponding to position 138 of SEQ ID NO: 4, a serine at a position corresponding to position 154 of SEQ ID NO: 16, a serine at a position corresponding to position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a serine at a position corresponding to position 154 of SEQ ID NO: 81 or SEQ ID NO: 118;

b) an alanine at a position corresponding to position 140 of SEQ ID NO: 1, an alanine at a position corresponding to position 139 of SEQ ID NO: 2, an alanine at a position corresponding to position 139 of SEQ ID NO: 3, an alanine at a position corresponding to position 140 of SEQ ID NO: 4, an alanine at a position corresponding to position 156 of SEQ ID NO: 16, an alanine at a position corresponding to position 156 of SEQ ID NO: 80 or SEQ ID NO: 117, or an alanine at a position corresponding to position 156 of SEQ ID NO: 81 or SEQ ID NO: 118; and/or

c) a threonine at a position corresponding to position 181 of SEQ ID NO: 1, a threonine at a position corresponding to position 180 of SEQ ID NO: 2, a threonine at a position corresponding to position 180 of SEQ ID NO: 3, a threonine at a position corresponding to position 181 of SEQ ID NO: 4, a threonine at a position corresponding to position 197 of SEQ ID NO: 16, a threonine at a position corresponding to position 197 of SEQ ID NO: 80 or SEQ ID NO: 117, or a threonine at a position corresponding to position 197 of SEQ ID NO: 81 or SEQ ID NO: 118.

49. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises:

a) a serine at position 138 of SEQ ID NO: 1, a serine at position 137 of SEQ ID NO: 2, a serine at position 137 of SEQ ID NO: 3, a serine at position 138 of SEQ ID NO: 4, a serine at position 154 of SEQ ID NO: 16, a serine at position 154 of SEQ ID NO: 80 or SEQ ID NO: 117, or a serine at position 154 of SEQ ID NO: 81 or SEQ ID NO: 118;

b) an alanine at position 140 of SEQ ID NO: 1, an alanine at position 139 of SEQ ID NO: 2, an alanine at position 139 of SEQ ID NO: 3, an alanine at position 140 of SEQ ID NO: 4, an alanine at position 156 of SEQ ID NO: 16, an alanine at position 156 of SEQ ID NO: 80 or SEQ ID NO: 117, or an alanine at position 156 of SEQ ID NO: 81 or SEQ ID NO: 118; and/or;

c) a threonine at position 181 of SEQ ID NO: 1, a threonine at position 181 of SEQ ID NO: 2, a threonine at position 181 of SEQ ID NO: 3, a threonine at position 181 of SEQ ID NO: 4, a threonine at position 197 of SEQ ID NO: 16, a threonine at position 197 of SEQ ID NO: 80 or SEQ ID NO: 117, or a threonine at position 197 of SEQ ID NO: 81 or SEQ ID NO: 118.

50. The polypeptide of any one of the preceding claims, wherein the variant IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 124.

51. A polypeptide comprising an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 124.

52. The polypeptide of any one of the preceding claims, wherein the polypeptide is glycoslylated.

53. The polypeptide of any one of claims 1 to 51, wherein the polypeptide is aglycosylated.

54. A contiguous polypeptide comprising the polypeptide of any one of claims 48 to 53 and a glucagon-like peptide-1 (GLP1) polypeptide.

55. A contiguous polypeptide comprising the polypeptide of any one of claims 48 to 53 and a glucagon polypeptide.

56. A heterodimeric protein comprising the contiguous polypeptide of claim 46 and the contiguous polypeptide of claim 54.

57. A heterodimeric protein comprising the contiguous polypeptide of claim 47 and the contiguous polypeptide of claim 55.

58. The contiguous polypeptide or heterodimeric protein of any one of claims 46, 47, or 54 to 57, wherein the GLP1 polypeptide is a wild-type GLP1 polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 85.

59. The contiguous polypeptide or heterodimeric protein of any one of claims 46, 47, or 54 to 58, wherein the GLP1 polypeptide is a variant GLP1 polypeptide.

60. The contiguous polypeptide or heterodimeric protein of any one of claims 46, 47, or 54 to 59, wherein the GLP1 polypeptide comprises the amino acid sequence of SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 98, or SEQ ID NO: 99.

61. The contiguous polypeptide or heterodimeric protein of any one of claims 46, 47, or 54 to 60, wherein the glucagon polypeptide is a wild-type glucagon polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 21.

62. The contiguous polypeptide or heterodimeric protein of any one of claims 46, 47, or 54 to 61, wherein the glucagon polypeptide is a variant glucagon polypeptide.

63. A heterodimeric protein comprising:

i) a first variant canine IgG Fc polypeptide comprising at least one amino acid modification relative to a first wild-type canine IgG Fc polypeptide and a second variant canine IgG Fc polypeptide comprising at least one amino acid modification relative to a second wild-type canine IgG Fc polypeptide; or

ii) a first variant feline IgG Fc polypeptide comprising at least one amino acid modification relative to a first wild-type feline IgG Fc polypeptide and a second variant feline IgG Fc

polypeptide comprising at least one amino acid modification relative to a second wild-type feline IgG Fc polypeptide, wherein:

a) the first variant canine IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 138 of SEQ ID NO: 1, position 137 of SEQ ID NO: 2, position 137 of SEQ ID NO: 3, or position 138 of SEQ ID NO: 4;

b) the second variant canine IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 138, position 140, and/or position 181 of SEQ ID NO: 1, position 137, position 139, and/or position 180 of SEQ ID NO: 2, position 137, position 139, and/or position 180 of SEQ ID NO: 3, or position 138, position 140, and/or position 181 of SEQ ID NO: 4;

c) the first variant feline IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 154 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118; and/or

d) the second variant feline IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 154, position 156, and/or position 197 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

64. The heterodimeric protein of claim 63, wherein the first wild-type canine IgG Fc polypeptide and the second wild-type canine IgG Fc polypeptide are from the same IgG subtype and/or the first wild-type feline IgG Fc polypeptide and the second wild-type feline IgG Fc polypeptide are from the same IgG subtype.

65. The heterodimeric protein of claim 63, wherein the first wild-type canine IgG Fc polypeptide and the second wild-type canine IgG Fc polypeptide are from a different IgG subtype and/or the first wild-type feline IgG Fc polypeptide and the second wild-type feline IgG Fc polypeptide are from the same IgG subtype.

66. The heterodimeric protein of any one of claims 63 to 65, wherein:

a) the first variant canine IgG Fc polypeptide comprises a tyrosine or tryptophan at a position corresponding to position 138 of SEQ ID NO: 1, position 137 of SEQ ID NO: 2, position 137 of SEQ ID NO: 3, or position 138 of SEQ ID NO: 4; and/or

b) the first variant feline IgG Fc polypeptide comprises a tryptophan at a position corresponding to position 154 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

67. The heterodimeric protein of any one of claims 63 to 66, wherein:

a) the second variant canine IgG Fc polypeptide comprises a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 1, a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 2, a serine at a position corresponding to position 137, an alanine at a position corresponding to position 139, and/or a threonine at a position corresponding to position 180 of SEQ ID NO: 3, and/or a serine at a position corresponding to position 138, an alanine at a position corresponding to position 140, and/or a threonine at a position corresponding to position 181 of SEQ ID NO: 4; and/or

b) the second variant feline IgG Fc polypeptide comprises a serine at a position corresponding to position 154, an alanine at a position corresponding to position 156, and/or a threonine at a position corresponding to position 197 of SEQ ID NO: 6, of SEQ ID NO: 80, of SEQ ID NO: 81, of SEQ ID NO: 117, or of SEQ ID NO: 118.

68. The heterodimeric protein of any one of claims 63 to 67, wherein:

a) the first variant canine IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, or SEQ ID NO: 115; and/or

b) the first variant feline IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 119, SEQ ID NO: 121, or SEQ ID NO: 123.

69. The heterodimeric protein of any one of claims 63 to 68, wherein:

a) the second variant canine IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, or SEQ ID NO: 116; and/or

b) the second variant feline IgG Fc polypeptide comprises an amino acid sequence of SEQ ID NO: 120, SEQ ID NO: 122, or SEQ ID NO: 123.

70. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 69, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type IgG Fc polypeptide and has increased binding affinity to Protein A relative to the wild-type IgG Fc polypeptide.

71. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 70, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 1, an amino acid substitution at a position corresponding to position 205 of SEQ ID NO: 1, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 1;

b) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 24 of SEQ ID NO: 3; or

c) an amino acid substitution at a position corresponding to position 21 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 23 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 25 of SEQ ID NO: 4, an amino acid substitution at a position corresponding to position 80 of SEQ ID NO: 4, and/or an amino acid substitution at a position corresponding to position 207 of SEQ ID NO: 4.

72. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 71, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 21 of SEQ ID NO: 1, an amino acid substitution at position 23 of SEQ ID NO: 1, an amino acid substitution at position 25 of SEQ ID NO: 1, an amino acid substitution at position 80 of SEQ ID NO: 1, an amino acid substitution at position 205 of SEQ ID NO: 1, and/or an amino acid substitution at position 207 of SEQ ID NO: 1;

b) an amino acid substitution at position 21 of SEQ ID NO: 3, an amino acid substitution at position 23 of SEQ ID NO: 3, and/or an amino acid substitution at position 24 of SEQ ID NO: 3; or

c) an amino acid substitution at position 21 of SEQ ID NO: 4, an amino acid substitution at position 23 of SEQ ID NO: 4, an amino acid substitution at position 25 of SEQ ID

NO: 4, an amino acid substitution at position 80 of SEQ ID NO: 4, and/or an amino acid substitution at position 207 of SEQ ID NO: 4.

73. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 72, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a threonine at a position corresponding to position 21 of SEQ ID NO: 1, a leucine at a position corresponding to position 23 of SEQ ID NO: 1, an alanine at a position corresponding to position 25 of SEQ ID NO: 1, a glycine at a position corresponding to position 80 of SEQ ID NO: 1, an alanine at a position corresponding to position 205 of SEQ ID NO: 1, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 1;

b) a threonine at a position corresponding to position 21 of SEQ ID NO: 3, a leucine at a position corresponding to position 23 of SEQ ID NO: 3, and/or an isoleucine at a position corresponding to position 24 of SEQ ID NO: 3; or

c) a threonine at a position corresponding to position 21 of SEQ ID NO: 4, a leucine at a position corresponding to position 23 of SEQ ID NO: 4, an alanine at a position corresponding to position 25 of SEQ ID NO: 4, a glycine at a position corresponding to position 80 of SEQ ID NO: 4, and/or a histidine at a position corresponding to position 207 of SEQ ID NO: 4.

74. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 73, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a threonine at position 21 of SEQ ID NO: 1, a leucine at position 23 of SEQ ID NO: 1, an alanine at position 25 of SEQ ID NO: 1, a glycine at position 80 of SEQ ID NO: 1, an alanine at position 205 of SEQ ID NO: 1, and/or a histidine at position 207 of SEQ ID NO: 1;

b) a threonine at position 21 of SEQ ID NO: 3, a leucine at position 23 of SEQ ID NO: 3, and/or an isoleucine at position 24 of SEQ ID NO: 3; or

c) a threonine at position 21 of SEQ ID NO: 4, a leucine at position 23 of SEQ ID NO: 4, an alanine at position 25 of SEQ ID NO: 4, a glycine at position 80 of SEQ ID NO: 4, and/or a histidine at position 207 of SEQ ID NO: 4.

75. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 74, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide,

and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type IgG Fc polypeptide and has decreased binding affinity to CD16 relative to the wild-type IgG Fc polypeptide.

76. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 75, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 2, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 2, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at a position corresponding to position 5 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 38 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 39 of SEQ ID NO: 3, an amino acid substitution at a position corresponding to position 97 of SEQ ID NO: 3, and/or an amino acid substitution at a position corresponding to position 98 of SEQ ID NO: 3.

77. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 76, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) an amino acid substitution at position 5 of SEQ ID NO: 2, an amino acid substitution at position 38 of SEQ ID NO: 2, an amino acid substitution at position 39 of SEQ ID NO: 2, an amino acid substitution at position 97 of SEQ ID NO: 2, and/or an amino acid substitution at position 98 of SEQ ID NO: 2; or

b) an amino acid substitution at position 5 of SEQ ID NO: 3, an amino acid substitution at position 38 of SEQ ID NO: 3, an amino acid substitution at position 39 of SEQ ID NO: 3, an amino acid substitution at position 97 of SEQ ID NO: 3, and/or an amino acid substitution at position 98 of SEQ ID NO: 3.

78. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 77, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a proline at a position corresponding to position 5 of SEQ ID NO: 2, a glycine at a position corresponding to position 38 of SEQ ID NO: 2, an arginine at a position corresponding to position 39 of SEQ ID NO: 2, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 2, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 2; or

b) a proline at a position corresponding to position 5 of SEQ ID NO: 3, a glycine at a position corresponding to position 38 of SEQ ID NO: 3, an arginine at a position corresponding to position 39 of SEQ ID NO: 3, an isoleucine at a position corresponding to position 97 of SEQ ID NO: 3, and/or a glycine at a position corresponding to position 98 of SEQ ID NO: 3.

79. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 78, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises:

a) a proline at position 5 of SEQ ID NO: 2, a glycine at position 38 of SEQ ID NO: 2, an arginine at position 39 of SEQ ID NO: 2, an isoleucine at position 97 of SEQ ID NO: 2, and/or a glycine at position 98 of SEQ ID NO: 2; or

b) a proline at position 5 of SEQ ID NO: 3, a glycine at position 38 of SEQ ID NO: 3, an arginine at position 39 of SEQ ID NO: 3, an isoleucine at position 97 of SEQ ID NO: 3, and/or a glycine at position 98 of SEQ ID NO: 3.

80. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 79, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises at least one additional amino acid modification relative to a wild-type canine IgG Fc polypeptide and has decreased binding affinity to C1q relative to the wild-type canine IgG Fc polypeptide.

81. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 80, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 2, or an amino acid substitution at a position corresponding to position 93 of SEQ ID NO: 3.

82. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 81, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide,

and/or the second variant IgG Fc polypeptide comprises an amino acid substitution at position 93 of SEQ ID NO: 2, or an amino acid substitution at position 93 of SEQ ID NO: 3.

83. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 82, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an arginine at a position corresponding to position 93 of SEQ ID NO: 2, or an arginine at a position corresponding to position 93 of SEQ ID NO: 3.

84. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 42 to 83, wherein the variant IgG Fc polypeptide, the first variant IgG Fc polypeptide, and/or the second variant IgG Fc polypeptide comprises an arginine at position 93 of SEQ ID NO: 2, or an arginine at position 93 of SEQ ID NO: 3.

85. The polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 1 to 84, wherein the polypeptide is an antibody, an antibody fusion, or a fusion polypeptide.

86. A contiguous polypeptide comprising:

a) a first glucagon-like peptide-1 (GLP1) polypeptide (GLP1A);
b) a first linker (L1);
c) an Fc polypeptide (Fc) of a companion animal species;
d) optionally, a second linker (L2); and
e) optionally, a second GLP1 polypeptide (GLP1B).

87. The contiguous polypeptide of claim 65 comprising:

formula (I): GLP1A—L1—Fc; or

formula (II): Fc—L1—GLP1A.

88. The contiguous polypeptide of claim 65 comprising:

formula (III): GLP1A—L1—Fc—L2—GLP1B.

89. The contiguous polypeptide of any one of claims 86 to 88, wherein GLP1B, if present, comprises the same amino acid sequence as GLP1A.

90. A contiguous polypeptide comprising:

a) a glucagon-like peptide-1 (GLP1) polypeptide;
b) a first linker (L1);

c) an Fc polypeptide (Fc);

d) a second linker (L2); and

e) a glucagon polypeptide (Gluc).

91. The contiguous polypeptide of claim 90 comprising:

Formula (IV): GLP1—L1—Fc—L2—Gluc; or

Formula (V): Gluc—L1—Fc—L2—GLP1.

92. The contiguous polypeptide of any one of claims 86 to 91, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises a wild-type GLP1 polypeptide.

93. The contiguous polypeptide of any one of claims 86 to 92, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises a variant GLP1 polypeptide.

94. The contiguous polypeptide of any one of claims 86 to 93, wherein GLP1A, GLP1, and/or GLP1B, if present, comprises an amino acid sequence of SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 98, or SEQ ID NO: 99.

95. The contiguous polypeptide of any one of claims 86 to 94, wherein the glucagon polypeptide comprises a wild-type glucagon polypeptide, optionally comprising the amino acid sequence of SEQ ID NO: 21.

96. The contiguous polypeptide of any one of claims 86 to 95, wherein the glucagon polypeptide is a variant glucagon polypeptide.

97. The contiguous polypeptide of any one of claims 86 to 96, wherein the Fc polypeptide is a human IgG Fc.

98. The contiguous polypeptide of any one of claims 86 to 97, wherein the Fc polypeptide is a human IgG1 Fc, IgG2 Fc, IgG3 Fc, or IgG4 Fc.

99. The contiguous polypeptide of any one of claims 86 to 98, wherein the Fc polypeptide is an Fc of a companion animal species.

100. The contiguous polypeptide of any one of claims 86 to 97 or 99, wherein the Fc polypeptide comprises:

a) a canine IgG-A Fc, IgG-B Fc, IgG-C Fc, or IgG-D Fc;

b) an equine IgG1 Fc, IgG2 Fc, IgG3 Fc, IgG4 Fc, IgG5 Fc, IgG6 Fc, or IgG7 Fc; or

c) a feline IgG1a Fc, IgG1b Fc, or IgG2 Fc.

101. The contiguous polypeptide of any one of claims 86 to 100, wherein the Fc polypeptide is a wild-type IgG Fc polypeptide.

102. The contiguous polypeptide of any one of claims 86 to 100, wherein the Fc polypeptide is a variant IgG Fc polypeptide.

103. The contiguous polypeptide of any one of claims 86 to 102, wherein the Fc polypeptide comprises the polypeptide, the contiguous polypeptide, or the heterodimeric protein of any one of claims 1 to 84.

104. The contiguous polypeptide of any one of claims 85 to 102, wherein the contiguous polypeptide has a longer serum half-life than a wild-type GLP1 polypeptide.

105. The contiguous polypeptide of any one of claims 86 to 104, wherein L1 and L2, if present, each independently is a flexible linker.

106. The contiguous polypeptide of any one of claims 86 to 105, wherein the amino acid sequence of L1 and L2, if present, each independently comprises 100%, at least 95%, at least 90%, at least 85% serine and/or glycine amino acid residues.

107. The contiguous polypeptide of any one of claims 86 to 106, wherein the contiguous polypeptide comprises an extension at its C-terminus.

108. The contiguous polypeptide of any one of claims 86 to 107, wherein the contiguous polypeptide comprises a glycine residue, two glycine residues, three glycine residues, four glycine residues, five glycine residues, six glycine residues, seven glycine residues, eight glycine residues, or greater than eight glycine residues at its C-terminus.

109. The contiguous polypeptide of any one of claims 86 to 108, wherein the contiguous polypeptide comprises an amino acid sequence of SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, or SEQ ID NO: 95 at its C-terminus.

110. The contiguous polypeptide of any one of claims 86 to 109, wherein the contiguous polypeptide comprises:

a) the amino acid sequence of SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 46; SEQ ID NO: 47, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, or SEQ ID NO: 106; or

b) the amino acid sequence of SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; or SEQ ID NO: 59.

111. A polypeptide comprising an amino acid sequence of SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 46; SEQ ID NO: 47, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 103; SEQ ID NO: 104, SEQ ID NO: 105, or SEQ ID NO: 106.

112. The polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of the preceding claims, wherein the at least one amino acid modification or substitution comprises an amino acid substitution with an amino acid derivative.

113. An isolated nucleic acid encoding the polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of the preceding claims.

114. A host cell comprising the nucleic acid of claim 113.

115. A method of producing a polypeptide comprising culturing the host cell of claim 114 and isolating the polypeptide.

116. A pharmaceutical composition comprising the polypeptide, the heterodimeric protein, or the contiguous polypeptide of any one of claims 1 to 112, and a pharmaceutically acceptable carrier.

117. A method of increasing production of cAMP in a cell, the method comprising exposing the cell to the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the

pharmaceutical composition of any one of claims 1 to 112 or 116 under conditions permissive for binding of the polypeptide, heterodimeric protein, or contiguous polypeptide to GLP1R.

118. The method of claim 117, wherein the cell is exposed to the polypeptide, heterodimeric protein, contiguous polypeptide, or the pharmaceutical composition ex vivo.

119. The method of claim 117, wherein the cell is exposed to the polypeptide, heterodimeric protein, contiguous polypeptide, or the pharmaceutical composition in vivo.

120. The method of any one of claims 118 to 119, whererin the cell is a human cell, a canine cell, a feline cell, or an equine cell.

121. A method of delivering a polypeptide to a subject comprising administering the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of claims 1 to 112 or 116 parenterally.

122. A method of delivering a polypeptide to a subject comprising administering the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of claims 1 to 112 or 116 by an intramuscular route, an intraperitoneal route, an intracerebrospinal route, a subcutaneous route, an intra-arterial route, an intrasynovial route, an intrathecal route, or an inhalation route.

123. A method of treating a subject having diabetes or obesity, the method comprising administering to the subject a therapeutically effective amount of the polypeptide, the heterodimeric protein, the contiguous polypeptide, or the pharmaceutical composition of any one of claims 1 to 112 or 116.

124. The method of claim 123, comprising administering insulin, a DPP4 inhibitor, a SGLT2 inhibitor, a biguanides sulfonylureas meglitinide derivative, an alpha-glucosidase inhibitor, a thiazolidinedion (TZD), an amylinomimetic, a bile acid sequestrant, a dopamine agonist.

125. The method of any one of claims 121 to 124, wherein the subject is a human subject.

126. The method of any one of claims 121 to 124, wherein the subject is a companion animal species.

127. The method of claim 126, wherein the companion animal species is canine, equine, or feline.

```
IgG-A    PVPEPLGGPSVLIFPPKPKDILRITRTPEVTCVVLDLGREDPEVQISWFVDGKEVHTAKT
IgG-D    PVPESLGGPSVFIFPPKPKDILRITRTPEITCVVLDLGREDPEVQISWFVDGKEVHTAKT
IgG-B    PAPEMLGGPSVFIFPPKPKDTLLIARTPEVTCVVVDLDPEDPEVQISWFVDGKQMQTAKT
IgG-C    PGCGLLGGPSVFIFPPKPKDILVTARTPTVTCVVVDLDPENPEVQISWFVDSKQVQTANT
         *    ******:******** *  :*** :****:**. *:**********.*:::**:*

IgG-A    QSREQQFNGTYRVVSVLPIEHQDWLTGKEFKCRVNHIDLPSPIERTISKARGRAHKPSVY
IgG-D    QPREQQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNHIGLPSPIERTISKARGQAHQPSVY
IgG-B    QPREEQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTISKARGQAHQPSVY
IgG-C    QPREEQSNGTYRVVSVLPIGHQDWLSGKQFKCKVNNKALPSPIEEIISKTPGQAHQPNVY
         * **:* *.********** *****.**:*.*:**:  ******. ***: *:**:*.**

IgG-A    VLPPSPKELSSSDTVSITCLIKDFYPPDIDVEWQSNGQQEPERKHRMTPPQLDEDGSYFL
IgG-D    VLPPSPKELSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPEPESKYHTTAPQLDEDGSYFL
IgG-B    VLPPSREELS-KNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTTPPQLDEDGSYFL
IgG-C    VLPPSRDEMS-KNTVTLTCLVKDFFPPEIDVEWQSNGQQEPESKYRMTPPQLDEDGSYFL
         *****  .*:*  .:**::***:***:**:********** *** *:: * **********

IgG-A    YSKLSVDKSRWQQGDPFTCAVMHETLQNHYTDLSLSHSPGK
IgG-D    YSKLSVDKSRWQQGDTFTCAVMHEALQNHYTDLSLSHSPGK
IgG-B    YSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK
IgG-C    YSKLSVDKSRWQRGDTFICAVMHEALHNHYTQISLSHSPGK
         ************:** * ******:*:****: ********

IgG-A    SEQ ID NO: 1
IgG-D    SEQ ID NO: 4
IgG-B    SEQ ID NO: 2
IgG-C    SEQ ID NO: 3
```

Fig. 1

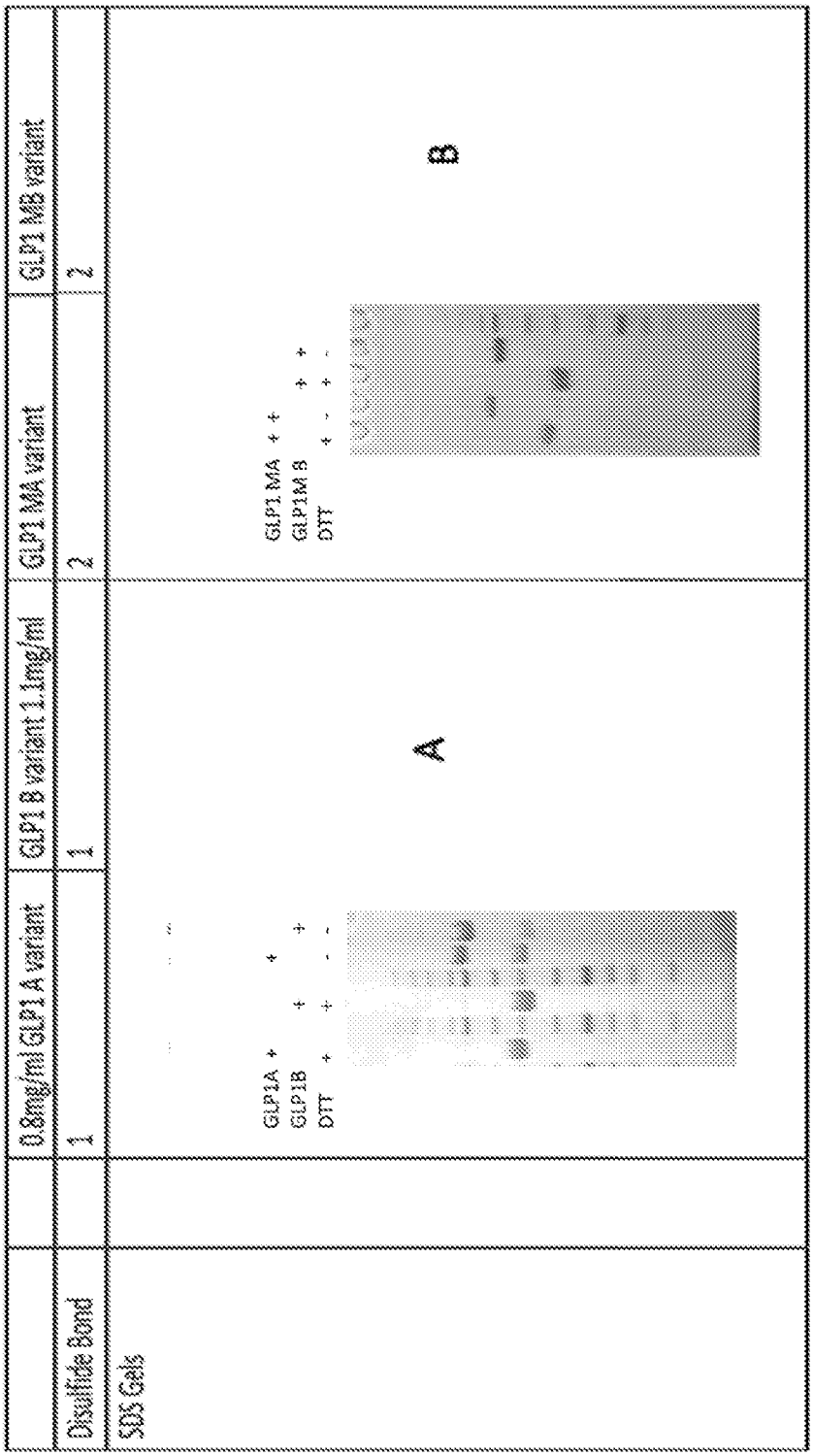
0.8mg/ml GLP1 A variant
GLP1 B variant 1.1mg/ml
GLP1 MA variant
GLP1 MB variant
Disulfide Bond
1
1
2
2
SDS Gels
GLP1A + +
GLP1B + +
DTT + + - -
A
GLP1 MA + +
GLP1M B + +
DTT + - + -
B

Fig. 2

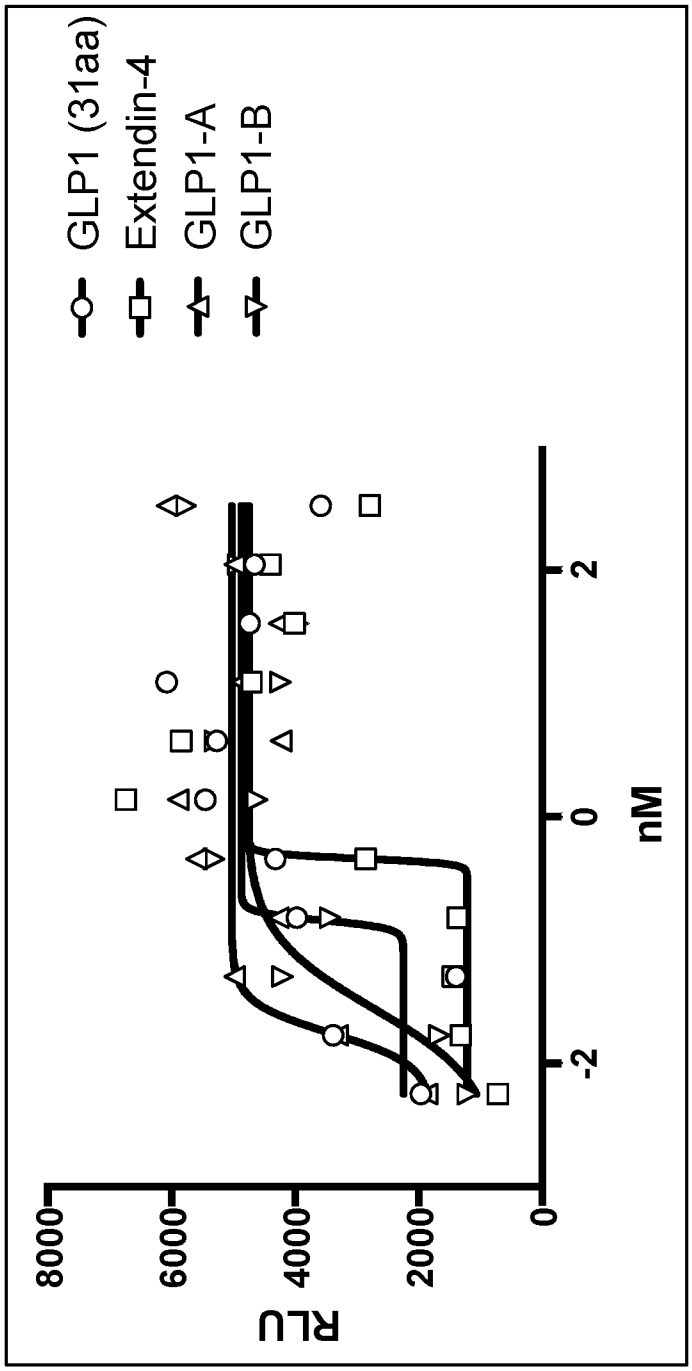
GLP1 (31aa)
Extendin-4
GLP1-A
GLP1-B
RLU
8000
6000
4000
2000
0
-2
0
2
nM

Fig. 3

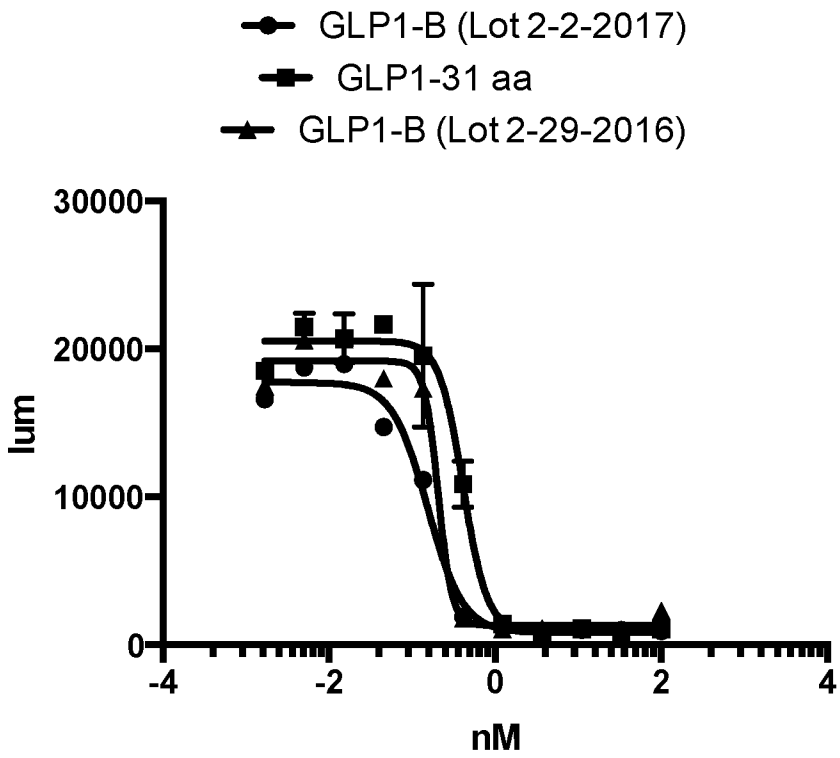
GLP1-B (Lot 2-2-2017)
GLP1-31 aa
GLP1-B (Lot 2-29-2016)
30000
20000
10000
0
lum
-4
-2
0
2
4
nM

Fig. 4

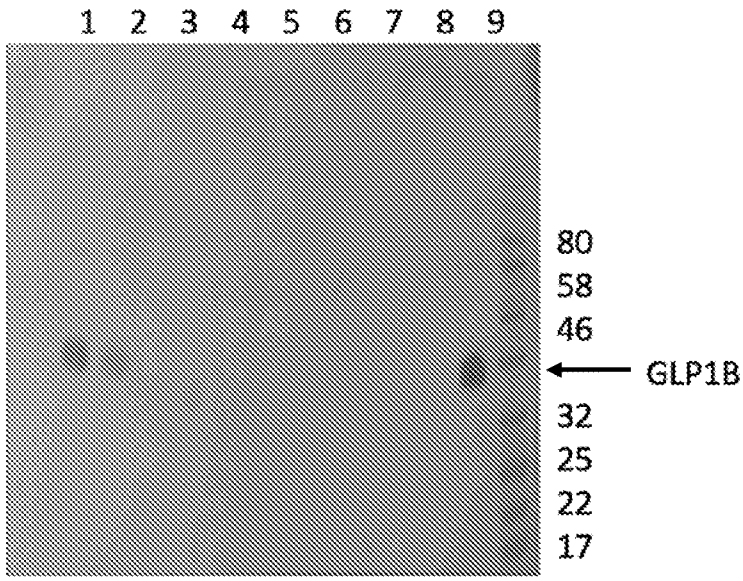
1 2 3 4 5 6 7 8 9
80
58
46
GLP1B
32
25
22
17

Fig. 5

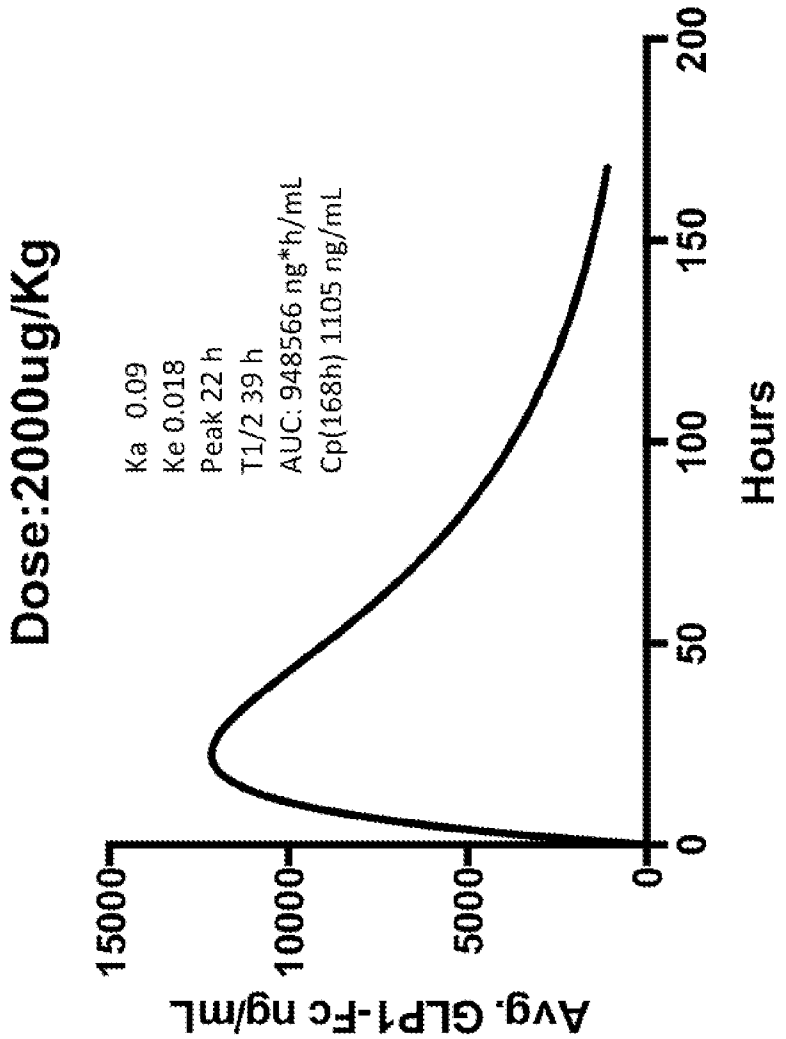
Dose:2000ug/Kg
Ka 0.09
Ke 0.018
Peak 22 h
T1/2 39 h
AUC: 948566 ng*h/mL
Cp(168h) 1105 ng/mL
Avg. GLP1-Fc ng/mL
15000
10000
5000
0
0
50
100
150
200
Hours

Fig. 6

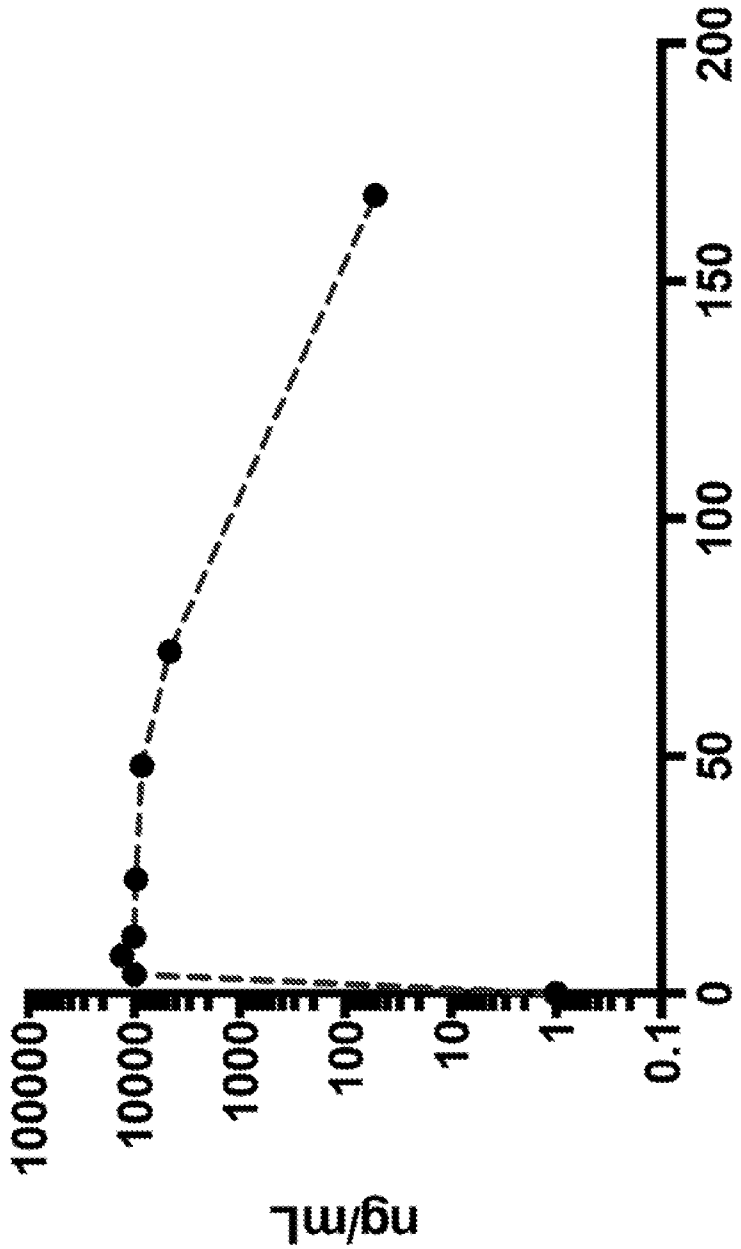

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB18/56142

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 38/17, 39/395, 39/40; C07K 14/31, 16/28; C12N 15/82; G01N 33/68 (2018.01)
CPC - A61K 38/1774, 39/395, 39/40; C07K 14/31, 16/283, C12N 15/8251; G01N 33/6857

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	(NAGAOKA, M et al.) Single amino acid substitution in the mouse IgG1 Fc region induces drastic enhancement of the affinity to protein A. Protein Engineering. April 2003, Vol. 16, No. 4; pages 243-245; abstract; page 243, 1st column, 1st paragraph; DOI: 10.1093/proeng/gzg037	1 -- 3
Y	(CHEN, W et al.) Stabilizing the CH2 domain of an Antibody by Engineering in an Enhanced Aromatic Sequon. ACS Chemical Biology. 15 July 2016, Epub 29 April 2016, Vol. 11, No. 7; pages 1852-1861; abstract; page 4, 3rd paragraph; page 8, 2nd paragraph; page 11, 4th paragraph; Table 1; DOI: 10.1021/acschembio.5b01035	3
A	US 2016/0193295 A1 (AMGEN, INC.) 7 July 2016; paragraph [0036]	15
A	US 2014/0170136 A1 (GEARING, D) 19 June 2014; paragraph [0024]	15
A	US 2014/0328838 A1 (GEARING, D) 6 November 2014; paragraph [0172]	15

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2018 (14.12.2018)	28 JAN 2019
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB18/56142

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-7, 9-14, 17-22, 24-28, 30-34, 36-40, 43, 44, 46, 47, 49, 50, 52-62, 67-85, 92-110, 112-127
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-3, 8, 15, 16, 23, 29, 35, 41, 42, 45, 48, 51, 63-66, a modification that increases binding affinity to Protein A (modification); and SEQ ID NO: 19 (polypeptide sequence) are directed toward variant IgG Fc polypeptides from companion animal species.

-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-3, 8, 15, 16, 23, 29, 35, 41, 42, 45, 48, 51, 63-66, a modification that increases binding affinity to Protein A (modification); and SEQ ID NO: 19 (polypeptide sequence)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

The variant IgG Fc polypeptide will be searched to the extent it encompasses a modification that increases binding affinity to Protein A (first exemplary modification); and SEQ ID NO: 19 (first exemplary polypeptide sequence). Applicant is invited to elect additional modification(s) and/or polypeptide sequence(s), with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO: such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), to be searched. Additional modification(s) and/or polypeptide sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 3 (in-part), and 15 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a modification that increases binding affinity to Protein A (modification); and SEQ ID NO: 19 (polypeptide sequence). Applicants must specify the claims that encompass any additionally elected modification(s) and/or polypeptide sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: a modification that reduces binding affinity to C1q (modification). (It should be noted that applicant will be afforded a first polypeptide SEQ ID NO: or SEQ ID NO: with specified substitution(s) at specified site(s) such that the sequence is fully specified in association with each additionally elected modification).

Groups II+, Claims 86-91, 111, and SEQ ID NO: 23 (polypeptide sequence) are directed toward contiguous polypeptides comprising a GLP1 polypeptide linked to an Fc polypeptide from a companion animal species.

The polypeptides can be searched to the extent that they comprise SEQ ID NO: 23 (first exemplary polypeptide sequence). Applicant is invited to elect additional polypeptide(s) with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), to be searched. Additional polypeptide sequence(s) can be searched upon the payment of additional fees. It is believed that claims 86-91, and 111 (in-part) encompass this first named invention of Groups II+ and thus these claims can be searched with payment of a fee for the search of Groups II+, to the extent that they encompass SEQ ID NO: 23 (polypeptide sequence). Applicants must specify the claims that encompass any additionally elected polypeptide sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups II+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups II+ to be searched/examined. An exemplary election would be SEQ ID NO: 24 (polypeptide sequence).

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include SEQ ID NO: 19, not present in any of Groups II+; the special technical features of Groups II+ include SEQ ID NO: 23, not present in any of Groups I+.

Groups I+ and II+ share the technical features including: an Fc polypeptide (Fc) of a companion animal species. However, these shared technical features are previously disclosed by US 2010/0105877 A1 to Song et al. (hereinafter 'Song').

Song discloses an Fc polypeptide of a companion animal species (an Fc polypeptide of rabbits, coats, hamsters or guinea pigs (a companion animal species); paragraph [0054]).

No technical features are shared between the variant polypeptide sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a polypeptide comprising a variant IgG Fc polypeptide; these shared technical features are previously disclosed by Song, as above.

Song discloses a polypeptide comprising a variant (a polypeptide comprising a variant; paragraph [0050]) IgG Fc polypeptide (IgG Fc polypeptide; paragraph [0050]).

No technical features are shared between the polypeptide sequences of Groups II+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups II+ were considered to share the technical features including: a contiguous polypeptide comprising: a) a glucagon-like peptide-1 (GLP1) polypeptide (GLP1); b) a linker (L1); c) an Fc polypeptide (Fc); these shared technical features are previously disclosed by Song, as above, in view of US 2016/0185837 A1 to Medimmune Limited (hereinafter 'Medimmune').

Song discloses a conjugate comprising: a) a glucagon-like peptide-1 (GLP1) polypeptide (GLP1) (a conjugate comprising: a) a glucagon-like peptide-1 (GLP1) polypeptide (GLP1); abstract; paragraphs [0027]-[0029]); b) a linker (L1) (a linker; abstract; paragraph [0027]); c) an Fc polypeptide (Fc) (an Fc polypeptide (Fc); abstract; paragraphs [0047], [0048]).

Song does not disclose a contiguous polypeptide, comprising a polypeptide linker.

Medimmune discloses GLP-1 agonist polypeptides (GLP-1 agonist polypeptides; abstract) fused to heterologous polypeptides, including a gly-ser type linker (fused to heterologous polypeptides, including a gly-ser type linker; paragraph [0024]) and an Fc domain (and an Fc domain; paragraph [0024]).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Song to have produced the conjugate as a contiguous polypeptide using a polypeptide linker, as disclosed by Medimmune, in order to simplify the production and purification of the conjugate.

Since none of the special technical features of the Groups I+ and II+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Song and Medimmune references, unity of invention is lacking.