CLAIMS

What is claimed is:

1. A water-soluble G-protein coupled receptor (GPCR) polypeptide variant comprising a modified α-helical domain,

   a. wherein the modified α-helical domain comprises an amino acid sequence in which a plurality of hydrophobic amino acid residues within the α-helical domain of a G-protein coupled receptor (GPCR) selected from the group consisting of phenylalanine, isoleucine, valine and leucine are replaced with hydrophilic, non-ionic amino acid residues,

   b. wherein the pI of the polypeptide variant is substantially the same as the pI of the corresponding native GPCR polypeptide.

2. The variant of claim 1, wherein the variant has a biological activity of the native GPCR polypeptide.

3. The variant of claim 2 wherein the biological activity is ligand binding.

4. The variant of claim 3, wherein the variant retains some of the ligand-binding activity of the GPCR.

5. The variant of claim 1 or 4, wherein the hydrophobic amino acid residues are located at α-helical positions b, c and f.

6. The variant of claim 1 or 4, wherein the hydrophobic amino acid residues at α-helical positions a, d, e and g are not replaced.

7. The variant of claim 1 or 4 wherein a plurality of leucines are replaced with glutamine (Q) and/or wherein a plurality of isoleucines are replaced with threonine (T) and/or wherein a plurality of valines are replaced with threonine (T) and/or wherein a plurality of phenylalanines are replaced with tyrosine (Y).

8. The variant of claim 7 wherein all or substantially all of the leucines in the α-helical positions b, c and f in the transmembrane domains are replaced and/or wherein all ~~or substantially all~~ of the isoleucines in the α-helical positions b, c and f in

the transmembrane domains are replaced and/or wherein all ~~or substantially all~~ of the valines in the α-helical positions b, c and f in the transmembrane domains are replaced and/or wherein a plurality of phenylalanines are replaced with tyrosine (Y).

9. The variant of claim 1 or 4 wherein at least one or more leucine residues of the α-helical domain of the native membrane protein are replaced with glutamine (Q), one or more isoleucine and/or valine residues of the α-helical domain of the protein are replaced with threonine (T), one or more phenylalanine residues of the α-helical domain of the native membrane protein are replaced with tyrosine (Y).

10. The variant of claim 1, wherein ~~about~~ 10% to ~~about~~ 100% of the hydrophobic amino acid residues present in the hydrophilic face of α-helical domain is replaced.

11. The variant of claim 10, wherein ~~at least about~~ 15%, or ~~about~~ 25%, or ~~about~~ 50%, or ~~about~~ 70% of the hydrophobic amino acid residues of the α-helical domain is replaced.

12. The variant of claim 1, wherein the GPCR is selected from the group comprising purinergic receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$), M_1 and M_3 muscarinic acetylcholine receptors, receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2], thromboxane (TXA_2), sphingosine 1-phosphate ($S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$), lysophosphatidic acid (LPA_1, LPA_2, LPA_3), angiotensin II (AT_1), serotonin (5-HT_{2c} and 5-HT_4), somatostatin (sst_5), endothelin (ET_A and ET_B), cholecystokinin (CCK_1), V_{1a} vasopressin receptors, D_5 dopamine receptors, fMLP formyl peptide receptors, GAL_2 galanin receptors, EP_3 prostanoid receptors, A_1 adenosine receptors, α_1 adrenergic receptors, BB_2 bombesin receptors, B_2 bradykinin receptors, calcium-sensing receptors, chemokine receptors, KSHV-ORF74 chemokine receptors, NK_1 tachykinin receptors, thyroid-stimulating hormone (TSH) receptors, protease-activated receptors, neuropeptide receptors, adenosine A2B receptors, P2Y purinoceptors, metabolic glutamate receptors, GRK5, GPCR-30, and CXCR4.

13. The variant of claim 1 wherein the GPCR is a CXCR4.

14. Use of the water-soluble polypeptide variant of claim 1 in the manufacture of a medicament for treating a mammal suffering from a disorder or disease that is mediated by the activity of a GPCR polypeptide.

15. A pharmaceutical composition comprising an effective amount of a variant of claim 1, and a pharmaceutically acceptable diluent or carrier.

16. A water soluble GPCR polypeptide variant wherein ~~at least~~ one or more transmembrane domain has been substituted with a peptide selected from the group consisting of SEQ ID NOs. 3, 4, 5, 6, 7, 8 or 9.

17. A water-soluble variant of a G-protein coupled receptor (GPCR) comprising a modified α-helical domain,

    a. wherein ~~at least~~ one or more leucine residues of the α-helical domain of the GPCR are replaced with glutamine (Q), one or more isoleucine and/or valine residues of the α-helical domain of the GPCR are replaced with threonine (T), one or more phenylalanine residues of the α-helical domain of the GPCR are replaced with tyrosine (Y);
    b. wherein said leucine residues, said isoleucine and/or valine residues, and said phenylalanine residues are located at α-helical positions b, c and f; and
    c. wherein hydrophobic amino acid residues at α-helical positions a, d, e and g are not replaced.

18. The water-soluble variant of claim 17, wherein in said variant, 7-transmembrane α-helical hydrophobic residues Leucine (L), isoleucine (I), valine (V), and phenylalanine (F) in hydrophilic surface α-helical positions *b*, *c*, and *f* but not positions *a*, *d*, *e*, and *g* of the GPCR have been substituted by glutamine (Q), threonine (T), threonine (T), and tyrosine (Y), respectively.

19. The variant of claim 1, wherein the variant has a biological activity of the GPCR.

20. The variant of claim 19, wherein the biological activity is ligand-binding.

21. The variant of claim 20, wherein the variant retains some of the ligand-binding activity of GPCR.

22. The variant of claim 18 or 21, wherein the pI of the variant is ~~substantially~~ the same as the pI of the GPCR.

23. The variant of claim 18 or 21, further comprising additional conservative substitutions at other parts of the variant.

24. The variant of claim 18, wherein the GPCR is a mammalian receptor.

25. The variant of claim 18, wherein the GPCR is selected from the group consisting of: purinergic receptors (P2Y1, P2Y2, P2Y4, P2Y6), M1 and M3 muscarinic acetylcholine receptors, receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2], thromboxane (TXA2), sphingosine 1-phosphate (S1P2, S1P3, S1P4 and S1P5), lysophosphatidic acid (LPA1, LPA2, LPA3), angiotensin II (AT1), serotonin (5-HT2c and 5-HT4), somatostatin (sst5), endothelin (ETA and ETB), cholecystokinin (CCK1), V1a vasopressin receptors, D5 dopamine receptors, fMLP formyl peptide receptors, GAL2 galanin receptors, EP3 prostanoid receptors, A1 adenosine receptors, α1 adrenergic receptors, BB2 bombesin receptors, B2 bradykinin receptors, calcium-sensing receptors, chemokine receptors, KSHV-ORF74 chemokine receptors, NK1 tachykinin receptors, thyroid-stimulating hormone (TSH) receptors, protease-activated receptors, neuropeptide receptors, adenosine A2B receptors, P2Y purinoceptors, metabolic glutamate receptors, GRK5, GPCR-30, and CXCR4.

26. The variant of claim 18 wherein the GPCR is a CXCR4.

27. Use of the water-soluble variant of claim 18 in the manufacture of a medicament for treating a mammal suffering from a disorder or disease that is mediated by the activity of the GPCR.

28. A pharmaceutical composition comprising an effective amount of the variant of claim 18, and a pharmaceutically acceptable diluent or carrier.

29. The variant of claim 18, wherein ~~at least~~ one or more transmembrane domain has a sequence of SEQ ID NO: 3, 4, 5, 6, 7, 8 or 9.

30. The use of claim 14 or claim 27, wherein the disorder or disease is selected from the group consisting of cancer, small cell lung cancer, melanoma, breast cancer, Parkinson's disease, Cardiovascular disease, hypertension, and asthma.