We claim:

1. A fusion protein comprising an insulin polypeptide and an Fc fragment, wherein the insulin polypeptide and the Fc fragment are connected by a linker, wherein the fusion protein comprises the following sequence:

FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGGAGGGGAGGGGAGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYSSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 87).

2. A fusion protein comprising an insulin polypeptide and an Fc fragment, wherein the insulin polypeptide and the Fc fragment are connected by a linker, wherein the Fc fragment is of human origin and comprises the following sequence:

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYX$_1$STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 77) wherein X_1 is S, D, A, or R, wherein the insulin polypeptide consists of an insulin B-chain analog linked to an insulin A-chain analog via a C-chain, wherein the 16th amino acid from the N-terminus of the insulin B-chain analog (i.e., B16) of the insulin polypeptide is alanine (i.e., B16A).

3. The fusion protein of claim 2, wherein the insulin polypeptide comprises the following sequence:
FVNQHLCGSX$_1$LVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCX$_2$STCSLDQLEN
YC (SEQ ID NO: 9), wherein X_1 is not D, and X_2 is not H.

4. The fusion protein of claim 3, wherein the insulin polypeptide comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
C (SEQ ID NO: 10).

5. The fusion protein of claim 2, wherein the linker comprises the following sequence: GGGGGAGGGGAGGGGAGGGGG (SEQ ID NO: 67).

6. The fusion protein of claim 2, wherein the linker comprises the following sequence: GGGGGQGGGGQGGGGQGGGGG (SEQ ID NO: 13).

7. The fusion protein of claim 6, wherein the fusion protein comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGGQGGGGQGGGGQGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYSSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 78).

8. The fusion protein of claim 6, wherein the fusion protein comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGGQGGGGQGGGGQGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYDSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 80).

9. The fusion protein of claim 6, wherein the fusion protein comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGGQGGGGQGGGGQGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 82).

10. The fusion protein of claim 6, wherein the fusion protein comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGGQGGGGQGGGGQGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYRSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 84).

11. The fusion protein of claim 2, wherein the linker comprises the following sequence:

GGGGAGGGG (SEQ ID NO: 11)

12. The fusion protein of claim 11, wherein the fusion protein comprises the following sequence:
FVNQHLCGSHLVEALALVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENY
CGGGGAGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYSSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV

EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG (SEQ ID NO: 89).

13. The fusion protein of claim 2 comprising domains in the following orientation from N- to C- terminus: (N-terminus) — insulin polypeptide — linker — Fc fragment — (C-terminus).

~~14. The fusion protein of claim 2, wherein the fusion protein is a homodimer.~~

~~15. The fusion protein of any of claim 1, claim 7, claim 8, claim 9, claim 10, of claim 12, wherein the fusion protein is a homodimer.~~

~~16~~14. The fusion protein of claim ~~14~~ 2~~or claim 15~~, wherein the fusion protein is a homodimer, and wherein the percentage homodimer of the fusion protein is greater than 90%.

~~17~~15. The fusion protein of claim ~~14 or claim 15~~2, wherein the fusion protein is made using one of HEK293 cells or CHO cells, and the resulting homodimer titer after purification using Protein A beads or a Protein A column is greater than 150 mg/L.

~~18~~16. The fusion protein of claim ~~14 or claim 15~~2, wherein the insulin receptor IC50 for the fusion protein is less than or equal to 5000 nM.

~~19. The fusion protein of claim 14 or 15, wherein the insulin receptor IC50 for the fusion protein is less than or equal to 2400 nM.~~

~~20~~17. The fusion protein of claim ~~14 or 15~~2, wherein the human FcRn receptor EC50 for the fusion protein is less than or equal to 1000 ng/mL.

~~21~~18. The fusion protein of claim ~~14 or 15~~2, wherein the human Fc(gamma)RI receptor assay OD450 Ratio at a biotinylated-Fc(gamma)RI concentration of 3000 ng/mL of the fusion protein is less than or equal to 0.50.

~~22~~19. The fusion protein of claim ~~14 or 15~~2, wherein the human C1q assay OD450 Ratio at a biotinylated-C1q concentration of 1000 ng/mL is less than or equal to 0.35.

~~23~~20. The fusion protein of claim ~~14 or 15~~2, wherein the fusion protein is formulated as a pharmaceutical composition~~.~~, and

~~24. The pharmaceutical composition of claim 23,~~ wherein the fusion protein is present in the pharmaceutical composition at a concentration of about 3 mg/mL or greater.

~~25. The pharmaceutical composition of claim 23, wherein the composition is suitable for subcutaneous administration.~~

26. A method for lowering the blood glucose level of a patient, the method comprising administering a physiologically effective amount of the fusion protein of claim 14 or 15 or a pharmaceutical composition thereof to the patient.

27. The method of claim 26 in which the patient is diagnosed with diabetes.

28. The method of claim 26, wherein the fusion protein is administered subcutaneously.

29. The method of claim 26, wherein the fusion protein is administered daily, twice weekly, or once weekly to the patient.

30. The method of claim 26, wherein the fusion protein is administered once weekly to the patient at a dose between 0.025 and 0.5 mg/kg/week.

31. A cell engineered to express the fusion protein of any of claim 1, claim 7, claim 8, claim 9, claim 10, of claim 12.

32. The cell of claim 31, wherein the cell is transfected with a nucleic acid encoding the fusion protein.

33. The cell of claim 31, wherein the cell is a HEK293 cell or a CHO cell.

34. A cDNA encoding the fusion protein of claim 2.

35. A cDNA encoding the fusion protein of SEQ ID NO: 87 comprising the following nucleic acid sequence:

atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctgg
tggaaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgt
ggaacagtgctgcacctccacctgctccctggaccagctggaaaactactgcggtggcggaggtggtgcaggaggcggtggagcc
ggtggaggtggggctggaggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggacc
gtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagc
cacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagt
acagcagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca
acaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccc
atcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggga
gagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcac
cgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaaga
gcctctccctgtctccgggttag (SEQ ID NO: 88).

36. A cDNA encoding the fusion protein of SEQ ID NO: 78 comprising the following nucleic acid sequence:

~~atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctgg tggaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgt ggaacagtgctgcacctccacctgctccctggaccagctggaaaactactgcggtggcggaggtggtcaaggaggcggtggacag ggtggaggtgggcagggaggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggacc gtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccgaggtcacatgcgtggtggtggacgtgagc cacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagt acagcagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca acaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccc atcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggga gagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcac cgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaaga gcctctccctgtctccgggttag (SEQ ID NO: 79).~~

~~37. A cDNA encoding the fusion protein of SEQ ID NO: 80 comprising the following nucleic acid sequence:~~

~~atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctgg tggaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgt ggaacagtgctgcacctccacctgctccctggaccagctggaaaactactgcggtggcggaggtggtcaaggaggcggtggacag ggtggaggtgggcagggaggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggacc gtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccgaggtcacatgcgtggtggtggacgtgagc cacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagt acgacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca acaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccc atcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggga gagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcac cgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaaga gcctctccctgtctccgggttag (SEQ ID NO: 81).~~

~~38. A cDNA encoding the fusion protein of SEQ ID NO: 82 comprising the following nucleic acid sequence:~~

~~atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctgg tggaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgt ggaacagtgctgcacctccacctgctccctggaccagctggaaaactactgcggtggcggaggtggtcaaggaggcggtggacag ggtggaggtgggcagggaggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggacc gtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccgaggtcacatgcgtggtggtggacgtgagc cacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagt acgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca acaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccc atcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggga~~

~~gagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttag (SEQ ID NO: 83).~~

~~39. A cDNA encoding the fusion protein of SEQ ID NO: 84 comprising the following nucleic acid sequence:~~

~~atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctggtggaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgtggaacagtgctgcacctccacctgctccctggaccagctggaaaaactactgcggtggcggaggtggtcaaggaggcggtggacaggggtggaggtgggcagggaggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacagaagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttag (SEQ ID NO: 85).~~

~~40. A cDNA encoding the fusion protein of SEQ ID NO: 89 comprising the following nucleic acid sequence:~~

~~atggaatggagctgggtctttctcttcttcctgtcagtaacgactggtgtccactccttcgtgaaccagcacctgtgcggctcccacctggtggaagctctggcactcgtgtgcggcgagcggggcttccactacgggggtggcggaggaggttctggtggcggcggaggcatcgtggaacagtgctgcacctccacctgctccctggaccagctggaaaaactactgcggtggcggaggtgccggaggcgggggagacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaeegtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacagcagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctg cacaaccactacacgcagaagagcctctccctgtctccgggttag (SEQ ID NO: 90).~~