CLAIMS

1. An Fc construct comprising:

a). a first polypeptide having the formula A-L-B; wherein

i). A comprises a first Fc domain monomer;

ii). L is a linker; and

iii). B comprises a second Fc domain monomer;

b). a second polypeptide having the formula A'-L'-B'; wherein

i). A' comprises a third Fc domain monomer;

ii). L' is a linker; and

iii). B' comprises a fourth Fc domain monomer;

c). a third polypeptide that comprises a fifth Fc domain monomer; and

d). a fourth polypeptide that comprises a sixth Fc domain monomer;

wherein A and A' combine to form a first Fc domain, B and the fifth Fc domain monomer combine to form a second Fc domain, and B' and the sixth Fc domain monomer combine to form a third Fc domain;

the first polypeptide comprises the same amino acid sequence as the second polypeptide, and the third polypeptide comprises the same amino acid sequence as the fourth polypeptide;

the second Fc domain monomer comprises a different amino acid sequence than the fifth Fc domain monomer, and the fourth Fc domain monomer comprises a different amino acid sequence than the sixth Fc domain monomer, and

each of the first, second, third, fourth, fifth, and sixth Fc domain monomers comprises a human IgG1 CH2 domain monomer and a human IgG1 CH3 domain monomer, wherein each CH3 domain monomer has no more than 10 single amino acid substitutions to promote complementary dimerization of Fc domain monomers.

2. The Fc construct of claim 1, wherein

each of the CH3 domain monomers of the first and third Fc domain monomers comprises a complementary dimerization selectivity module that promote dimerization between the first Fc domain monomer and the third Fc domain monomer,

each of the CH3 domain monomers of the second and fifth Fc domain monomers comprises a complementary dimerization selectivity module that promote dimerization between the second Fc domain monomer and the fifth Fc domain monomer, and/or

each of the CH3 domain monomers of the fourth and sixth Fc domain monomers comprises a complementary dimerization selectivity module that promote dimerization between the fourth Fc domain monomer and the sixth Fc domain monomer.

3. The Fc construct of claim 2, wherein the complementary dimerization selectivity modules of the first and third Fc domain monomers each comprise reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domain monomers of the first and third Fc domain monomers.

4. The Fc construct of claim 3, wherein the reverse charge mutations in at least two positions are K409D/D399K, K392D/D399K, E357K/K370E, D356K/K439D, K409E/D399K, K392E/D399K, E357K/K370D, or D356K/K439E (all positions by EU Kabat numbering system).

5. The Fc construct of claim 2, wherein the complementary dimerization selectivity modules of the first and third Fc domain monomers comprise quadruple reverse charge mutations in four positions at the interface between the C_H3 domain monomers of the first and third Fc domain monomers.

6. The Fc construct of claim 5, wherein the quadruple reverse charge mutations combine any pair of double mutations selected from K409D/D399K, K392D/D399K, E357K/K370E, D356K/K439D, K409E/D399K, K392E/D399K, E357K/K370D, and D356K/K439E (all positions by EU Kabat numbering system).

7. The Fc construct of claim 2, wherein one of the complementary dimerization selectivity modules of the second and fifth Fc domain monomers comprises an

engineered protuberance and the other of the complementary dimerization selectivity modules of the second and fifth Fc domain monomers comprises an engineered cavity.

8. The Fc construct of claim 2, wherein one of the complementary dimerization selectivity modules of the fourth and sixth Fc domain monomers comprises an engineered protuberance and the other of the complementary dimerization selectivity modules of the fourth and sixth Fc domain monomers comprises an engineered cavity.

9. The Fc construct of claim 2, wherein the complementary dimerization selectivity modules of the second and fourth Fc domain monomers each comprise an engineered protuberance and the complementary dimerization selectivity modules of the fifth and sixth Fc domain monomers each comprise an engineered cavity.

10. The Fc construct of claim 9, wherein the engineered protuberance comprises at least one mutation selected from the group consisting of S354C, T366W, T366Y, T394W, T394F, and F405W and the engineered cavity comprises at least one mutation selected from the group consisting of Y349C, T366S, L368A, Y407V, Y407T, Y407A, F405A, and T394S (all positions by EU Kabat numbering system).

11. The Fc construct of claim 2, wherein the complementary dimerization selectivity modules of the second and fourth Fc domain monomers each comprise an engineered cavity and the complementary dimerization selectivity modules of the fifth and sixth Fc domain monomers each comprise an engineered protuberance.

12. The Fc construct of claim 11, wherein the engineered cavity comprises at least one mutation selected from the group consisting of Y349C, T366S, L368A, Y407V, Y407T, Y407A, F405A, and T394S and the engineered protuberance comprises at least one mutation selected from the group consisting of S354C, T366W, T366Y, T394W, T394F, and F405W (all positions by EU Kabat numbering system).

13. The Fc construct of claim 1, wherein the Fc construct contains no more than three Fc domains.

14. The Fc construct of claim 1, wherein one or more linker in said Fc construct is a spacer.

15. A pharmaceutical composition comprising a substantially homogenous population of the Fc construct of claim 1 and one or more pharmaceutically acceptable carriers or excipients.

16. The Fc construct of any of claims 1-14 and 17-23 for use as a medicament.

17. The Fc construct of claim 2,

wherein the CH3 domain monomers of the first and the third Fc domain monomers dimerize and each of the complementary dimerization selectivity modules of the first and third Fc domain monomers comprises reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domain monomers of the first and the third Fc domain monomers;

wherein the CH3 domain monomers of the second and the fifth Fc domain monomers dimerize, the complementary dimerization selectivity module of the second
Fc domain monomer comprises an engineered protuberance, and the complementary dimerization selectivity module of the fifth Fc domain monomer comprises an engineered cavity; and

wherein the CH3 domain monomers of the fourth and sixth Fc domain monomers dimerize, the complementary dimerization selectivity module of the fourth Fc domain monomer comprises an engineered protuberance, and the complementary dimerization selectivity module of the sixth Fc domain monomer comprises an engineered cavity.

18. The Fc construct of claim 2,

wherein the CH3 domain monomers of the first and the third Fc domain monomers dimerize, the complementary dimerization selectivity module of the first Fc domain monomer comprises an engineered protuberance, and the complementary dimerization selectivity module of the third Fc domain monomer comprises an engineered cavity;

wherein the CH3 domain monomers of the second and the fifth Fc domain monomers dimerize and each of the complementary dimerization selectivity modules of the second and fifth Fc domain monomers comprises reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domains of the second and the fifth Fc domain monomers; and

wherein the CH3 domain monomers of the fourth and sixth Fc domain monomers dimerize and each of the complementary dimerization selectivity modules of the fourth and sixth Fc domain monomers comprises reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domains of the fourth and sixth Fc domain monomers.

19. The Fc construct of claim 2,

wherein the CH3 domain monomers of the first and third Fc domain monomers dimerize, the complementary dimerization selectivity module of the first Fc domain monomer comprises an engineered cavity, and the complementary dimerization selectivity module of the third Fc domain monomer comprises an engineered protuberance;

wherein the CH3 domain monomers of the second and the fifth Fc domain monomers dimerize and each of the complementary dimerization selectivity modules of the second and fifth Fc domain monomers comprises reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domains of the second and the fifth Fc domain monomers; and

wherein the CH3 domain monomers of the fourth and sixth Fc domain monomers dimerize and each of the complementary dimerization selectivity modules of the fourth and sixth Fc domain monomers comprises reverse charge mutations in at least two positions within a ring of charged residues at the interface between the CH3 domains of the fourth and the sixth Fc domain monomers.

20. The Fc construct of claim 1,

wherein the amino acid sequences of the second and fifth Fc domain monomers differ by two amino acids, and the amino acid sequences of the fourth and sixth Fc domain monomers differ by two amino acids.

21. The pharmaceutical composition of claim 19, wherein the substantially homogenous population is 85% homogenous.

22. The Fc construct of claim 1, wherein each of the first, second, third, fourth, fifth, and sixth Fc domain monomers further comprises a hinge domain or functional fragment thereof.

23. The Fc construct of claim 1, wherein each of the first, second, and third Fc domains are capable of binding to an Fc receptor.

24. A pharmaceutical composition comprising a substantially homogenous population of the Fc construct of any of claims 2-14 and 17-23 and one or more pharmaceutically acceptable carriers or excipients.