Claims

1. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical and,
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH3 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 88, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, and 90 and, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 85.1 and/or 86 and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 88,

and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 86, 88, and 90,
wherein the amino acid residue substituted at position 88 in the parent domain of the first engineered immunoglobulin chain is interacting with the amino acid residue substituted at position 85.1 and/or 86 in the parent domain of the second engineered immunoglobulin chain,
wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

2. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a naturally occurring CH3 domain.

3. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain.

4. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

5. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is not a charged amino acid or is not 88I, wherein the amino acid position is indicated according to the IMGT® numbering.

6. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is 88W and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

7. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted at position 85 and/or 86 in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 85.1A, 85.1S, 85.1C and 85.1N and conservative amino acid substitutions thereof and/or is selected from the group consisting of 86S and 86V and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

8. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88Y, 88K and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20E, 20S, 20K, 20W, 22A, 22G, 22T, 22L, 22I, 22V, 26R, 26Q, 26T, 26K, 26V, 26S, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1F, 85.1C, 85.1N, 85.1W, 86S, 86I, 86T, 86H, 86Q, 86V, 86W, 86Y and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

9. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88Y, and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20E, 20S, 20K, 22A, 22G,

22T, 22L, 22I, 22V, 26Q, 26T, 26K, 26V, 26S, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1F, 85.1C, 85.1N, 86S, 86I, 86T, 86H, 86Q, 86V, and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

10. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3E, 3K, 5A, 5T, 7F, 7M, 20K, 20N, 20T, 22A, 22L, 22V, 26E, 26T, 27E, 27K, 79F, 79Y, 81A, 81G, 81D, 84L, 84M, 84.2E, 84.2S, 85.1A, 85.1C, 85.1M, 85.1N, 85.1S, 86F, 86S, 86V, 90K, 90N, and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

11. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residues at position 88 and at position 20, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

12. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and/or 86 and at position 26 and optionally an amino acid residue at a further position, wherein the amino acid position is indicated according to the IMGT® numbering.

13. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is at a position selected from the group consisting of 20, 22, 26, 79, 85.1, 86, and 90, wherein

the amino acid position of each group member is indicated according to the IMGT® numbering.

14. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20K, 22V, 26T, 79Y, 85.1S, 86V, and 90N and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

15. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at position 84 or is 84L and conservative amino acid substitutions thereof, and optionally a further amino acid at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

16. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

17. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and 86 or comprises 85.1C and conservative amino

acid substitutions thereof and 86S and conservative amino acid substitutions thereof, and wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 3E, 5A, 7F, 20T, 22V, 26T, 81D, 84L, 84.2E, 88R and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

18. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 17, wherein the amino acid residue substitution 85.1C is replaced by amino acid residue substitution 85.1A or 85.1S, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

19. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is at a position selected from the group consisting of 3, 5, 20, 22, 26, 27, 81, 84, 85.1, and 86, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

20. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3K, 5T, 20T, 22L, 26E, 27K, 81G, 84M, 85.1M, 86F and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

21. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at a position selected from the group consisting of 7, 20, 22, 27, 79, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 79, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 79, 81, 84.2,

86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

22. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at position 79 or is 79F and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

23. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and 86 or comprises 85.1N and conservative amino acid substitutions thereof and 86V and conservative amino acid substitutions thereof, and wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 7M, 20N, 22A, 27E, 79F, 81A, 84.2S, 85.1N, 86V, 88L, and 90K and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

24. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is 88I and conservative amino acid substitutions therof and the optional further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is 81W and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the

IMGT® numbering.

25. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical and,
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH3 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 20, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, 88 and 90 and, wherein the amino acid residues which are substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprise the amino acid residues at position 26 and at a further position selected from the group consisting of 3, 22, 27, 79, 81, 84, 85.1, 86, and 88, wherein the amino acid residue substituted at position 20 in the parent domain of the first engineered immunoglobulin chain is interacting with the amino acid residue

substituted at position 26 in the parent domain of the second engineered immunoglobulin chain, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

26. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 20, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, 88 and 90 and, wherein the amino acid residues which are substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at positions 26 and 86 and optionally at a further position selected from the group consisting of 3, 5, 22, 27, 79, 81, 84, 85.1, 88 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

27. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residues which are substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprise the amino acid residues at positions 20 and 22, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 26, 27, 79, 81, 84, 84.2, 85.1, 86, 88 and 90 and, wherein the amino acid residues which are substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprise the amino acid residues at positions 26 and at a further position selected from the group consisting of 3, 5, 22, 27, 79, 81, 84, 85.1, 86, 88 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

28. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residues which are substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprise the amino acid residues at positions 20 and 22, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 26, 27, 79, 81, 84, 84.2, 85.1, 86, 88 and 90 and, wherein the amino acid residues which are substituted in the protein-

protein interface of the parent domain of the second engineered immunoglobulin chain comprise the amino acid residues at positions 26 and 86 and optionally at a further position selected from the group consisting of 3, 5, 22, 27, 79, 81, 84, 85.1, 88 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

29. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a naturally occurring CH3 domain.

30. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain.

31. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

32. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residue which is substituted at position 20 in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20N and 20T, and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

33. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residue which is substituted at position 26 in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is

selected from the group consisting of 26T and 26E and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

34. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residue which is substituted at position 20 in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20K, 20S, 20W and 20E and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 22A, 22G, 22L, 22I, 22V, 22T, 26K, 26R, 26Q, 26T, 26V, 26S, 26N, 26E, 85.1W, 85.1F, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1C, 85.1N, 86W, 86Y, 86S, 86I, 86H, 86Q, 86V, 86T, 86F, 88Q, 88L, 88V, 88R, 88E, 88T, 88I, 88Y, 88K and 88W, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

35. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the amino acid residue which is substituted at position 20 in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20K, 20S and 20E and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 22A, 22G, 22L, 22I, 22V, 26K, 26Q, 26T, 26V, 26S, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1C, 85.1N, 86S, 86I, 86H, 86Q, 86V, 86T, 86F, 88Q, 88L, 88V, 88R, 88E, 88T, 88I, 88Y, and 88W, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

36. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 25, wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3E, 3K, 5A, 5T, 7F, 7M, 22A, 22L, 22V, 26E, 26T, 27E, 27K, 79F, 79Y, 81A, 81G, 81D, 84L, 84M, 84.2E, 84.2S, 85.1A, 85.1C, 85.1M, 85.1N, 85.1S, 86F, 86S, 86V, 88L, 88R, 88W, 90K, 90N, and 90R and conservative amino acid

substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

37. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1-36, wherein the parent domains of the first and second engineered immunoglobulin is the IgG1 CH3 domain.

38. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1-36, wherein the parent domain of the first engineered immunoglobulin chain is an IgG1 CH3 domain and the parent domain of the second engineered immunoglobulin chain is an IgG3 CH3 domain or wherein the parent domain of the first engineered immunoglobulin chain is an IgG3 CH3 domain and the parent domain of the second engineered immunoglobulin chain is an IgG1 CH3 domain.

39. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical and,
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-

dimer or a naturally occurring homo-dimer and,
wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH2 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 88, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3, 85.1, 86 and 90 and, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 85.1 and/or 86 and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3 and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3, 85.1 and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3, 86 and 90, wherein the amino acid residue substituted at position 88 in the parent domain of the first engineered immunoglobulin chain is interacting with the amino acid residue substituted at position 85.1 and/or 86 in the parent domain of the second engineered immunoglobulin chain, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

40. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the parent domain of the first and the second engineered immunoglobulin chain is a naturally occurring CH2 domain.

41. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is 88W and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

42. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain at position 85 and/or 86 is selected from the group consisting of 85.1A and 85.1N and conservative

amino acid substitutions thereof, and/or is 86S and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

43. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88I, 88T, 88K, 88E, 88Y, and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20K, 20W, 20S, 20E, 20Q, 22A, 22G, 22T, 22L, 22V, 26Q, 26T, 26K, 26V, 26S, 26R, 26N, 26E, 85.1R, 85.1H, 85.1K, 85.1T, 85.1M, 85.1A, 85.1S, 85.1W, 85.1F, 85.1C, 85.1N, 86S, 86I, 86H, 86T, 86W, 86Y, 86V, 86Q and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

44. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88I, 88T, 88K, 88E, 88Y, and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20K, 20W, 20S, 22A, 22G, 22T, 22L, 22V, 26Q, 26T, 26K, 26V, 26S, 26R, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1W, 85.1F, 85.1C, 85.1N, 86S, 86I, 86H, 86T, 86W, 86Y, 86V, and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

45. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3E, 3K, 5A, 5T, 5Y, 7M, 7L, 20K, 20N, 20T, 20S, 22A, 22L, 22V, 26E, 26T, 27E, 27K, 79F, 79Y, 81A, 81G, 81D, 83M, 83T, 84L, 84.2E, 84.2S, 84.3D, 85.1S,

85.1A, 85.1N, 85.1M, 85.1F, 86S, 86F, 86Y, 90K, 90N, and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

46. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residues at position 88 and at position 20, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3, 85.1, 86 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

47. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and/or 86 and at position 26 and optionally an amino acid residue at a further position, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

48. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the engineered domain of the first engineered immunoglobulin chain and the

engineered domain of the second engineered immunoglobulin chain are not identical and,

wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,

wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH2 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 20, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 83, 84, 84.2, 84.3, 85.1, 86, 88 and 90 and, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 26 and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 27, 79, 81, 83, 84, 84.2, 84.3, 85.1, 86, 88 and 90, wherein the amino acid residue substituted at position 20 in the parent domain of the first engineered immunoglobulin chain is interacting with the amino acid residue substituted at position 26 in the parent domain of the second engineered immunoglobulin chain, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

49. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a naturally occurring CH2 domain.

50. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the amino acid residue which is substituted at position 20 in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20N and 20T, and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

51. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the amino acid residue which is substituted at position 26 in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 26T and 26E and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering.

52. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 20 is selected from the group consisting of 20V, 20T, 20A, 20N, 20K, 20Q, 20E, 20W and 20S and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 22A, 22G, 22T, 22L, 22V, 22I, 26Q, 26T, 26K, 26V, 26S, 26R, 26N, 26E, 85.1R, 85.1H, 85.1K, 85.1T, 85.1M, 85.1A, 85.1S, 85.1W, 85.1F, 85.1C, 85.1N, 86Q, 86S, 86I, 86H, 86T, 86W, 86Y, 86V, 86F, 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88K, 88Y, and 88W, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

53. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 20 is selected from the group consisting of 20V, 20T, 20A, 20N, 20K, 20W and 20S and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 22A, 22G, 22T, 22L, 22V, 26Q, 26T, 26K, 26V, 26S, 26R, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1W, 85.1F, 85.1C, 85.1N, 86S, 86I, 86H, 86T, 86W, 86Y, 86V, 86F, 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88K, 88Y, and 88W, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

54. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 48, wherein the further amino acid residue substituted in the protein-protein interface of the

parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3E, 3K, 5A, 5T, 5Y, 7M, 7L, 22A, 22L, 22V, 26E, 26T, 27E, 27K, 79F, 79Y, 81A, 81G, 81D, 83M, 83T, 84L, 84.2E, 84.2S, 84.3D, 85.1S, 85.1A, 85.1N, 85.1M, 85.1F, 86S, 86F, 86Y, 88K, 88L, 88R, 88W, 90K, 90N, and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

55. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 39-54, wherein the parent domains of the first and second engineered immunoglobulin chains are an IgG1 CH2 domain or wherein the parent domain of the first engineered immunoglobulin chain is an IgG1 CH2 domain and the parent domain of the second engineered immunoglobulin chain is an IgG3 CH2 domain or wherein the parent domain of the first engineered immunoglobulin chain is an IgG3 CH2 domain and the parent domain of the second engineered immunoglobulin chain is an IgG1 CH2 domain.

56. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1-55, wherein the amino acid residues of the protein-protein interface of the parent domain of the first and/or second engineered immunoglobulin chain which are substituted are not adjacent.

57. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1-55, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the first and/or second engineered immunoglobulin chain are substituted.

58. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and

(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,

wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical and,

wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,

wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH4 domain, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue substitution at a position selected from the group consisting of 20, 22, 85.1, 86, and 88, and/or wherein the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue substitution at a position selected from the group consisting of 22, 26, 85.1, 86, and 88, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

59. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 58, wherein the parent domain of the first and the second engineered immunoglobulin chain is a naturally occurring CH4 domain.

60. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 58, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or

the second engineered immunoglobulin chain.

61. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 58, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

62. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1-61, wherein the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain comprise a further engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said further engineered domain of said first engineered immunoglobulin chain and/or said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family, and
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is interacting with the protein-protein interface of an engineered domain of a third engineered immunoglobulin chain by hetero-dimerization or by homo-dimerization, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said engineered domain of said third engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family, and
wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and of the engineered domain of the third engineered immunoglobulin chain is different

from the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain and of the engineered domain of the second engineered immunoglobulin chain.

63. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 62, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain are naturally occurring domains.

64. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 62, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

65. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 64, wherein the third and the fourth member of the naturally occurring immunoglobulin super-family are selected from the TCR constant domain family.

66. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 62-65, wherein the parent domain of the further engineered domain of the first and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain form a hetero-dimer.

67. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 62-65, wherein the parent domain of the further engineered domain of the first and/or second engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 or is an IGKC domain and the parent domain of the engineered domain of the third engineered immunoglobulin chain is a CH1 domain or, wherein the parent domain of the further engineered domain of the first and/or second engineered immunoglobulin chain is a CH1 domain and the parent domain of the engineered domain of the third engineered

immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 or is an IGKC domain.

68. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 62, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family form a naturally occurring homo-dimer.

69. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 68, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin is a CH3 domain.

70. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 68, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family is the IgG1 CH3 domain.

71. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 68, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family is an IgA1 CH3 domain or an IgA2 CH3 domain.

72. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 62-67, wherein the protein-protein interface of the further engineered domain of the first and/or second engineered immunoglobulin chain is interacting with the protein-protein interface of the engineered domain of the third engineered immunoglobulin chain by hetero-dimerization.

73. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 68-71, wherein the protein-protein interface of the further engineered domain of

the first and/or second engineered immunoglobulin chain is interacting with the protein-protein interface of the engineered domain of the third engineered immunoglobulin chain by homo-dimerization.

74. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 62-73, wherein the amino acid residues from the protein-protein interface of the donor domain of the third and the fourth member of the naturally occurring immunoglobulin super-family are amino acids non essential to the core integrity of the domain.

75. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1-74, wherein the first and second engineered immunoglobulin chains comprise an Fc region.

76. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 62-75, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and/or of the parent domain of the engineered domain of the third engineered immunoglobulin chain are substituted.

77. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1-76, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof is a full-length antibody.

78. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 62 or 77, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the full-length antibody is bispecific.

79. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 78, wherein the bispecific hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the bispecific full-length antibody binds to antigens selected from the group

consisting of HER2, EGFR, CD19, and VLA-2.

80. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof any one of claims 1-79 wherein at least one additional polypeptide is fused to the first and/or second engineered immunoglobulin chain.

81. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 80, wherein said additional polypeptide is selected from the group consiting of Fab, scFv, diabody, domain antibody, pharmacologically active peptide or protein, receptor extracellular domain, CDR grafted polypeptide, and therapeutic engineered protein scaffold.

82. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the parent domains of the first and the second engineered immunoglobulin chain are not a CH2 domain, not a CH3 domain, not a VL domain and not a VH domain and, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue substitution at a

position selected from the group consisting of 20, 22, 85.1, 86, and 88, and wherein, if the parent domain of the first engineered immunoglobulin chain is an IGLC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 5 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 20, the substituted amino acid residue at position 5 and the substituted amino acid residue at position 20 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 20 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 26, the substituted amino acid residue at position 20 and the substituted amino acid residue at position 26 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 86 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 86, the substituted amino acid residues at both positions 86 are not a charged pair,

wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

83. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82, wherein the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue substitution at a position selected from the group consisting of 22, 26, 85.1, 86, and 88, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

84. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the parent domains of the first and the second engineered immunoglobulin chain are naturally occurring domains.

85. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 wherein, if the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 20 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 5, the substituted amino acid residue at position 5 and the substituted amino acid residue at position 20 are not a charged pair and wherein, if the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 86 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 86, the substituted amino acid residues at both positions 86 are not a charged pair, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

86. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain is interacting with the protein-protein interface of the engineered domain of the second engineered immunoglobulin chain by hetero-dimerization.

87. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is not a CH4 domain.

88. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a domain selected from the group consisting of CH1 domain, CH4 domain, IGKC domain, IGLC1 domain, IGLC2 domain, IGLC3 domain, IGLC6 domain, and IGLC7 domain.

89. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain.

90. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 and the parent domain of the second engineered immunoglobulin chain is a CH1 domain.

91. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20E, 20K, 20W, 20S, 22A, 22G, 22T, 22L, 22I, 22V, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1W, 85.1F, 85.1C, 85.1N, 86S, 86I, 86T, 86H, 86Q, 86V, 86W, 86Y, 86F, 88Q, 88L, 88V, 88R, 88E, 88T, 88I, 88K, 88Y, and 88W and/or wherein the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 22A, 22G, 22T, 22L, 22I, 22V, 26Q, 26T, 26K, 26V, 26S, 26R, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1W, 85.1F, 85.1C, 85.1N, 86S, 86I, 86T, 86H, 86Q, 86V, 86W, 86Y, 86F, 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88K, 88Y, and 88W, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

92. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 20K, 20N, 20T, 20S, 22A, 22L, 22V, 22T, 85.1S, 85.1A, 85.1N, 85.1M, 85.1F, 86S, 86T, 86F, 86Y, 86V, 88W, 88R, 88L, 88I, and 88K and conservative amino acid substitutions thereof and/or the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 22A, 22L, 22V, 22T, 26E, 26T, 26K, 26R, 85.1S, 85.1A, 85.1N, 85.1M, 85.1F, 86S, 86T, 86F, 86Y, 86V, 88W, 88R, 88L, 88I and 88K and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

93. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 83, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 20K, 20N, 20T, 20S, 22A, 22L, 22V, 22T, 85.1S, 85.1A, 85.1N, 85.1M, 85.1F, 86S, 86F, 86Y, 86V, 88W, 88R, 88L, and 88K and conservative amino acid substitutions thereof and/or, wherein the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue substitution selected from the group consisting of 22A, 22L, 22V, 22T, 26E, 26T, 26K, 85.1S, 85.1A, 85.1N, 85.1M, 85.1F, 86S, 86F, 86Y, 86V, 88W, 88R, 88L, and 88K and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

94. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-93, wherein if the substitution in the parent domain of the first engineered immunoglobulin chain is at position 88, the substituted amino acid residue in the parent domain of the second engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 88 in the parent domain of the first engineered immunoglobulin chain is at position 85.1 and/or 86, or if the substitution in the parent domain of the second engineered immunoglobulin chain is at position 88, the substituted amino acid residue in the parent domain of the first engineered

immunoglobulin chain which interacts with the substituted amino acid residue at position 88 in the parent domain of the second engineered immunoglobulin chain is at position 85.1 and/or 86, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

95. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-93, wherein if the substitution in the parent domain of the first engineered immunoglobulin chain is at position 85.1, the substituted amino acid residue in the parent domain of the second engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 85.1 in the parent domain of the first engineered immunoglobulin chain is at position 86, or if the substitution in the parent domain of the second engineered immunoglobulin chain is at position 85.1, the substituted amino acid residue in the parent domain of the first engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 85.1 in the parent domain of the second engineered immunoglobulin chain is at position 86, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

96. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-93, wherein if the substitution in the parent domain of the first engineered immunoglobulin chain is at position 22, the substituted amino acid residue in the parent domain of the second engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 22 in the parent domain of the first engineered immunoglobulin chain is at position 22 and/or 86, or if the substitution in the parent domain of the second engineered immunoglobulin chain is at position 22, the substituted amino acid residue in the parent domain of the first engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 22 in the parent domain of the second engineered immunoglobulin chain is at position 22 and/or 86, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

97. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-93, wherein if the substitution in the parent domain of the first engineered

immunoglobulin chain is at position 20, the substituted amino acid residue in the parent domain of the second engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 20 in the parent domain of the first engineered immunoglobulin chain is at position 26, or if the substitution in the parent domain of the second engineered immunoglobulin chain is at position 20, the substituted amino acid residue in the parent domain of the first engineered immunoglobulin chain which interacts with the substituted amino acid residue at position 20 in the parent domain of the second engineered immunoglobulin chain is at position 26, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

98. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-97, wherein the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises a further amino acid residue substitution at a position selected from the group consisting of 3, 5, 7, 11, 12, 13, 18, 26, 27, 79, 81, 83, 84, 84.2 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

99. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 83-97, wherein the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises a further amino acid residue substitution at a position selected from the group consisting of 3, 5, 7, 11, 12, 13, 18, 20, 27, 79, 81, 83, 84, 84.2 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

100. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with

a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,

wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,

wherein the parent domains of the first and the second engineered immunoglobulin chain are not a CH2 domain, not a CH3 domain, not a VL domain and not a VH domain and wherein,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 12 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 119, the substituted amino acid residue at position 12 and the substituted amino acid residue at position 119 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 26 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 13, the substituted amino acid residue at position 26 and the substituted amino acid residue at position 13 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 5 and the protein-protein interface of the parent domain of the second engineered

immunoglobulin chain is substituted with an amino acid residue at position 20, the substituted amino acid residue at position 5 and the substituted amino acid residue at position 20 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 27 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 18, the substituted amino acid residue at position 27 and the substituted amino acid residue at position 18 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 20 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 26, the substituted amino acid residue at position 20 and the substituted amino acid residue at position 26 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 79 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position 84.3, the substituted amino acid residue at position 79 and the substituted amino acid residue at position 84.3 are not a charged pair,

if the parent domain of the first engineered immunoglobulin chain is an IGLC domain or an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is substituted with an amino acid residue at position 86 and the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is substituted with an amino acid residue at position

86, the substituted amino acid residues at both positions 86 are not a charged pair, if the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is at position 11 and the parent domain of the second engineered immunoglobulin chain is a domain which comprises a hinge region, the parent domain of the second engineered immunoglobulin chain is not substituted at position 3 of the hinge region,
wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

101. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 100, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a domain selected from the group consisting of CH1 domain, CH4 domain, IGKC domain, IGLC1 domain, IGLC2 domain, IGLC3 domain, IGLC6 domain, and IGLC7 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first and/or the second engineered immunoglobulin chain comprises an amino acid residue at a position selected from the group consisting of 3, 5, 7, 11, 12, 13, 18, 20, 22, 26, 27, 79, 81, 83, 84, 84.2, 85.1, 86, 88 and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

102. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the parent domains of the first and the second engineered immunoglobulin chain form a hetero-dimer.

103. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 102, wherein the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain is interacting with the protein-protein interface of the engineered domain of the second engineered immunoglobulin chain by homo-dimerization.

104. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the parent domains of the first and the second engineered

immunoglobulin chain form a homo-dimer.

105. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

106. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the first and the second member of the naturally occurring immunoglobulin super-family are selected from the TCR constant domain family.

107. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) or
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1).

108. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 107, wherein the cysteine (C) at amino acid position 75 in SEQ ID NO: 2 is substituted with alanine (A) or serine (S).

109. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32) or
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32) and

the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33).

110. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring homo-dimer.

111. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 110, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin is a CH3 domain.

112. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 110, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the IgG1 CH3 domain.

113. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 110, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family is an IgA1 CH3 domain or an IgA2 CH3 domain.

114. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-113, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family and additionally at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position

from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family and wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family and additionally at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family.

115. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-114, wherein at least one 3D structural position of the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain is different in amino acid residue compared to the identical 3D structural position of the protein-protein interface of the engineered domain of the second engineered immunoglobulin chain.

116. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-115, wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical.

117. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-116, wherein the amino acid residues from the protein-protein interface of the donor domain of the first and the second member of the naturally occurring immunoglobulin super-family are amino acids non essential to the core integrity of the domain.

118. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-117, wherein the hetero-dimeric immunoglobulin fragment comprises at least two engineered domains, wherein the first engineered domain is non identical to the second engineered domain, and wherein both engineered domains assemble by

interaction through their protein-protein interfaces.

119. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue at a position selected from the group consisting of 114, 116, 118, 123, 124, 131, 133, 137, 138, 160, 162, 164, 165, 167, 174, 176, 178, and 180, wherein the amino acid position of each group member is indicated according to the EU numbering.

120. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 90, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue at a position selected from the group consisting of 114, 116, 118, 122, 131, 133, 137, 138, 160, 162, 165, 167, 174, 176, 178, and 180, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

121. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of S131V, S131T, S131A, S131N, S131Q, S131E, S131K, S131W, V133A, V133G, V133T, V133L, V133I, N137Q, N137T, N137K, N137V, N137S, N137R, N137E, S174T, S174M, S174A, S174R, S174H, S174K, S174W, S174F, S174C, S174N, S176I, S176T, S176H, S176Q, S176V, S176W, S176Y, S176F, T178Q, T178L, T178V, T178R, T178E, T178I, T178K, T178Y, and T178W, wherein the amino acid position of each group member is indicated according to the EU numbering.

122. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC

domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of S114E, S114K, S114Q, F116A, F116T, F116Y, F118M, F118L, E123D, Q124E, S131K, S131T, S131N, V133L, V133A, V133T, N137T, N137E, N137K, N138K, N138E, Q160Y, Q160F, Q160K, S162A, S162G, S162D, S162T, T164V, T164M, E165L, D167E, D167S, S174A, S174M, S174N, S174F, S176F, S176V, S176Y, T178W, T178R, T178L, T178K, T180N, T180R, and T180K and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the EU numbering.

123. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 90, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of 131V, 131A, 131N, 131Q, 131E, 131K, 131W, 131S, 133A, 133G, 133T, 133L, 133I, 137Q, 137T, 137K, 137V, 137R, 137N, 137E, 174T, 174M, 174S, 174R, 174H, 174K, 174W, 174F, 174C, 174N, 176I, 176T, 176H, 176Q, 176W, 176Y, 176V, 176F, 178Q, 178L, 178V, 178R, 178E, 178T, 178I, 178K, 178E, and 178W, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

124. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 90, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of 114E, 114K, 114Q, 116A, 116Y, 118M, 118L, 122D, 131K, 131N, 133A, 133L, 133T, 137T, 137E, 137K, 138E, 138K, 160Y, 160F, 160K, 162D, 162A, 162G, 165L, 165M, 167E, 167S, 174N, 174M, 174F, 174S, 176V, 176F, 176Y, 178W, 178R, 178L, 178K, 180N, 180R, and 180K and conservative amino acid substitutions thereof, wherein the amino acid position of each

group member is indicated according to the Kabat numbering.

125. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 178 or comprises T178W and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 131, 137, 160, 176, and 180, wherein the amino acid position of each group member is indicated according to the EU numbering.

126. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 174 or comprises S174A and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 114, 116, 131, 137, 162, 165, 167, 178, and 180, wherein the amino acid position of each group member is indicated according to the EU numbering.

127. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 178 or comprises T178W and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 114, 116, 131, 133, 137, 138, 162, 164, 174, and 176, wherein the amino acid position of each group member is indicated according to the EU numbering.

128. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC

domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 176 or comprises S176V and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 118, 131, 133, 138, 160, 162, 167, 174, 178, and 180, wherein the amino acid position of each group member is indicated according to the EU numbering.

129. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 176 or comprises S176Y and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 114, 116, 118, 123, 124, 133, 137, 160, 162, 164, 174, and 178, wherein the amino acid position of each group member is indicated according to the EU numbering.

130. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue at a position selected from the group consisting of 124, 126, 128, 133, 134, 139, 141, 143, 147, 148, 168, 170, 173, 175, 181, 183, 185, and 187, wherein the amino acid position of each group member is indicated according to the EU numbering.

131. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of 141V, 141T, 141N, 141Q, 141E, 141K, 141W, 141S, 143A, 143T, 143L, 143I, 143V, 147Q, 147T,

147V, 147S, 147R, 147N, 147E, 181T, 181M, 181A, 181R, 181H, 181K, 181W, 181F, 181C, 181N, 183I, 183H, 183Q, 183V, 183T, 183W, 183Y, 183F, 185Q, 185L, 185R, 185E, 185I, 185T, 185K, 185Y, and 185W, wherein the amino acid position of each group member is indicated according to the EU numbering.

132. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises an amino acid residue selected from the group consisting of S124E, S124K, S124Q, F126A, F126T, F126Y, L128F, L128M, K133D, S134E, T139Q, A141K, A141T, A141N, A141S, G143V, G143A, G143L, G143T, K147T, K147E, D148E, D148K, H168Y, H168F, H168K, F170D, F170A, F170G, F170T, V173L, V173M, Q175E, Q175S, Q175D, S181A, S181N, S181M, S181F, S183V, S183F, S183Y, V185W, V185R, V185L, V185K, T187N, T187K and T187R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the EU numbering.

133. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 185 or comprises V185W and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 141, 143, 147, 168, 183, and 187, wherein the amino acid position of each group member is indicated according to the EU numbering.

134. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 181 or comprises S181A and conservative

amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 124, 126, 128, 141, 143, 147, 170, 173, 175, 185, and 187, wherein the amino acid position of each group member is indicated according to the EU numbering.

135. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 185 or comprises V185W and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 124, 126, 141, 143, 147, 148, 170, 173, 181, and 183, wherein the amino acid position of each group member is indicated according to the EU numbering.

136. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 183 or comprises S183V and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 128 , 141, 143, 148, 168, 170, 175, 181, 185, and 187, wherein the amino acid position of each group member is indicated according to the EU numbering.

137. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 89 or 90, wherein the parent domain of the second engineered immunoglobulin chain is a CH1 domain and the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 183 or comprises S183Y and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 124, 126, 133, 134, 139, 141, 143, 168, 170, 175, 181, and 185, wherein the amino acid position of each group member is

indicated according to the EU numbering.

138. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-137, wherein the amino acid residues of the protein-protein interface of the parent domain of the first and/or the second engineered immunoglobulin chain which are substituted are not adjacent.

139. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-138, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the first and/or the second engineered immunoglobulin chain are substituted.

140. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-139, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain.

141. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-140, wherein the first and the second engineered immunoglobulin chains have amino acid sequences which are different from each other by at least one amino acid or by at least two amino acids or by at least three amino acids or by at least four amino acids or by at least five amino acids or by at least five to ten amino acids or by at least ten to thirty amino acids.

142. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof any one of claims 82-141, wherein at least one additional polypeptide is fused to the first and/or second engineered immunoglobulin chain.

143. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 142, wherein said additional polypeptide is selected from the group consiting of Fab, scFv, diabody, domain antibody, pharmacologically active peptide or protein, receptor

extracellular domain, CDR grafted polypeptide, and therapeutic engineered protein scaffold.

144. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 82 or 100, wherein the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain comprise a further engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said further engineered domain of said first engineered immunoglobulin chain and/or said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family, and
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is interacting with the protein-protein interface of an engineered domain of a third engineered immunoglobulin chain by hetero-dimerization or by homo-dimerization, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said engineered domain of said third engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family, and
wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and of the engineered domain of the third engineered immunoglobulin chain is different from the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain and of the engineered domain of the second engineered immunoglobulin chain.

145. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the third and the fourth member of the naturally occurring immunoglobulin super-family are selected from the TCR constant domain family.

146. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2), the donor domain of the third member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32) and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33).

147. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33), the donor domain of the third member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2).

148. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) or the TCR constant domain delta (SEQ ID NO: 32), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) or the TCR constant domain gamma (SEQ ID NO: 33), the donor domain of the third and the fourth member of the naturally occurring immunoglobulin super-family is the IgG1 CH3 domain (SEQ ID NO: 47), with the proviso that if the first member of the naturally occurring immunoglobulin super-family

is the TCR constant domain alpha (SEQ ID NO: 1), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) and if the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33).

149. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) or the TCR constant domain delta (SEQ ID NO: 32), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) or the TCR constant domain gamma (SEQ ID NO: 33), the donor domain of the third and the fourth member of the naturally occurring immunoglobulin super-family is the human IGHA1 CH3 domain (SEQ ID NO: 96) or the human IGHA2 CH3 domain (SEQ ID NO: 97), with the proviso that if the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2) and if the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32), the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33).

150. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family is an IgA1 CH3 domain or an IgA2 CH3 domain.

151. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the

parent domain of the engineered domain of the third engineered immunoglobulin chain are naturally occurring domains.

152. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is selected from the group consisting of CH1, CH2, CH3, CH4, IGKC, IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7.

153. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the engineered domain of the third engineered immunoglobulin chain is selected from the group consisting of CH1, CH2, CH3, CH4, IGKC, IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7.

154. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain form a hetero-dimer.

155. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain form a homo-dimer.

156. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the engineered domain of the third engineered immunoglobulin chain are not identical.

157. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered

immunoglobulin chain and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain is a CH3 domain.

158. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the parent domain of the engineered domain of the third engineered immunoglobulin chain is the IgG1 CH3 domain.

159. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is an IgG1 CH3 domain and the parent domain of the engineered domain of the third engineered immunoglobulin chain is an IgG3 CH3 domain or wherein the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is an IgG3 CH3 domain and the parent domain of the engineered domain of the third engineered immunoglobulin chain is an IgG1 CH3 domain.

160. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein the amino acid residues of the protein-protein interface of the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and/or the parent domain of the engineered domain of the third engineered immunoglobulin chain which are substituted are not adjacent.

161. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and/or the parent domain of the engineered domain of the third engineered immunoglobulin chain are substituted.

162. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-161, comprising an Fc region.

163. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 82-161, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof is a full-length antibody.

164. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 144 or 163, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the full-length antibody is bispecific.

165. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 164, wherein the bispecific hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the bispecific full-length antibody binds to antigens selected from the group consisting of HER2, EGFR, CD19 and VLA-2.

166. A method to produce a hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) substituting at least one amino acid residue of the protein-protein interface of a parent domain of a first parent immunoglobulin chain at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family to obtain a first engineered immunoglobulin chain comprising an engineered domain,
(b) substituting at least one amino acid residue of the protein-protein interface of the parent domain of a second parent immunoglobulin chain at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family to obtain a second engineered immunoglobulin chain comprising an engineered domain,
(c) culturing a host cell comprising a nucleic acid encoding said engineered immunoglobulin chains, wherein the culturing is such that the nucleic acid is expressed and the engineered immunoglobulin chains produced; and
(d) recovering the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof

from the host cell culture.

167. The method of claim 166, wherein the amino acid residue of the protein-protein interface of the parent domain of the parent immunoglobulin chain which is substituted at the equivalent 3D structural position from the protein-protein interface of a donor domain is an amino acid residue in the protein-protein interface of a donor domain which when overlaid on the protein-protein interface of the parent domain by superimposing the carbon alpha traces of both domains, occupies a 3D position within less than a distance of 6 Å to the closest residue of the parent domain, wherein the donor domain is different from the parent domain.

168. The method of claim 166, wherein the parent domain of the first parent immunoglobulin chain is selected from the group consisting of CH1, CH2, CH3, CH4, IGKC, IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7.

169. The method of claim 166, wherein the parent domain of the second parent immunoglobulin chain is selected from the group consisting of CH1, CH2, CH3, CH4, IGKC, IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7.

170. The method of claim 166, wherein the parent domains of the first and the second engineered immunoglobulin chain form a homo-dimer.

171. The method of claim 166, wherein the parent domain of the first and/or second parent immunoglobulin chain is a CH3 domain.

172. The method of claim 166, wherein the parent domain of the first and/or second parent immunoglobulin chain is a CH4 domain.

173. The method of claim 166, wherein the parent domains of the first and the second engineered immunoglobulin chain form a hetero-dimer.

174. The method of claim 166, wherein the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second

engineered immunoglobulin chain is an IGKC domain or, wherein the parent domain of the first engineered immunoglobulin chain is an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1domain.

175. The method of claim 166, wherein the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 or is an IGKC domain or, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 or is an IGKC domain and the parent domain of the second engineered immunoglobulin chain is a CH1 domain.

176. The method of claim 166, wherein the parent domain of the first engineered immunoglobulin chain is a CH1 domain and the parent domain of the second engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 or, wherein the parent domain of the first engineered immunoglobulin chain is an IGLC domain selected from the group consisting of IGLC1, IGLC2, IGLC3, IGLC6, and IGLC7 and the parent domain of the second engineered immunoglobulin chain is a CH1 domain.

177. The method of claim 166-176, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

178. The method of any one of claims 166-177, wherein the first and the second member of a naturally occurring immunoglobulin super-family are selected from the TCR constant domain family.

179. The method of claim 178, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the second member of the naturally occurring

immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2).

180. The method of claim 179, wherein the cysteine (C) at amino acid position 75 in SEQ ID NO: 2 is substituted with alanine (A) or serine (S).

181. The method of claim 178, wherein the the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33) and second member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32).

182. The method of claim 166, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring homo-dimer.

183. The method of claim 182, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin is a CH3 domain.

184. The method of claim 166, wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical.

185. The method of claim 166, wherein the amino acid residues of the protein-protein interface of the parent domain of the first and/or the second parent immunoglobulin chain which are substituted are not adjacent.

186. The method of claim 166, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain.

187. The method of claim 166, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the first and/or the second parent immunoglobulin chain are substituted.

188. The method of claim 166, wherein the first and the second parent immunoglobulin chains comprise an Fc region.

189. The method of any one of claims 166-188, wherein the amino acid residues from the protein-protein interface of the donor domain of the first and the second member of the naturally occurring immunoglobulin super-family are amino acids non essential to the core integrity of the domain.

190. The method of claim 166, wherein the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain comprise a further engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said further engineered domain of said first engineered immunoglobulin chain and/or said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family, and
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is interacting with the protein-protein interface of an engineered domain of a third engineered immunoglobulin chain by hetero-dimerization or by homo-dimerization, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said engineered domain of said third engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family and,
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and of the engineered domain of the third engineered immunoglobulin chain is different from the protein-protein interface of the engineered domain of the first engineered

immunoglobulin chain and of the engineered domain of the second engineered immunoglobulin chain.

191. The method of claim 190, wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer.

192. The method of claim 190, wherein the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and the engineered domain of the third engineered immunoglobulin chain are not identical.

193. The method of any one of claims 166 or 190, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof is a full-length antibody.

194. The method of claim 166 or 193, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the full-length antibody is bispecific.

195. The method of claim 194 wherein the bispecific hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the bispecific antibody binds to antigens selected from the group consisting of HER2, EGFR, CD19 and VLA-2.

196. The method of any one of claims 166-190, wherein at least one additional polypeptide is fused to the first and/or second engineered immunoglobulin chain.

197. The method of claim 196, wherein said additional polypeptide is selected from the group consiting of Fab, scFv, diabody, domain antibody, pharmacologically active peptide or protein, receptor extracellular domain, CDR grafted polypeptide, and therapeutic engineered protein scaffold.

198. A method to engineer a protein-protein interface of a domain of a multidomain protein comprising:

(a) providing a multidomain protein comprising a domain with a protein-protein

interface;

(b) selecting as a donor domain a naturally occurring immunoglobulin super-family member comprising a domain with a protein-protein interface which is different from the domain of (a);

(c) overlaying 3D structures of the domain with the protein-protein interface of (a) and the donor domain with the protein-protein interface of (b);

(d) identifying exposed protein-protein interface residues in the overlayed 3D structures of the domain with the protein-protein interface of (a) and the donor domain with the protein-protein interface of (b);

e) substituting at least one amino acid residue of the identified exposed protein-protein interface amino acid residues of the domain with the protein-protein interface of (a) with amino acid residues at the equivalent 3D structural position from the identified exposed protein-protein interface amino acid residues from the donor domain with the protein-protein interface of (b).

199. The method of claim 198, wherein the domain with a protein-protein interface of the multidomain protein of (a) is capable to form a homo-dimer with another domain.

200. The method of claim 198, wherein the domain with a protein-protein interface of the multidomain protein of (a) is capable to form a hetero-dimer with another domain.

201. The method of claim 198, wherein the exposed interface residues identified in the domain of the multidomain protein and in the donor domain of the naturally occurring immunoglobulin super-family member are non essential to the domain core integrity.

202. The method of claim 198, wherein the naturally occurring immunoglobulin super-family member is a naturally occurring hetero-dimer.

203. The method of claim 198, wherein the naturally occurring immunoglobulin super-family member is selected from the TCR constant domain family.

204. The method of claim 198, wherein the donor domain of the naturally occurring member of the immunoglobulin super-family is the TCR constant domain alpha (SEQ

ID NO: 1) or the TCR constant domain beta (SEQ ID NO: 2).

205. The method of claim 204, wherein the cysteine (C) at amino acid position 75 in SEQ ID NO: 2 is substituted with alanine (A) or serine (S).

206. The method of claim 198, wherein the donor domain of the naturally occurring member of the immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33) or the TCR constant domain delta (SEQ ID NO: 32).

207. The method of claim 198, wherein the naturally occurring immunoglobulin super-family member is a naturally occurring homo-dimer.

208. Use of a donor domain of a first and a second member of the naturally occurring immunoglobulin super-family to engineer a hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising a first engineered immunoglobulin chain comprising at least one engineered domain which has a protein-protein interface which is substituted with at least one amino acid residue from the protein-protein interface of the donor domain of the first member of the naturally occurring immunoglobulin super-family and a second engineered immunoglobulin chain comprising at least one engineered domain which has a protein-protein interface which is substituted with at least one amino acid residue from the protein-protein interface of the donor domain of the second member of the naturally occurring immunoglobulin super-family, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer.

209. Use according to claim 208, wherein the donor domain of the first and the second member of the naturally occurring immunoglobulin super-family is selected from T cell receptor chains.

210. Use according to claim 208, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the second member of the naturally occurring

immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2).

211. Use according to claim 208, wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33).

CLAIMS

1. A hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof comprising:
(a) a first engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said first engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family; and
(b) a second engineered immunoglobulin chain comprising an engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family,
wherein the engineered domain of the first engineered immunoglobulin chain and the engineered domain of the second engineered immunoglobulin chain are not identical and,
wherein the donor domain of the first member of the naturally occurring immunoglobulin super-family and the donor domain of the second member of the naturally occurring immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a CH3 domain, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residue at position 88, and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, and 90 and, wherein the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residue at position 85.1 and/or 86 and optionally a further amino acid residue at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 27, 79, 81, 84, 84.2, 86, 88, and 90,
wherein the amino acid residue substituted at position 88 in the parent domain of the first engineered immunoglobulin chain is interacting with the amino acid residue substituted at position 85.1 and/or 86 in the parent domain of the second engineered immunoglobulin chain,
wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

2. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the parent domain of the first and/or the second engineered immunoglobulin chain is a naturally occurring CH3 domain.

3. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein:
a) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is 88W and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering;
b) the amino acid residue which is substituted at position 85 and/or 86 in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 85.1A, 85.1S, 85.1C and 85.1N and conservative amino acid substitutions thereof and/or is selected from the group consisting of 86S and 86V and conservative amino acid substitutions thereof, wherein the amino acid position is indicated according to the IMGT® numbering;
c) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88Y, 88K and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20E, 20S, 20K, 20W, 22A, 22G, 22T, 22L, 22I, 22V, 26R, 26Q, 26T, 26K, 26V, 26S, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1F, 85.1C, 85.1N, 85.1W, 86S, 86I, 86T, 86H, 86Q, 86V, 86W, 86Y and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
d) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain at position 88 is selected from the group consisting of 88Q, 88L, 88V, 88R, 88E, 88I, 88T, 88Y, and 88W and/or wherein the further amino acid residue substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20V, 20T, 20A, 20N, 20Q, 20E, 20S, 20K, 22A, 22G, 22T, 22L, 22I, 22V, 26Q, 26T, 26K, 26V, 26S, 26N, 26E, 85.1T, 85.1M, 85.1A, 85.1S, 85.1R, 85.1H, 85.1K, 85.1F, 85.1C, 85.1N, 86S, 86I, 86T, 86H, 86Q, 86V, and 86F, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
e) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain comprises the amino acid residues at position 88 and at position 20, and optionally a further amino acid residue at a position

selected from the group consisting of 3, 5, 7, 22, 26, 27, 79, 81, 84, 84.2, 85.1, 86, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;

f) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and/or 86 and at position 26 and optionally an amino acid residue at a further position, wherein the amino acid position is indicated according to the IMGT® numbering;

g) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and 86 or comprises 85.1C and conservative amino acid substitutions thereof and 86S and conservative amino acid substitutions thereof, and wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 3E, 5A, 7F, 20T, 22V, 26T, 81D, 84L, 84.2E, 88R and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;

h) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain comprises the amino acid residues at position 85.1 and 86 or comprises 85.1N and conservative amino acid substitutions thereof and 86V and conservative amino acid substitutions thereof, and wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is selected from the group consisting of 7M, 20N, 22A, 27E, 79F, 81A, 84.2S, 85.1N, 86V, 88L, and 90K and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering; or

i) the amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is 88I and conservative amino acid substitutions therof and the optional further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is 81W and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

4. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein:

a) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3E, 3K, 5A, 5T, 7F, 7M, 20K, 20N, 20T, 22A, 22L, 22V, 26E, 26T, 27E, 27K, 79F, 79Y, 81A, 81G, 81D, 84L, 84M, 84.2E, 84.2S, 85.1A, 85.1C, 85.1M, 85.1N, 85.1S, 86F,

86S, 86V, 90K, 90N, and 90R and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
b) wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is at a position selected from the group consisting of 20, 22, 26, 79, 85.1, 86, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
c) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 20K, 22V, 26T, 79Y, 85.1S, 86V, and 90N and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
d) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at position 84 or is 84L and conservative amino acid substitutions thereof, and optionally a further amino acid at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
e) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 3, 5, 7, 20, 22, 26, 81, 84, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
f) wherein the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is at a position selected from the group consisting of 3, 5, 20, 22, 26, 27, 81, 84, 85.1, and 86, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
g) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the first engineered immunoglobulin chain is selected from the group consisting of 3K, 5T, 20T, 22L, 26E, 27K, 81G, 84M, 85.1M, 86F and conservative amino acid substitutions thereof, wherein the amino acid position of each group member is indicated according to the IMGT® numbering;
h) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at a position selected from

the group consisting of 7, 20, 22, 27, 79, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 79, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 79, 81, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering; or

i) the further amino acid residue which is substituted in the protein-protein interface of the parent domain of the second engineered immunoglobulin chain is at position 79 or is 79F and conservative amino acid substitutions thereof, and optionally a further amino acid residue at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 85.1, 88, and 90 or at a position selected from the group consisting of 7, 20, 22, 27, 81, 84.2, 86, 88, and 90, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

5. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 4, wherein the amino acid residue substitution 85.1C is replaced by amino acid residue substitution 85.1A or 85.1S, wherein the amino acid position of each group member is indicated according to the IMGT® numbering.

6. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 1, wherein the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain comprise a further engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said further engineered domain of said first engineered immunoglobulin chain and/or said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family, and

wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is interacting with the protein-protein interface of an engineered domain of a third engineered immunoglobulin chain by hetero-dimerization or by homo-dimerization,

wherein at least one amino acid residue of the protein-protein interface of the parent domain of said engineered domain of said third engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family, and

wherein the donor domain of the third member of the naturally occurring immunoglobulin super-family and the donor domain of the fourth member of the naturally occurring

immunoglobulin super-family form a naturally occurring hetero-dimer or a naturally occurring homo-dimer and,
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and of the engineered domain of the third engineered immunoglobulin chain is different from the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain and of the engineered domain of the second engineered immunoglobulin chain.

7. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 6, wherein the first and second engineered immunoglobulin chains comprise an Fc region.

8. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 6, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and/or of the parent domain of the engineered domain of the third engineered immunoglobulin chain are substituted.

9. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 6, wherein the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the full-length antibody is bispecific.

10. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 9, wherein the bispecific hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof or the bispecific full-length antibody binds to antigens selected from the group consisting of HER2, EGFR, CD19, and VLA-2.

11. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 10, wherein at least one additional polypeptide is fused to the first and/or second engineered immunoglobulin chain.

12. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of claim 11, wherein said additional polypeptide is selected from the group consisting of Fab, scFv, diabody, domain antibody, pharmacologically active peptide or protein, receptor extracellular domain, CDR grafted polypeptide, and therapeutic engineered protein scaffold.

13. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 12, wherein the amino acid residues of the protein-protein interface of the parent domain of

the first and/or second engineered immunoglobulin chain which are substituted are not adjacent.

14. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 13, wherein at least two amino acid residues of the protein-protein interface of the parent domain of the first and/or second engineered immunoglobulin chain are substituted.

15. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 14, wherein the parent domain of the first engineered immunoglobulin chain is an IgG1 CH3 domain and the parent domain of the second engineered immunoglobulin chain is an IgG3 CH3 domain or wherein the parent domain of the first engineered immunoglobulin chain is an IgG3 CH3 domain and the parent domain of the second engineered immunoglobulin chain is an IgG1 CH3 domain.

16. The hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 15, wherein the amino acid sequence of the engineered domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain do not contain an insertion of one or more amino acid residues compared to the amino acid sequence of the parent domains of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain.

17. A method of producing a hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof of any one of claims 1 to 16, the method comprising:
(a) substituting at least one amino acid residue of the protein-protein interface of a parent domain of a first parent immunoglobulin chain at the equivalent 3D structural position from a protein-protein interface of a donor domain of a first member of the naturally occurring immunoglobulin super-family to obtain a first engineered immunoglobulin chain comprising an engineered domain;
(b) substituting at least one amino acid residue of the protein-protein interface of the parent domain of a second parent immunoglobulin chain at the equivalent 3D structural position from a protein-protein interface of a donor domain of a second member of the naturally occurring immunoglobulin super-family to obtain a second engineered immunoglobulin chain comprising an engineered domain;
(c) culturing a host cell comprising a nucleic acid encoding said engineered immunoglobulin chains, wherein the culturing is such that the nucleic acid is expressed and the engineered immunoglobulin chains produced; and

(d) recovering the hetero-dimeric immunoglobulin or hetero-dimeric fragment thereof from the host cell culture.

18. The method of claim 17, wherein the amino acid residue of the protein-protein interface of the parent domain of the parent immunoglobulin chain which is substituted at the equivalent 3D structural position from the protein-protein interface of a donor domain is an amino acid residue in the protein-protein interface of a donor domain which when overlaid on the protein-protein interface of the parent domain by superimposing the carbon alpha traces of both domains, occupies a 3D position within less than a distance of 6 Å to the closest residue of the parent domain, wherein the donor domain is different from the parent domain.

19. The method of claim 17, wherein:
a) the first and the second member of a naturally occurring immunoglobulin super-family are selected from the TCR constant domain family;
b) the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2);
c) the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain alpha (SEQ ID NO: 1) and the donor domain of the second member of the naturally occurring immunoglobulin super-family is the TCR constant domain beta (SEQ ID NO: 2), wherein the cysteine (C) at amino acid position 75 in SEQ ID NO: 2 is substituted with alanine (A) or serine (S); or
d) the donor domain of the first member of the naturally occurring immunoglobulin super-family is the TCR constant domain gamma (SEQ ID NO: 33) and second member of the naturally occurring immunoglobulin super-family is the TCR constant domain delta (SEQ ID NO: 32).

20. The method of claim 17, wherein the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain comprise a further engineered domain with a protein-protein interface, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said further engineered domain of said first engineered immunoglobulin chain and/or said second engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a third member of the naturally occurring immunoglobulin super-family, and wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain is interacting with

the protein-protein interface of an engineered domain of a third engineered immunoglobulin chain by hetero-dimerization or by homo-dimerization, wherein at least one amino acid residue of the protein-protein interface of the parent domain of said engineered domain of said third engineered immunoglobulin chain is substituted with an amino acid residue at the equivalent 3D structural position from a protein-protein interface of a donor domain of a fourth member of the naturally occurring immunoglobulin super-family and,
wherein the protein-protein interface of the further engineered domain of the first engineered immunoglobulin chain and/or the second engineered immunoglobulin chain and of the engineered domain of the third engineered immunoglobulin chain is different from the protein-protein interface of the engineered domain of the first engineered immunoglobulin chain and of the engineered domain of the second engineered immunoglobulin chain.