WE CLAIM:

1. A TCR construct comprising a TCR alpha chain polypeptide and a TCR beta chain polypeptide, the TCR alpha chain polypeptide comprising a variable alpha (Vα) domain and a constant alpha (Cα) domain and the TCR beta chain polypeptide comprising a variable beta (Vβ) domain and a constant beta (Cβ) domain,

wherein the Cα domain and Cβ domain comprise stabilizing mutations, the stabilizing mutations comprising a first interchain disulfide bond between the Cα domain and the Cβ domain and one or more additional stabilizing mutations, the one or more additional stabilizing mutations selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11;

h) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11;

i) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 39 and TRAC 85;

j) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 26 and TRAC 85.1;

k) an amino acid substitution at position TRAC 4 from Val to Ala, Thr, Ile, Leu or Met;

l) an amino acid substitution at position TRAC 26 from Thr to Ala, Val, Ile, Leu or Met;

m) an amino acid substitution at position TRAC 39 from Val to Ala, Thr, Ile, Leu or Met;

n) an amino acid substitution at position TRAC 85 from Ala to Ser, Thr, Val, Ile or Met;

o) an amino acid substitution at position TRAC 105 from Ala to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

p) an amino acid substitution at position TRAC 120 from Phe to Tyr or His;

q) an amino acid substitution at position TRBC 6 from Val to Ala, Thr, Ile, Leu or Met;

r) an amino acid substitution at position TRBC 36 from His to Phe, Tyr or Trp;

s) an amino acid substitution at position TRBC 86 from Ser to Ala or Thr;

t) an amino acid substitution at position TRBC 45.3 from Val to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

u) a deletion of 1 to 4 consecutive amino acids of the DE loop in the Cβ domain of the TCR construct, and

v) a replacement of the amino acids at positions TRBC 84.4 to 85.4 with an amino acid sequence of 2 to 4 amino acids, wherein the amino acid sequence allows for formation of a beta-turn,

wherein the numbering of amino acids is IMGT numbering,

and wherein the TCR construct has an increased TCR melting temperature (Tm) as compared to a corresponding TCR construct comprising the first disulfide bond alone.

2. The TCR construct according to claim 1, wherein the first interchain disulfide bond is selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

h) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11, and

i) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11,

and wherein the first interchain disulfide bond and any additional interchain disulfide bonds are different.

3. The TCR construct according to claim 1, wherein the first interchain disulfide bond is selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, where the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84 and TRBC 79, and

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79,

and wherein the first interchain disulfide bond and any additional interchain disulfide bonds are different.

4. The TCR construct according to claim 1, wherein the first interchain disulfide bond is selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, where the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide, and

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79,

and wherein the first interchain disulfide bond and any additional interchain disulfide bonds are different.

5. The TCR construct according to any one of claims 1 to 4, wherein the one or more additional stabilizing mutations comprise an additional interchain disulfide bond selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, where the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

c) a disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12;

d) a disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

e) a disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

f) a disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

g) a disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11, and

h) a disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11.

6. The TCR construct according to claim 1, wherein the first interchain disulfide bond is a disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79.

7. The TCR construct according to claim 6, wherein the one or more additional stabilizing mutations comprise an additional interchain disulfide bond selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, where the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) a disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12;

c) a disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

d) a disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

e) a disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

f) a disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11, and

g) a disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11.

8. The TCR construct according to any one of claims 1 to 7, wherein the one or more additional stabilizing mutations comprise an intrachain disulfide bond selected from:

an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 39 and TRAC 85, and

an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 26 and TRAC 85.1.

9. The TCR construct according to any one of claims 1 to 8, wherein the one or more additional stabilizing mutations comprise:

a) an amino acid substitution at position TRAC 26 from Thr to Ala, Val, Ile, Leu or Met;

b) an amino acid substitution at position TRAC 85 from Ala to Ser, Thr, Val, Ile or Met;

c) an amino acid substitution at position TRBC 6 from Val to Ala, Thr, Ile, Leu or Met, and

d) an amino acid substitution at position TRBC 36 from His to Phe, Tyr or Trp.

10. A TCR construct comprising a TCR alpha chain polypeptide and a TCR beta chain polypeptide, the TCR alpha chain polypeptide comprising a variable alpha (Vα) domain and a constant alpha (Cα) domain and the TCR beta chain polypeptide comprising a variable beta (Vβ) domain and a constant beta (Cβ) domain,

wherein the Cα domain and/or Cβ domain comprise one or more stabilizing mutations selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11;

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11;

h) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 39 and TRAC 85;

i) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 26 and TRAC 85.1;

j) an amino acid substitution at position TRAC 4 from Val to Ala, Thr, Ile, Leu or Met;

k) an amino acid substitution at position TRAC 26 from Thr to Ala, Val, Ile, Leu or Met;

l) an amino acid substitution at position TRAC 39 from Val to Ala, Thr, Ile, Leu or Met;

m) an amino acid substitution at position TRAC 85 from Ala to Ser, Thr, Val, Ile or Met;

n) an amino acid substitution at position TRAC 105 from Ala to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

o) an amino acid substitution at position TRAC 120 from Phe to Tyr or His;

p) an amino acid substitution at position TRBC 6 from Val to Ala, Thr, Ile, Leu or Met;

q) an amino acid substitution at position TRBC 36 from His to Phe, Tyr or Trp;

r) an amino acid substitution at position TRBC 86 from Ser to Ala or Thr;

s) an amino acid substitution at position TRBC 45.3 from Val to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

t) a deletion of 1 to 4 consecutive amino acids of the DE loop in the Cβ domain of the TCR construct, and

u) a replacement of the amino acids at positions TRBC 84.4 to 85.4 with an amino acid sequence of 2 to 4 amino acids, wherein the amino acid sequence allows for formation of a beta-turn,

wherein the numbering of amino acids is IMGT numbering,

and wherein the TCR construct has an increased TCR melting temperature (Tm) as compared to a corresponding TCR construct that does not comprise the one or more stabilizing mutations.

11. The TCR construct according to claim 10, further comprising an interchain disulfide bond selected from:

an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84 and TRBC 79, and

an interchain disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12.

12. The TCR construct according to claim 10 or 11, wherein the stabilizing mutations comprise a first interchain disulfide bond selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11, and

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11.

13. The TCR construct according to claim 12, wherein the stabilizing mutations comprise a second interchain disulfide bond selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide,

wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11, and

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11,

wherein the first and second interchain disulfide bonds are different.

14. A TCR construct comprising a TCR alpha chain polypeptide and a TCR beta chain polypeptide, the TCR alpha chain polypeptide comprising a variable alpha (Vα) domain and a constant alpha (Cα) domain and the TCR beta chain polypeptide comprising a variable beta (Vβ) domain and a constant beta (Cβ) domain,

wherein the Cα domain and Cβ domain together comprise two or more stabilizing mutations selected from:

a) an interchain disulfide bond formed between: i) a cysteine residue comprised by an amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide, wherein the amino acid extension is 1 to about 10 amino acids in length, and ii) a cysteine residue at position TRAC 128 in the Cα domain of the TCR alpha chain polypeptide;

b) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84 and TRBC 79;

c) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 84.2 and TRBC 79;

d) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 124 and TRBC 11;

e) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 122 and TRBC 12;

f) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 125 and TRBC 11;

g) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 126 and TRBC 11;

h) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 127 and TRBC 11;

i) an interchain disulfide bond between cysteine residue substitutions at positions TRAC 128 and TRBC 11;

j) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 39 and TRAC 85;

k) an intrachain disulfide bond between cysteine residue substitutions at positions TRAC 26 and TRAC 85.1;

l) an amino acid substitution at position TRAC 4 from Val to Ala, Thr, Ile, Leu or Met;

m) an amino acid substitution at position TRAC 26 from Thr to Ala, Val, Ile, Leu or Met;

n) an amino acid substitution at position TRAC 39 from Val to Ala, Thr, Ile, Leu or Met;

o) an amino acid substitution at position TRAC 85 from Ala to Ser, Thr, Val, Ile or Met;

p) an amino acid substitution at position TRAC 105 from Ala to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

q) an amino acid substitution at position TRAC 120 from Phe to Tyr or His;

r) an amino acid substitution at position TRBC 6 from Val to Ala, Thr, Ile, Leu or Met;

s) an amino acid substitution at position TRBC 36 from His to Phe, Tyr or Trp;

t) an amino acid substitution at position TRBC 86 from Ser to Ala or Thr;

u) an amino acid substitution at position TRBC 45.3 from Val to Ser, Thr, Glu, Gln, Asp, Asn, His, Lys or Arg;

v) a deletion of 1 to 4 consecutive amino acids of the DE loop in the Cβ domain of the TCR construct, and

w) a replacement of the amino acids at positions TRBC 84.4 to 85.4 with an amino acid sequence of 2 to 4 amino acids, wherein the amino acid sequence allows for formation of a beta-turn,

wherein the numbering of amino acids is IMGT numbering,

and wherein the TCR construct has an increased TCR melting temperature (Tm) as compared to a corresponding TCR construct that does not comprise the two or more stabilizing mutations.

15. The TCR construct according to claim 14, wherein the stabilizing mutations comprise a first interchain disulfide bond and a second interchain disulfide bond, wherein the first and second interchain disulfide bonds are different.

16. The TCR construct according to any one of claims 1 to 15, wherein the amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide is 5 amino acids or less in length.

17. The TCR construct according to any one of claims 1 to 16, wherein the amino acid extension at the C-terminus of the Cβ domain of the TCR beta chain polypeptide comprises all or a part of a sequence of an IgG1 upper hinge region.

18. The TCR construct according to claim 17, wherein the amino acid extension comprises the sequence: EPKSC [SEQ ID NO:19] or EPKSCDKTHT [SEQ ID NO:16].

19. A TCR construct comprising a TCR alpha chain polypeptide and a TCR beta chain polypeptide, the TCR alpha chain polypeptide comprising a variable alpha (Vα) domain and a constant alpha (Cα) domain and the TCR beta chain polypeptide comprising a variable beta (Vβ) domain and a constant beta (Cβ) domain, the TCR construct comprising a combination of amino acid mutations selected from the combinations of amino acid mutations set forth for any one of the variants shown in Table 2, wherein the numbering of amino acids is IMGT numbering.

20. A TCR construct comprising a TCR alpha chain polypeptide and a TCR beta chain polypeptide, the TCR alpha chain polypeptide comprising a variable alpha (Vα) domain and a

constant alpha (Cα) domain and the TCR beta chain polypeptide comprising a variable beta (Vβ) domain and a constant beta (Cβ) domain, the TCR construct comprising a combination of amino acid mutations selected from the combinations of amino acid mutations set forth for any one of the variants shown in Table 3, wherein the numbering of amino acids is IMGT numbering.

21. The TCR construct according to any one of claims 1 to 20, wherein the TCR alpha chain polypeptide or the TCR beta chain polypeptide or both the TCR alpha chain and the TCR beta chain are fused to an immunoglobulin (Ig) Fc region.

22. The TCR construct according to claim 21, wherein the Ig Fc region is an IgG Fc region.

23. The TCR construct according to claim 22, wherein the IgG Fc region is an IgG1 Fc region.

24. A TCR fusion protein comprising one or more TCR constructs according to any one of claims 1 to 20 and a scaffold, wherein at least one of the TCR constructs is fused to the scaffold.

25. The TCR fusion protein according to claim 24, wherein the scaffold comprises an immunoglobulin (Ig) Fc region.

26. The TCR fusion protein according to claim 25, wherein the Ig Fc region is an IgG Fc region, optionally an IgG1 Fc region.

27. The TCR fusion protein according to any one of claims 24 to 26, wherein the TCR fusion protein comprises one, two, three or four TCR constructs.

28. The TCR fusion protein according to any one of claims 24 to 26, wherein the TCR fusion protein comprises two or more TCR constructs, optionally wherein two of the TCR constructs are fused in tandem.

29. The TCR fusion protein according to any one of claims 24 to 28, wherein at least one of the TCR constructs is fused to the scaffold via the TCR beta chain polypeptide.

30. The TCR fusion protein according to any one of claims 24 to 39, wherein the TCR fusion protein further comprises one or more additional biologically active moieties, optionally wherein at least one of the biologically active moieties is fused to the scaffold.

31. The TCR fusion protein according to claim 30, wherein the one or more additional biologically active moieties comprise an antigen-binding domain, optionally wherein the antigen-binding domain is an scFv or a Fab.

32. A pharmaceutical composition comprising a TCR construct according to any one of claims 1 to 23 or a TCR fusion protein according to any one of claims 24 to 31 and a pharmaceutically acceptable carrier or diluent.

33. A polynucleotide or set of polynucleotides encoding a TCR construct according to any one of claims 1 to 23 or a TCR fusion protein according to any one of claims 24 to 31.

34. A method of preparing a TCR construct according to any one of claims 1 to 23 or a TCR fusion protein according to any one of claims 24 to 31 comprising transfecting a cell with a polynucleotide or set of polynucleotides according to claim 33, and culturing the cell under conditions suitable for expression of the TCR construct.

35. The method according to claim 34, wherein the cell is cultured at a temperature of 30^{o}C to 35^{o}C.

36. A TCR construct according to any one of claims 1 to 23 or a TCR fusion protein according to any one of claims 24 to 31 for use in therapy.