CLAIMS

1. A multispecific polypeptide comprising a first binding domain, designated B1, which is capable of specifically binding to GITR, and a second binding domain, designated B2, which is capable of specifically binding to CTLA-4.

2. A polypeptide according to Claim 1, in which the first and/or second binding domains are selected from the group consisting of: antibodies or antigen-binding fragments thereof; optionally, in which the antigen-binding fragment is selected from the group consisting of: an Fv fragment (such as a single chain Fv fragment, or a disulphide-bonded Fv fragment), a Fab-like fragment (such as a Fab fragment; a Fab' fragment or an $F(ab)_2$ fragment) and domain antibodies.

3. A polypeptide according to Claim 1 or 2, in which the polypeptide is a bispecific antibody.

4. A polypeptide according to Claim 1 or 2, in which the first and/or second binding domains is non-antibody polypeptide; optionally, in which B1 comprises or consists of an IgG1 antibody and B2 comprises or consists of a non-immunoglobulin polypeptide, or *vice versa*; and/or in which B2 comprises or consists of a CD86 domain or variant thereof capable of binding to CTLA-4.

5. A polypeptide according to any preceding claim, in which B1 comprises at least one heavy chain (H) and/or at least one light chain (L) and B2 is attached to the at least one heavy chain (H) or least one light chain (L);

optionally, in which B1 comprises:

(a) at least one heavy chain (H) and at least one light chain (L) and B2 is attached to either the heavy chain or the light chain; or

(b) two identical heavy chains (H) and two identical light chains (L) and B2 is attached to both heavy chains or to both light chains;

and/or in which the polypeptide comprises or consists of a polypeptide chain arranged according to any of the following formulae, written in the direction N-C:

(a) L-(X)n-B2;

(b) B2-(X)n-L;

(c) B2-(X)n-H; or

(d) H-(X)n-B2;

in which X is a linker and n is 0 or 1; optionally, in which X is a peptide with the amino acid sequence SGGGGSGGGGS (SEQ ID NO: 47), SGGGGSGGGGSAP (SEQ ID NO: 48), NFSQP (SEQ ID NO:49), KRTVA (SEQ ID NO: 50), GGGGSGGGGSGGGGS (SEQ ID NO: 51) or (SG)m, where m = 1 to 7.

6. A polypeptide according to any preceding claim, comprising a human Fc region or a variant of a the region, where the region is an IgG1, IgG2, IgG3 or IgG4 region, preferably an IgG1 or IgG4 region; optionally, in which the Fc region is a naturally occurring (*i.e.* wildtype) human Fc region or in which the Fc region is a non-naturally occurring (*e.g.* mutated) human Fc region.

7. A polypeptide according to Claim 6, in which the Fc region is afucosylated.

8. A polypeptide according to any preceding claim, in which the polypeptide is capable of inducing antibody dependent cell cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), apoptosis, tumour immunity, and/or i) killing GITR expressing tumour cells and ii) activating the immune system via activation of effector T cells.

9. A polypeptide according to any preceding claim, which binds to human GITR with a Kd of less than 10 $x10^{-9}$M, 4 $x10^{-9}$M, or $1x10^{-9}$M and/or which binds to human CTLA-4 with a Kd value which is less than $60x10^{-9}$M, $25x10^{-9}$M, or $10x10^{-9}$M.

10. A polypeptide according to any preceding claim, which induces an increase in the activity of an effector T cell; optionally, in which the increase is at least 1.5-fold, 4.5-fold or 7-fold higher than the increase in activity of an effector T cell induced by a combination of the first and second binding domains administered to the T cell as separate molecules; optionally, in which the increase in T cell activity is an increase in proliferation and/or IFNγ or IL-2 production by the T cell.

11. A polypeptide according to any preceding claim, in which B1 is an antibody, or antigen binding fragment thereof, specific for GITR; and B2 is a polypeptide binding domain specific for CTLA-4, which comprises or consists of:

(a) the amino acid sequence of SEQ ID NO: 3; or

(b) an amino acid sequence in which at least one amino acid is changed when compared to the amino acid sequence of SEQ ID NO: 3 provided that the binding domain binds to human CTLA-4 with higher affinity than wild-type human CD86.

12. A polypeptide according to any of Claims 6 to 10, in which 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids in the amino acid sequence of B2 (ii) are substituted when compared to the amino acid sequence of SEQ ID NO: 3; optionally, in which there are no insertions or deletions compared to the amino acid sequence of SEQ ID NO: 3; optionally, in which at least one of the amino acid substitutions in the amino acid sequence of B2 is at position 122, and optionally, in which the amino acid sequence is also substituted in at least one of positions 107, 121 and 125.

13. A polypeptide according to any preceding claim, in which the amino acid sequence of B2 comprises or consists of an amino acid sequence selected from any one of SEQ ID NOs 6 to 24.

14. A polypeptide according to any preceding claim, in which the GITR binding domain (B1) is capable of competitively inhibiting the binding to human GITR of an antibody comprising a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 61, 63, 65 and 67 and a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 54, 56 and 58 or in which the GITR binding domain (B1) comprises a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 61, 63, 65 and 67 and/or a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 54, 56 and 58; optionally, in which B1 comprises a light chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 88, 89 and 90 and/or a heavy chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 76, 77 and 78 or in which B1 comprises a light chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 91, 92 and 93 and/or a heavy chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 79, 80 and 81 or in which B1 comprises a light chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 94, 89 and 95 and/or a heavy chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 82, 83 and 84 or in which B1 comprises a light chain variable region amino acid sequence

comprising the CDRs of SEQ ID NOs: 94, 89 and 96 and/or a heavy chain variable region amino acid sequence comprising the CDRs of SEQ ID NOs: 85, 86 and 87.

15. A polypeptide according to any preceding claim, comprising or consisting of:

(a) a light chain amino acid sequence selected from SEQ ID NOs: 69, 71, 73 and 75; and

(b) a heavy chain variable region amino acid sequence selected from the group consisting of 52, 54, 56 and 58.

16. A polypeptide according to any preceding claim, further comprising at least one further binding domain; optionally, in which the at least one further binding domain is an antigen-binding fragment selected from the group consisting of: an Fv fragment (such as a single chain Fv fragment, or a disulphide-bonded Fv fragment), a Fab-like fragment (such as a Fab fragment; a Fab' fragment or a $F(ab)_2$ fragment) and domain antibodies.

17. A polypeptide according to any preceding claim, further comprising an additional therapeutic moiety.

18. A composition comprising a bispecific polypeptide according to any of Claims 1 to 14 and at least one pharmaceutically acceptable diluent or carrier.

19. A polynucleotide encoding a bispecific polypeptide according to any of Claims 1 to 16, or a component polypeptide chain thereof.

20. A bispecific polypeptide according to any of Claims 1 to 16 for use in the treatment or prevention of a neoplastic disease or condition in an individual.

21. Use of a bispecific polypeptide according to any of Claims 1 to 16 in the preparation of a medicament for treating or preventing a neoplastic disease or condition in an individual.