CLAIMS:

1. An isolated CTLA-4 polypeptide, the polypeptide comprising an amino acid sequence that is a variant of SEQ ID NO: 35, wherein the variant comprises the following combination of mutations:

R at I16; T at A24; N at S25; S at G27; A at L58; A at S70; Q at M85; and Q at K93,

wherein the CTLA-4 polypeptide has greater affinity for binding human CD80, greater potency and/or greater stability compared with wild type CTLA-4 SEQ ID NO: 35.

2. A CTLA-4 polypeptide comprising the amino acid sequence of SEQ ID NO: 43.

3. A CTLA-4 polypeptide according to claim 1 or 2, having an affinity of 50 nM or less for binding human CD80, wherein affinity is K_D as determined by surface plasmon resonance, optionally wherein the polypeptide has an affinity of 20 nM or less for binding human CD80.

4. A CTLA-4 polypeptide according to any one of claims 1-3, wherein the polypeptide has greater affinity than wild type CTLA-4 (SEQ ID NO: 35) for binding human CD86.

5. A CTLA-4 polypeptide according to any one of claims 1 to 4, which has at least 10-fold greater affinity for binding CD80 than for binding CD86, optionally wherein the polypeptide has at least 50-fold greater affinity for binding CD80 than for binding CD86.

6. A CTLA-4 polypeptide according to any one of claims 1-5, conjugated to an IgG Fc amino acid sequence,

optionally wherein the IgG Fc is a human IgG1 Fc modified to reduce Fc effector function, and comprises a native human IgG1 Fc hinge region,

optionally wherein the IgG Fc amino acid sequence comprises a human IgG1 Fc region in which one or both of the following groups of residues are substituted as follows:

F at residue 20; E at residue 21; S at residue 117; and

Y at residue 38, T at residue 40, E at residue 42,

the residue numbering being defined with reference to SEQ ID NO: 56.

7. A CTLA-4 polypeptide according to claim 6, wherein the IgG Fc amino acid sequence comprises SEQ ID NO: 59.

8. A CTLA-4 polypeptide according to any one of claims 1-7, wherein the polypeptide comprises the sequence of SEQ ID NO: 13.

9. A CTLA-4 polypeptide according to any one of claims 1-8, wherein the polypeptide is in a multimer, optionally wherein the CTLA-4 polypeptide is in a dimer or a tetramer, and optionally, when the polypeptide is in a tetramer, the tetramer comprises two pairs of CTLA-4 polypeptides, each pair comprising a CTLA-4 polypeptide fused to an antibody light chain constant region and a CTLA-4 polypeptide fused to an antibody heavy chain constant region.

10. A host cell containing a nucleic acid, wherein the nucleic acid encodes a CTLA-4 polypeptide according to any one of claims 1-9.

11. A composition comprising:
a CTLA-4 polypeptide according to any one of claims 1-9; and
one or more pharmaceutical excipients.

12. A composition according to claim 11, comprising the CTLA-4 polypeptide at a concentration of at least 70 mg/ml, optionally at a concentration of at least 100 mg/ml.

13. A CTLA-4 polypeptide according to any one of claims 1-9, or a composition according to claim 11 or 12, for use in therapy of a patient by subcutaneous or intravenous administration.

14. A CTLA-4 polypeptide according to any one of claims 1-9, or a composition according to claim 11 or 12, for use in the treatment of rheumatoid arthritis, multiple sclerosis, asthma, Crohn's disease, ulcerative colitis, systemic lupus erythematosus or transplant rejection.

15. A host cell containing a nucleic acid, wherein the nucleic acid encodes a CTLA-4 polypeptide conjugated to IgG Fc amino acid sequence according to any one of claims 6-7.

16. A composition comprising:
a CTLA-4 polypeptide conjugated to IgG Fc amino acid sequence according to any one of claims 6-7; and
one or more pharmaceutical excipients.

17. A composition according to claim 16, comprising the CTLA-4 polypeptide conjugated to IgG Fc amino acid sequence, at a concentration of at least 70 mg/ml, optionally at a concentration of at least 100 mg/ml.

18. A CTLA-4 polypeptide conjugated to IgG Fc amino acid sequence according to any one of claims 6-7, or a composition according to claim 16 or 17, for use in therapy of a patient by subcutaneous or intravenous administration.

19. A CTLA-4 polypeptide conjugated to IgG Fc amino acid sequence according to any one of claims 6-7, or a composition according to claim 16 or 17, for use in the treatment of rheumatoid arthritis, multiple sclerosis, asthma, Crohn’s disease, ulcerative colitis, systemic lupus erythematosus or transplant rejection.