TGFb1 is a dimeric cytokine which shares a cysteine knot structure connected together by intramolecular disulfide bonds. TGFb1 is synthesized as a monomeric 390-amino acid precursor protein, which is referred to interchangeably as: TGFb1 pre-protein; TGFb1 precursor; full-length TGFb1; pre-pro-TGFb1. The full-length sequence of the TGFb1 pre-protein is provided as SEQ ID NO: 1.

The TGFb1 pre-protein monomer has a molecular weight of about 25 kDa. The TGFb1 protein monomer has three distinct domains: the signal peptide (SP: amino acids 1-29; SEQ ID NO: 2), the latency associated peptide (LAP: amino acids 30-278; SEQ ID NO: 3) and the mature peptide (mature TGFb1: amino acids 279-390; SEQ ID NO: 4), as shown in Figure 1E.

The TGFb1 SP targets the protein to a secretory pathway; the SP is cleaved off in the rough endoplasmatic reticulum. TGFb1 monomers comprising the LAP and mature TGFb1 may dimerize in the endoplasmic reticulum via disulfide bridges between cysteine residues in the LAP (e.g. Cys 223 and Cys 225) and the mature TGFb1 peptide (e.g. Cys 356) to form a TGFb1 homodimer. This TGFb1 homodimer is referred to as the small latent complex (SLC). The SLC may be bound by so-called latent TGF-β-Binding Protein (LTBP) to form a larger complex referred to as the large latent complex (LLC). The LLC may be secreted into extracellular media (ECM). However, the presence of LAP and the LTBP prevent TGFb1 from binding to, and activating, its extracellular receptors. Active TGFb1 consists of a homodimer of mature TGFb1 peptides. There are various mechanisms by which the mature TGFb1 homodimer is released from LAP and LTBP, which include degradation of LAP by proteases, induction of conformational change in LAP by interaction with thrombospondin, and rupture of noncovalent bonds between LAP and TGFβ-1.

In one aspect, the present disclosure refers to a polypeptide which is an immunogenic fragment of human transforming growth factor 1 (TGFb1) and which comprises of a sequence of at least 9 consecutive amino acids of SEQ ID NO: 1, wherein (a) the polypeptide consists of up to 18 consecutive amino acids of SEQ ID NO: 1 and comprises the amino acid sequence of SEQ ID NO: 66, or (b) the polypeptide consists of up to 50 consecutive amino acids of SEQ ID NO: 1 and comprises the amino acid sequence of SEQ ID NO: 28. In another aspect, the present disclosure refers to a polynucleotide encoding a polypeptide as disclosed herein, optionally comprised within a vector. In another aspect, the present disclosure refers to a composition comprising a polypeptide as disclosed herein, and optionally an adjuvant. In another aspect, the present disclosure refers to the polypeptide as disclosed herein, and/or the composition as disclosed herein for use in therapy.

In another aspect, the present disclosure refers to the use of the polypeptide as disclosed herein, and/or the composition as disclosed herein in the manufacture of a medicament for treating or preventing a disease or condition in a subject, wherein the disease or condition is a cancer. In yet another aspect, the present disclosure refers to a method of stimulating TGFb1-specific T cells, the method comprising contacting the T cells with: the polypeptide as disclosed herein; and/or a composition as disclosed herein, wherein the composition comprises at least one polypeptide as defined herein.

An object of the present disclosure is the development of a T-cell-mediated mechanism for depriving TGFb1 from TME. The present inventors investigated the existence of spontaneous TGFb1-specific T-cell responses *in vivo* by screening PBMCs from healthy donors and cancer patients. TGFb1-specific T-cell populations were then be isolated, expanded and characterized by various assays regarding HLA restriction, cytokines production and cytotoxicity.

The present inventors have identified regions of human TGFb1 which have greatest immunogenicity. Surprisingly, these immunogenic “hot spot” regions are located throughout the human TGFb1 pre-protein, including within the SP and LAP domains, as well as the mature TGFb1 peptide. The present inventors have also identified a sub-region within the

CLAIMS

1. A polypeptide which is an immunogenic fragment of human transforming growth factor 1 (TGFb1) and which comprises a sequence of at least 9 consecutive amino acids of SEQ ID NO: 1, wherein

(a) the polypeptide consists of up to 18 consecutive amino acids of SEQ ID NO: 1 and comprises the amino acid sequence of SEQ ID NO: 66, or

(b) the polypeptide consists of up to 50 consecutive amino acids of SEQ ID NO: 1 and comprises the amino acid sequence of SEQ ID NO: 28.

2. The polypeptide of claim 1, which comprises or consists of up to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45 or 50 consecutive amino acids of SEQ ID NO: 1.

3. The polypeptide of claim 1 or 2, which comprises or consists of the amino acid sequence of any one of SEQ ID NOs: 66, 28-31 or 65, or comprises the amino acid sequence of any one of SEQ ID NOs: 23-26.

4. The polypeptide of claim 3, which comprises or consists of the amino acid sequence of SEQ ID NOs: 66 or 28, or comprises the amino acid sequence of SEQ ID NO: 23.

5. The polypeptide of any one of claims 1-4, which has a maximum length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45 or 50 amino acids and/or in which the C terminal amino acid is replaced with the corresponding amide.

6. The polypeptide of any one of claims 1-5, which comprises a HLA-A2 restricted epitope, optionally wherein the HLA-A2-restricted epitope comprises or consists of the amino acid sequence of SEQ ID NO: 66.

7. A polynucleotide encoding a polypeptide according to any one of claims 1-6, optionally comprised within a vector.

8. A composition comprising a polypeptide according to any one of claims 1-6 and/or a polynucleotide according to claim 7; and optionally an adjuvant.

9. The composition of claim 8 further comprising at least one different polypeptide according to any one of claims 1-6; at least one different polynucleotide according to claim 7; and/or at least one pharmaceutically acceptable diluent, carrier or preservative.

10. The composition of claim 8 or 9, which comprises an adjuvant selected from the group consisting of bacterial DNA based adjuvants, oil/surfactant based adjuvants, viral dsRNA based adjuvants, imidazoquinolines, and a Montanide ISA adjuvant.

11. The polypeptide of any one of claims 1-6, the polynucleotide of claim 7, and/or the composition of any one of claims 8-10 for use in therapy.

12. Use of the polypeptide of any one of claims 1-6, the polynucleotide of claim 7, and/or the composition of any one of claims 8-10 in the manufacture of a medicament for treating or preventing a disease or condition in a subject, wherein the disease or condition is a cancer.

13. The use of claim 12, wherein the cancer is selected from the group consisting of a breast cancer, a cervical cancer, a gastric cancer, a liver cancer, an ovarian cancer, a pancreatic cancer, a lung cancer (such as a non-small-cell lung carcinoma (NSCLC)), a melanoma, a leukemia (such as an acute myeloid leukemia), or a prostate cancer.

14. The use of claim 12 or 13, wherein the use further comprises that an additional cancer therapy, preferably an antibody, is to be administered to the subject simultaneously or sequentially.

15. A method of stimulating TGFb1-specific T cells, the method comprising contacting the T cells with: the polypeptide of any one of claims 1-6; and/or a composition of any one of claims 8-10, wherein the composition comprises at least one polypeptide as defined in any one of claims 1-6.

16. The method of claim 15, wherein the T cells are present in a sample taken from a healthy subject or from a cancer patient, optionally a tumour sample.