

MULTIMERIC T-CELL MODULATORY POLYPEPTIDES AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/023,834, filed May 12, 2020, and U.S. Provisional Patent Application No. 63/041,451, filed June 19, 2020, which applications are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING PROVIDED AS A TEXT FILE

[0002] A Sequence Listing is provided herewith as a text file, “CUEB-133WO_SEQ_LIST2_ST25.txt” created on May 7, 2021 and having a size of 800 KB. The contents of the text file are incorporated by reference herein in their entirety.

INTRODUCTION

[0003] An adaptive immune response involves the engagement of the T cell receptor (TCR), present on the surface of a T cell, with a small peptide antigen non-covalently presented on the surface of an antigen presenting cell (APC) by a major histocompatibility complex (MHC; also referred to in humans as a human leukocyte antigen (HLA) complex). This engagement represents the immune system’s targeting mechanism and is a requisite molecular interaction for T cell modulation (activation or inhibition) and effector function. Following epitope-specific cell targeting, the targeted T cells are activated through engagement of costimulatory proteins found on the APC with counterpart costimulatory proteins the T cells. Both signals – epitope/TCR binding and engagement of APC costimulatory proteins with T cell costimulatory proteins – are required to drive T cell specificity and activation or inhibition. The TCR is specific for a given epitope; however, the costimulatory protein not epitope specific and instead is generally expressed on all T cells or on large T cell subsets.

SUMMARY

[0004] The present disclosure provides T-cell modulatory multimeric polypeptides (TMMPs) that comprise an immunomodulatory polypeptide and that comprise an epitope-presenting Wilms tumor peptide. A T-cell modulatory multimeric polypeptide is useful for modulating the activity of a T cell, and for modulating an immune response in an individual.

[0004a] In one aspect, the present disclosure refers to a T-cell modulatory multimeric polypeptide comprising

at least one heterodimer, wherein the at least one heterodimer comprises:

- a) a first polypeptide comprising
 - i) a Wilms tumor-1 (WT-1) peptide epitope, wherein the WT-1 peptide epitope has a length from 8 amino acids to 16 amino acids,
 - ii) a beta-2 microglobulin (β 2M) polypeptide, and
 - iii) a linker between the WT-1 peptide and the β 2M polypeptide, wherein the linker comprises a Cys residue; and
 - b) a second polypeptide comprising
 - i) a major histocompatibility complex (MHC) class I heavy chain polypeptide,
 - ii) an immunoglobulin (Ig) Fc polypeptide, and
 - iii) at least one activating immunomodulatory polypeptide,
- wherein the heterodimer comprises a first disulfide bond formed between (i) the Cys residue in the linker between the WT-1 peptide epitope and the β 2M polypeptide, and (ii) a Cys residue in the MHC class I heavy chain polypeptide,
- wherein the heterodimer comprises a second disulfide bond formed between a Cys residue in the β 2M polypeptide and a Cys residue in the MHC class I heavy chain polypeptide, and wherein the Ig Fc polypeptide does not comprise a C-terminal lysine.

[0004b] In one aspect, the present disclosure refers to a composition comprising one or more nucleic acids encoding the first and second polypeptides of a T cell modulatory multimeric polypeptide as disclosed herein.

[0004c] In one aspect, the present disclosure refers to a composition comprising one or more expression vectors comprising the one or more nucleic acids as disclosed herein.

[0004d] In one aspect, the present disclosure refers to use of a T-cell modulatory multimeric polypeptide as disclosed herein in the manufacture of a medicament for selectively modulating the activity of a T cell specific for a Wilms tumor-1 (WT-1) epitope.

[0004e] In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising T-cell modulatory multimeric polypeptide as disclosed herein in the manufacture of a medicament for treating cancer in a patient.

[0004f] In one aspect, the present disclosure refers to use of a T-cell modulatory multimeric polypeptide as disclosed herein in the manufacture of a medicament for delivering an immunomodulatory polypeptide selectively to a target T cell in a mixed population comprising non-target T cells and the target T cell, wherein the target T cell is specific for the WT-1 epitope present within the T-cell modulatory multimeric polypeptide, and wherein said immunomodulatory polypeptide present within the T-cell modulatory multimeric polypeptide is delivered to the target T cell.

[0004g] In one aspect, the present disclosure refers to a method of detecting, in a mixed population of T cells obtained from an individual, the presence of a target T cell that binds a WT-1 epitope, the method comprising:

- a) contacting *in vitro* the mixed population of T cells with the T-cell modulatory multimeric polypeptide as disclosed herein, wherein the T-cell modulatory multimeric polypeptide comprises the WT-1 epitope; and
- b) detecting activation and/or proliferation of T cells in response to said contacting, wherein activated and/or proliferated T cells indicates the presence of the target T cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0001] FIG. 1A-1F are schematic depictions of various TMMPs of the present disclosure.