In WO 2005/099361 are reported MHC class I - peptide-antibody conjugates with modified beta-2-microglobulin. Exemplary conjugates as reported in WO 2005/099361 are obtained by in vitro conjugation of the alpha chain of the MHC-multi-function protein (HLA) or by the co-expression from separate genes in the same cell.

In US 2004/0091488 antigenic constructs of major histocompatibility multi-function protein class I antigens with specific carrier molecules are reported. These reported fusion polypeptides lack the hinge region.

In WO 99/13095 the use of multivalent chimeric peptide-loaded MHC/IG molecules to detect, activate or suppress antigen-specific T cell-dependent immune responses. Methods and pharmaceutical compositions for immune depletion, particularly useful in the treatment of cancer are reported in WO 02/102299. Oelke, M., et al. (Nat. Med. 9 (2003) 619-624) report the ex vivo induction and expansion of antigen-specific cytotoxic T cells by HLA-Ig coated artificial antigen presenting cells. The removal of target cells by circulating virus-specific cytotoxic T-cells using MHC class I comprising complexes is reported in WO 2012/175508. Robert, B., et al. (Eur. J. Immunol. 30 (2000) 3165-3170) report that antibody-conjugated MHC class I tetramers can target tumor cells for specific lysis by T lymphocytes.

Summary ~~of the Invention~~

Herein is reported a disulfide-linked multivalent multi-function protein comprising one, two or more, in one embodiment one, in another embodiment two or four, antigen presenting domains as first part, one antibody Fc-region as second part, and at least one antigen binding site that is derived from an antibody and that specifically binds to a target antigen as third part.

With the disulfide-linked multivalent multi-function protein as reported herein existing virus-specific circulating cytotoxic T-cells (T-memory-cells and/or T-effector-cells) of an individual can be directed to cells expressing the target antigen, to which the antibody derived part of the disulfide-linked multivalent multi-function protein specifically binds to. Thereafter by dressing these cells with a MHC class I complex an acute viral infection by the virus-derived peptide linked to the MHC class I protein multi-function protein is mimicked and cytotoxic cells are attracted resulting in the removal of the targeted cell.

The present disclosure relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one, two or more than two antigen presenting domains,

- exactly one antibody Fc-region, and

- one or more antigen binding sites,

wherein the antigen presenting domains comprise independently of each other in N- to C-terminal direction

either

(i) a β2-microglobulin, and

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %,

or

(i) a T-cell response eliciting peptide,

(ii) a β2-microglobulin, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

or

(i) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %, and

(ii) a β2-microglobulin,

or

(i) a T-cell response eliciting peptide,

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and

(iii) a β2-microglobulin,

wherein the antigen binding site or sites bind to a cancer cell surface antigen or a virus-infected cell surface antigen, and

wherein the antigen presenting domain has at least two non-naturally occurring cysteine residues that form an intrachain/interdomain disulfide bond.

One aspect as reported herein is a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains,
- one antibody Fc-region, and
- one or more antigen binding sites,

wherein the antigen presenting domain comprises in N- to C-terminal direction

either

(i) a β2-microglobulin, and

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %,

or

(i) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %, and

(ii) a β2-microglobulin,

or

(i) a T-cell response eliciting peptide,

(ii) a β2-microglobulin, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

or

(i) a T-cell response eliciting peptide,

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and

(iii) a β2-microglobulin,

wherein the antigen binding site binds to a cancer cell surface antigen,

wherein the antigen presenting domain has at least two non-naturally occurring cysteine residues that form an intrachain/interdomain disulfide bond.

In one embodiment one non-naturally occurring cysteine residue in the antigen presenting domain is in the linker between T-cell response eliciting peptide and one

D265, D270, N297, E318, K320, K322, A327, P329, A330, and/or P331 (numbering according to the EU index of Kabat).

In one embodiment the antibody Fc-region is of a human antibody of the subclass IgG1 or the human subclass IgG2 with the mutations L234A and L235A, and/or the mutations D265A and N297A, and/or contains the PVA236 mutation, and/or contains the mutation P329G.

In one embodiment the antibody Fc-region is of a human antibody of the subclass IgG1 with the mutations L234A and L235A and/or P329G.

In one embodiment the antibody Fc-region is of a human antibody of the subclass IgG4 with the mutation S228P and/or L235E.

In one embodiment the first and second antibody Fc-region polypeptide is selected independently of each other from the group comprising SEQ ID NO: 87 to 101.

In one embodiment the antibody Fc-region comprises two Fc-region polypeptides with the amino acid sequence of SEQ ID NO: 94.

In one embodiment the antibody Fc-region comprises two Fc-region polypeptides with the amino acid sequence of SEQ ID NO: 100.

In one embodiment the antibody Fc-region comprises two Fc-region polypeptides with the amino acid sequence of SEQ ID NO: 101.

In one embodiment the antibody Fc-region comprises a first Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 89 and a second Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 90.

In one embodiment the antibody Fc-region comprises a first Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 97 and a second Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 98.

In one embodiment the antibody Fc-region comprises a first Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 102 and a second Fc-region polypeptide with the amino acid sequence of SEQ ID NO: 103.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise independently of each other in N- to C-terminal direction

  either
  (i) a β2-microglobulin, and
  (ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %,

  or
  (i) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %, and
  (ii) a β2-microglobulin,

  or
  (i) a T-cell response eliciting peptide,
  (ii) a β2-microglobulin, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

  or
  (i) a T-cell response eliciting peptide,
  (ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and
  (iii) a β2-microglobulin,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 or position 227 and the cysteine residues at position 11 and position 108 or 227 form a disulfide bond,

- exactly one antibody Fc-region, and

- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide,
  (ii) a β2-microglobulin, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

(i) a T-cell response eliciting peptide,
(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and
(ii) a β2-microglobulin,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond,

- exactly one antibody Fc-region, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprises in N- to C-terminal direction

(i) a T-cell response eliciting peptide of SEQ ID NO: 01,
(ii) a β2-microglobulin of SEQ ID NO: 71, and
(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprises in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72, and
  (ii) a β2-microglobulin of SEQ ID NO: 71, and

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond,

- exactly one antibody Fc-region, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,
  (iii) a β2-microglobulin of SEQ ID NO: 71, and

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprises in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprises in N- to C-terminal direction

(i) a T-cell response eliciting peptide of SEQ ID NO: 01,
(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,
(iii) a β2-microglobulin of SEQ ID NO: 71, and

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and
- one or more antigen binding sites.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

    (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
    (ii) a β2-microglobulin of SEQ ID NO: 71, and
    (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

    wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- one or more antigen binding sites, which comprise an antibody light chain variable domain comprising an amino acid sequence selected from SEQ ID NO: 104 to 106, and an antibody heavy chain variable domain comprising SEQ ID NO: 108 to 110, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP).

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

    (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
    (ii) a β2-microglobulin of SEQ ID NO: 71, and
    (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

    wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and

- one or more antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which comprises an antibody light chain with a variable domain comprising SEQ ID NO: 104 to 106 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 108 to 110.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domain, which comprises in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- two antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which each comprise an antibody light chain with a variable domain comprising SEQ ID NO: 105 to 107 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 110 to 112.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and

- one or more antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which comprises an antibody light chain with a variable domain comprising SEQ ID NO: 105 to 107 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 110 to 112, whereby the Fc-region of the antibody heavy chain is one of the disulfide-linked Fc-region polypeptides.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- one or more antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which comprise an antibody light chain with a variable domain comprising SEQ ID NO: 104 to 106 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 108 to 110, whereby the Fc-region of the antibody heavy chain is one of the disulfide-linked Fc-region polypeptides,

wherein the antigen presenting domain is linked to the N-terminus of one of the variable domains.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and

- two antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which each comprise an antibody light chain with a variable domain comprising SEQ ID NO: 104 to 106 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 108 to 110, whereby the Fc-regions of the antibody heavy chains are the disulfide-linked Fc-region polypeptides,

wherein the antigen presenting domain is linked to the N-terminus of one of the variable domains.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 97 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 98, and

- two antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which each comprise an antibody light chain with a variable domain comprising SEQ ID NO: 105 to 107 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 110 to 112, whereby the Fc-regions of the antibody heavy chains are the disulfide-linked Fc-region polypeptides,

wherein the antigen presenting domain is linked to the N-terminus of one of the heavy chain variable domains.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains, which comprise in N- to C-terminal direction

  (i) a T-cell response eliciting peptide of SEQ ID NO: 01,
  (ii) a β2-microglobulin of SEQ ID NO: 71, and
  (iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule of SEQ ID NO: 72,

  wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond,

- exactly one antibody Fc-region, which comprises two disulfide-linked Fc-region polypeptides, whereof the first disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 102 and the second disulfide-linked Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 103, and

- two antigen binding sites, which specifically bind to melanoma-associated chondroitin sulfate proteoglycan (MCSP), and which each comprise an antibody light chain with a variable domain comprising SEQ ID NO: 105 to 107 and an antibody heavy chain with a variable domain comprising SEQ ID NO: 110 to 112, whereby the Fc-regions of the antibody heavy chains are the disulfide-linked Fc-region polypeptides,

wherein the antigen presenting domain is linked to the N-terminus of one of the heavy chain variable domains.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one polypeptide chain of SEQ ID NO: 117,

- one polypeptide chain of SEQ ID NO: 118,

- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one polypeptide chain of SEQ ID NO: 137,
- one polypeptide chain of SEQ ID NO: 118,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one polypeptide chain of SEQ ID NO: 117,
- one polypeptide chain of SEQ ID NO: 118,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one polypeptide chain of SEQ ID NO: 137,
- one polypeptide chain of SEQ ID NO: 118,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- two polypeptide chains of SEQ ID NO: 117,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- two polypeptide chains of SEQ ID NO: 137,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- two polypeptide chains of SEQ ID NO: 117,
- two polypeptide chains each of SEQ ID NO: 119,

wherein the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond.

The present disclosure also relates to ~~One aspect as reported herein is~~ a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- two polypeptide chains of SEQ ID NO: 137,
- two polypeptide chains each of SEQ ID NO: 119,

and an antibody light chain variable domain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 107; an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 105; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 106.

In one embodiment the MCSP binding site comprises an antibody heavy chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 114; and an antibody light chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 113.

In one embodiment the MCSP binding site comprises an antibody heavy chain variable domain of SEQ ID NO: 114 and an antibody light chain variable domain of SEQ ID NO: 113.

In one embodiment the MCSP binding site comprises SEQ ID NO: 114 and SEQ ID NO: 113.

In one embodiment the MCSP binding site comprises an antibody heavy chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 116; and an antibody light chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 115.

In one embodiment the MCSP binding site comprises an antibody heavy chain variable domain of SEQ ID NO: 116; and an antibody light chain variable domain of SEQ ID NO: 115.

In one embodiment the MCSP binding site comprises SEQ ID NO: 116 and SEQ ID NO: 115.

The present disclosure also relates to ~~In one aspect, the invention provides~~ disulfide-linked multivalent multi-function proteins comprising the binding specificity, i.e. HVRs or variable domains, of isolated antibodies that bind to MCSP. In particular, the anti-MCSP antibody binding specificity, i.e. HVRs or variable domains, comprised in the disulfide-linked multivalent multi-function proteins as provided herein bind to a membrane proximal epitope of human MCSP. As discussed in Staub, E., et al. (FEBS Lett. 527 (2002) 114-118), the membrane proximal region of MCSP is comprised of multiple novel repeated domains, referred to as CSPG repeat domains.

The present disclosure also relates to ~~One aspect as reported herein is~~ a nucleic acid encoding the disulfide-linked multivalent multi-function protein as reported herein.

In one embodiment the nucleic acid comprises two to four expression cassettes comprising structural genes encoding polypeptides with different amino acid sequence.

The present disclosure also relates to ~~One aspect as reported herein is~~ a host cell comprising the nucleic acid as reported herein.

The present disclosure also relates to ~~One aspect as reported herein is~~ a method of producing a disulfide-linked multivalent multi-function protein as reported herein comprising culturing the host cell as reported herein so that the disulfide-linked multivalent multi-function protein is produced.

In one embodiment the disulfide-linked multivalent multi-function protein is recovered from the cells or the cultivation medium and thereby the disulfide-linked multivalent multi-function protein is produced.

One aspect as reported herein is a pharmaceutical formulation comprising the disulfide-linked multivalent multi-function protein as reported herein and optionally a pharmaceutically acceptable carrier.

In one embodiment the pharmaceutical formulation further comprises an additional therapeutic agent.

One aspect as reported herein is the disulfide-linked multivalent multi-function protein as reported herein for use as a medicament.

One aspect as reported herein is the disulfide-linked multivalent multi-function protein as reported herein for use in treating cancer.

~~One aspect as reported herein is t~~The present disclosure also relates to the disulfide-linked multivalent multi-function protein as reported herein for use in treating a virus infection.

One aspect as reported herein is the disulfide-linked multivalent multi-function protein as reported herein for use in attracting virus-specific cytotoxic T-cells of an individual to a target.

One aspect as reported herein is the disulfide-linked multivalent multi-function protein as reported herein for use in elimination (removal) of cancer cells or virus infected cells.

~~One aspect as reported herein is the disulfide-linked multivalent multi-function protein as reported herein for use in elimination (removal) of virus-infected cells.~~

~~One aspect as reported herein is t~~The present disclosure also relates to use of the disulfide-linked multivalent multi-function protein as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for treatment of cancer.

In one embodiment the medicament is for treatment of a viral infection.

In one embodiment the medicament is for attracting virus-specific cytotoxic T-cells of an individual to a target.

In one embodiment the medicament is for elimination (removal) of cancer cells.

In one embodiment the medicament is for elimination (removal) of virus infected cells.

The present disclosure also relates to ~~One aspect as reported herein is a~~ method of treating an individual having cancer comprising administering to the individual an effective amount of the disulfide-linked multivalent multi-function protein as reported herein.

In one embodiment the method further comprises administering an additional therapeutic agent to the individual.

The present disclosure also relates to ~~One aspect as reported herein is a~~ method of treating an individual having a viral infection comprising administering to the individual an effective amount of the disulfide-linked multivalent multi-function protein as reported herein.

In one embodiment the method further comprises administering an additional therapeutic agent to the individual.

The present disclosure also relates to ~~One aspect as reported herein is a~~ method of attracting virus-specific cytotoxic T-cells of an individual to a target in an individual comprising administering to the individual an effective amount of the disulfide-linked multivalent multi-function protein as reported herein to attract virus-specific cytotoxic T-cells of an individual to a target.

The present disclosure also relates to ~~One aspect as reported herein is a~~ method of removal of cancer cells in an individual comprising administering to the individual an effective amount of the disulfide-linked multivalent multi-function protein as reported herein to remove/disintegrate cancer cells.

The present disclosure also relates to ~~One aspect as reported herein is~~ a method of removal of virus-infected cells in an individual comprising administering to the individual an effective amount of the disulfide-linked multivalent multi-function protein as reported herein to remove/disintegrate virus-infected cells.

The present disclosure also relates to ~~One aspect as reported herein is~~ a method for the recombinant production of a disulfide-linked multivalent multi-function protein comprising i) a fusion polypeptide of β2-microglobulin and the extracellular domains α1, α2 and α3 of a class I MHC molecule, ii) a pair of disulfide-linked polypeptide chains each comprising an antibody hinge region, and iii) at least one pair of an antibody light chain variable domain and an antibody heavy chain variable domain in a eukaryotic cell, comprising the steps of i) cultivating a eukaryotic cell comprising one or more nucleic acids encoding the disulfide-linked multivalent multi-function protein, and ii) recovering the disulfide-linked multivalent multi-function protein from the cell or the cultivation medium, wherein the disulfide-linked multivalent multi-function protein comprises one, two or more disulfide-linked fusion polypeptides of β2-microglobulin and the extracellular domains α1, α2 and α3 of a class I MHC molecule, wherein the disulfide bind is between residues 11 and 227.

In one embodiment the disulfide-linked multivalent multi-function protein comprises one MHC-derived polypeptide or one fusion polypeptide comprising an MHC-derived molecule.

In one embodiment the disulfide-linked multivalent multi-function protein comprises two MHC-derived polypeptides or two fusion polypeptides comprising an MHC-derived molecule.

In one embodiment the disulfide-linked multivalent multi-function protein is obtained with a concentration of 1 mg/L or more in the cultivation medium. In one embodiment the disulfide-linked multivalent multi-function protein is obtained with a concentration of 4 mg/L or more in the cultivation medium.

In one embodiment the eukaryotic cell is a mammalian cell. In one embodiment the mammalian cell is a human embryonic kidney cell, or a chinese hamster ovary cell, or a baby hamster kidney cell, or a mouse myeloma cell.

The following embodiments can be combined with any of the aspects as reported herein. Also any embodiment as reported herein can be combined with any other embodiment or combination of embodiments as reported herein.