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-complex (HLA) or by the co-expression from separate genes in the same cell.

In US 2004/0091488 antigenic constructs of major histocompatibility complex class I antigens with specific carrier molecules is reported. Herein fusion polypeptides are reported lacking a hinge region.

Summary

Herein is reported a method for recombinantly producing a complex comprising as first part an antibody derived part that specifically binds to a target antigen, and as second part a virus-derived peptide covalently linked to a MHC class I protein complex as well as the complex itself.

With the complex 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 complex specifically binds to, by dressing these cells with a MHC class I complexes mimicking an acute viral infection by the virus-derived peptide linked to the MHC class I protein complex.

As reported herein is a method for the recombinant production of a complex 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 complex, and ii) recovering the complex from the cell or the cultivation medium, wherein the complex comprises exactly one fusion polypeptide of β2-microglobulin and the extracellular domains α1, α2 and α3 of a class I MHC molecule.

One aspect as reported herein is a method for the recombinant production of a complex comprising

i) a fusion polypeptide comprising in N- to C-terminal direction a T-cell response eliciting peptide, β2-microglobulin and the extracellular domains α1, α2, and α3 of a class I MHC molecule,

ii) a pair of disulfide-linked polypeptide chains derived from an antibody hinge region, wherein each disulfide-linked polypeptide chain comprises a CH2 domain and a CH3 domain of human origin, 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 following steps:

- cultivating a eukaryotic cell comprising one or more nucleic acids encoding the complex, and
- recovering the complex from the cell or the cultivation medium,

wherein the complex comprises exactly one fusion polypeptide of β2-microglobulin and the extracellular domains α1, α2, and α3 of a class I MHC molecule.

In one embodiment the complex comprises exactly one MHC-derived polypeptide or exactly one fusion polypeptide comprising an MHC-derived molecule.

(iii) a β2-microglobulin that has an amino acid sequence of SEQ ID NO: 10,
(iv) a second linker peptide that has an amino acid sequence selected from SEQ ID NO: 16, 17, 18, 21, 22, and 23,
(v) the extracellular domains α1, α2 and α3 of a class I MHC molecule that has an amino acid sequence of SEQ ID NO: 11, and
(vi) a third linker peptide that has an amino acid sequence selected from SEQ ID NO: 12, 16, 17, 18, 21, 22, and 23.

In one embodiment the first disulfide-linked polypeptide chain and the second disulfide-linked polypeptide chain comprise i) a human IgG1 CH2 domain comprising an amino acid sequence selected from SEQ ID NO: 31, 32, and 33, and a human IgG1 CH3 domain comprising an amino acid sequence selected from SEQ ID NO: 34, 35, and 36.

In one embodiment the complex comprises i) a first linker peptide that has the amino acid sequence of SEQ ID NO: 21, and/or ii) a second linker peptide that has the amino acid sequence of SEQ ID NO: 22, and/or iii) a third linker peptide that has the amino acid sequence of SEQ ID NO: 12, and/or iv) a human IgG1 CH2 domain that has the amino acid sequence of SEQ ID NO: 32 or 33, and/or v) in the first disulfide-linked polypeptide a human IgG1 CH3 domain that has the amino acid sequence of SEQ ID NO: 35 and in the second disulfide-linked polypeptide a human IgG1 CH3 domain that has the amino acid sequence of SEQ ID NO: 36.

As reported herein is a complex, characterized in that it comprises

- one fusion polypeptide that 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) 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,

and

- two polypeptide chains, which are linked by one or more disulfide bonds, wherein the first disulfide-linked polypeptide chain comprises in N- to C-terminal direction
  (i) an immunoglobulin light or heavy chain variable domain,
  (ii) an immunoglobulin light or heavy chain constant domain, and
  (iii) an antibody heavy chain hinge region polypeptide,

  and wherein the second disulfide-linked polypeptide chain comprises an antibody heavy chain hinge region polypeptide,

wherein the fusion polypeptide is

- covalently bound either to the C-terminus or the N-terminus of one of the disulfide-linked polypeptide chains, or
- covalently bound to the N-terminus of an antibody variable domain that is the complementary heavy or light chain variable domain to that comprised in the first disulfide-linked polypeptide chain, or
- covalently bound to the C-terminus of an antibody constant domain that is the complementary heavy or light chain constant domain to that comprised in the first disulfide-linked polypeptide chain.

Another aspect as reported herein is a complex, characterized in that it comprises

- one fusion polypeptide that comprises 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,

  and
- two polypeptide chains, which are linked by one or more disulfide bonds, wherein the first disulfide-linked polypeptide chain comprises in N- to C-terminal direction
  (i) an immunoglobulin light or heavy chain variable domain,
  (ii) an immunoglobulin light or heavy chain constant domain, and
  (iii) an antibody heavy chain hinge region polypeptide,

and

wherein the second disulfide-linked polypeptide chain comprises an antibody heavy chain hinge region polypeptide, and

wherein the first disulfide-linked polypeptide chain and the second disulfide-linked polypeptide chain comprise, respectively, a CH2 domain and a CH3 domain of human origin,

wherein the fusion polypeptide is

- covalently bound either to the C-terminus or the N-terminus of one of the disulfide-linked polypeptide chains, or
- covalently bound to the N-terminus of an antibody variable domain that is the complementary heavy or light chain variable domain to that comprised in the first disulfide-linked polypeptide chain, or
- covalently bound to the C-terminus of an antibody constant domain that is the complementary heavy or light chain constant domain to that comprised in the first disulfide-linked polypeptide chain

with the proviso that the complex comprises exactly one fusion polypeptide.

In one embodiment the complex is an antigen binding complex.

In one embodiment the complex is a covalent complex.

In one embodiment the class I MHC molecule with a relative frequency of 1 % or more has a relative frequency of 10 % or more. In one embodiment the class I MHC molecule with a relative frequency of 10 % or more is HLA-A*0201, or HLA-A*1101, or HLA-A*2402, or HLA-A*340101, or HLA-C*0304, or HLA-C*0401, or HLA-C*0702.

In one embodiment the class I MHC molecule with a relative frequency of 10 % or more is selected depending on the region of the individual to whom the complex is to be administered as follows:

- for an individual of European origin the class I MHC molecule is selected from the group comprising HLA-A*0101, HLA-A*0201, HLA-A*0301, HLA-B*0702, HLA-B*0801, HLA-B*4402, HLA-C*0401, HLA-C*0501, HLA-C*0701, and HLA-C*0702,

- for an individual of Australian origin the class I MHC molecule is selected from the group comprising HLA-A*0201, HLA-A*1101, HLA-A*2402, HLA-A*340101, HLA-B*1301, HLA-B*1521, HLA-B*5601, HLA-B*5602, HLA-C*0102, HLA-C*0401, HLA-C*0403, and HLA-C*1502,
- for an individual of North American origin the class I MHC molecule is selected from the group comprising HLA-A*0201, HLA-A*2402, HLA-C*0202, HLA-C*0304, HLA-C*0401, and HLA-C*0702, and
- for an individual of South-East-Asian origin the class I MHC molecule is selected from the group comprising HLA-A*1101, HLA-A*2402, HLA-B*1504, HLA-C*0102, HLA-C*0304, HLA-C*0702, and HLA-C*0801.

In one embodiment the class I MHC molecule with a relative frequency of 10 % or more is selected depending on the region of the individual to whom the complex is to be administered as follows:

- for an individual of European origin the class I MHC molecule is HLA-A*0201,
- for an individual of Australian origin the class I MHC molecule is selected from the group comprising HLA-A*2402, HLA-B*1301, HLA-C*0102, and HLA-C*0401,
- for an individual of North American origin the class I MHC molecule is selected from the group comprising HLA-A*2402, and HLA-C*0304, and
- for an individual of South-East-Asian origin the class I MHC molecule is HLA-A*2402.

In one embodiment the fusion polypeptide that comprises in N- to C-terminal direction a β2-microglobulin and the extracellular domains α1, α2 and α3 of a class I MHC molecule with a relative frequency of less than 1 % further comprises at its N-terminus a peptide binding to the MHC-peptide binding grove.

In one embodiment the T-cell response eliciting peptide is a $CD8^+$-T-cell response eliciting peptide. In one embodiment the T-cell response eliciting peptide is a virus-derived peptide.

In one embodiment the class I MHC molecule with a relative frequency of less than 1 % is selected from the group comprising HLA-B*4201, HLA-B*5901, HLA-B*6701, and HLA-B*7802.

In one embodiment the fusion polypeptide comprises

(i) a virus-derived peptide,
(ii) β2-microglobulin, and
(iii) the soluble HLA-A allele A*0201.

In one embodiment the virus is selected from adenovirus, human herpesvirus 1, human herpesvirus 2, human herpesvirus 4 (Epstein-Barr virus), hepatitis-B-virus, hepatitis-C-virus, human cytomegalovirus, human immunodeficiency virus, human papillomavirus type 16, human papillomavirus type 18, human papillomavirus type 31, human papillomavirus type 33, human papillomavirus type 35, human papillomavirus type 39, human papillomavirus type 45, human papillomavirus type 51, human papillomavirus type 52, human papillomavirus type 56, human papillomavirus type 58, human papillomavirus type 59, human papillomavirus type 68, human papillomavirus type 73, human papillomavirus type 82, human T-cell lymphotropic virus type I, human influenza A virus, human influenza B virus, vaccinia virus, dengue virus.

In one embodiment the virus-derived peptide is selected from NLVPMVATV (SEQ ID NO: 01), SLYNTVATL (SEQ ID NO: 02), GLCTLVAML (SEQ ID NO: 03), GILGFVFTL (SEQ ID NO: 04), STNRQSGRQ (SEQ ID NO: 05), LLFGYPVYV (SEQ ID NO: 06), FAEGFVRAL (SEQ ID NO: 07), LIVIGILIL (SEQ ID NO: 08), or ILHTPGCV (SEQ ID NO: 09), WYAQIQPHW (SEQ ID NO: 52), AFSGVSWTM (SEQ ID NO: 53), ILIGVVITW (SEQ ID NO: 54), MMIPTVVAF (SEQ ID NO: 55), PFPQSNAPI (SEQ ID NO: 56), LLLTLLATV (SEQ ID NO: 57), IVLEHGSCV (SEQ ID NO: 58), LLFKTENGV (SEQ ID NO: 59), PLNEAIMAV (SEQ ID NO: 60), NLVRLQSGV (SEQ ID NO: 61), LVISGLFPV (SEQ ID NO: 62), LLLVAHYAI (SEQ ID NO: 63), LALLAAFKV (SEQ ID NO: 64), VILAGPMPV (SEQ ID NO: 65), HVLGRLITV (SEQ ID NO: 66), VTEHDTLLY (SEQ ID NO: 67), NTDFRVLEL (SEQ ID NO: 68), CVETMCNEY (SEQ ID NO: 69), VLEETSVML (SEQ ID NO: 70), NLVPMVATV (SEQ ID NO: 71), RIFAELEGV (SEQ ID NO: 72), IIYTRNHEV (SEQ ID NO: 73), VLAELVKQI (SEQ ID NO: 74), AVGGAVASV (SEQ ID NO: 75), TVRSHCVSK (SEQ ID NO: 76), IMREFNSYK (SEQ ID NO: 77), GPISHGHVLK (SEQ ID NO: 78), ATVQGQNLK (SEQ ID NO: 79), VYALPLKML (SEQ ID NO: 80), AYAQKIFKIL (SEQ ID NO: 81), QYDPVAALF (SEQ ID NO: 82), YVKVYLESF (SEQ ID NO: 83), DIYRIFAEL (SEQ ID NO: 84), VFETSGGLVV

(SEQ ID NO: 85), KARDHLAVL (SEQ ID NO: 86), QARLTVSGL (SEQ ID NO: 87), KARAKKDEL (SEQ ID NO: 88), QIKVRVDMV (SEQ ID NO: 89), RRRHRQDAL (SEQ ID NO: 90), ARVYEIKCR (SEQ ID NO: 91), KMQVIGDQY (SEQ ID NO: 92), NVRRSWEEL (SEQ ID NO: 93), CPSQEPMSIYVY (SEQ ID NO: 94), KPGKISHIMLDVA (SEQ ID NO: 95), ELRRKMMYM (SEQ ID NO: 96), IPSINVHHY (SEQ ID NO: 97), FEQPTETPP (SEQ ID NO: 98), YAYIYTTYL (SEQ ID NO: 99), QEFFWDANDIY (SEQ ID NO: 100), YEQHKITSY (SEQ ID NO: 101), QEPMSIYVY (SEQ ID NO: 102), SEHPTFTSQY (SEQ ID NO: 103), QAIRETVEL (SEQ ID NO: 104), TRATKMQVI (SEQ ID NO: 105), DALPGPCI (SEQ ID NO: 106), CEDVPSGKL (SEQ ID NO: 107), HERNGFTVL (SEQ ID NO: 108), PTFTSQYRIQGKL (SEQ ID NO: 109), QMWQARLTV (SEQ ID NO: 110), HELLVLVKKAQL (SEQ ID NO: 111), or DDYSNTHSTRYV (SEQ ID NO: 112), or a variant thereof comprising of from 1 to 3 amino acid exchanges, additions, and/or deletions.

In one embodiment the β2-microglobulin is human β2-microglobulin. In one embodiment the β2-microglobulin is wild-type human β2-microglobulin. In one embodiment the β2-microglobulin is consisting of the amino acid sequence of SEQ ID NO: 10 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions.

In one embodiment the β2-microglobulin is human β2-microglobulin and the class I MHC molecule with a relative frequency of 10 % or more is human HLA-A*0201. In one embodiment the extracellular domains α1, α2 and α3 of a class I MHC molecule is consisting of the amino acid sequence of SEQ ID NO: 11 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions.

In one embodiment the virus-derived peptide is fused to the β2-microglobulin via a first linker peptide. In one embodiment the virus-derived peptide is fused to the N-terminus of the β2-microglobulin.

In one embodiment the β2-microglobulin is fused to the extracellular domain α1 of a class I MHC molecule via a second linker peptide.

In one embodiment the extracellular domains α3 of a class I MHC molecule is fused to one of the disulfide-linked polypeptide chains via a third linker peptide.

In one embodiment the first, second, and third linker peptide is the same or different.

In one embodiment the first linker peptide, the second linker peptide, and the third linker peptide are selected independently from each other from the amino acid sequences GS (SEQ ID NO: 12), GGS (SEQ ID NO: 13), GGGS (SEQ ID NO: 14), GGGSGGGS (SEQ ID NO: 15), GGGSGGGSGGGS (SEQ ID NO: 16), GGGSGGGSGGGSGGGS (SEQ ID NO: 17), GGGSGGGSGGGSGGGSGGGS (SEQ ID NO: 18), GGGGS (SEQ ID NO: 19), GGGGSGGGGS (SEQ ID NO: 20), GGGGSGGGGSGGGGS (SEQ ID NO: 21), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 22), and GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 23).

In one embodiment the first linker peptide comprises the amino acid sequence of SEQ ID NO: 21.

In one embodiment the second linker peptide comprises the amino acid sequence of SEQ ID NO: 22.

In one embodiment the third linker peptide comprises the amino acid sequence of SEQ ID NO: 12.

In one embodiment the antibody heavy chain hinge region polypeptide is selected from an antibody heavy chain hinge region polypeptide of a human antibody of the class IgG or the class IgE.

In one embodiment the antibody heavy chain hinge region polypeptide is selected from an antibody heavy chain hinge region polypeptide of a human antibody of the subclass IgG1, or IgG2, or IgG3, or IgG4.

In one embodiment the antibody heavy chain hinge region polypeptide comprises or is consisting of the amino acid sequence of EPKSCDKTHTCPPCP (SEQ ID NO: 24), EPKSADKTHTCPPCP (SEQ ID NO: 25), ERKCCVECPPCP (SEQ ID NO: 26), ERKCAVECPPCP (SEQ ID NO: 27), ERKACVECPPCP (SEQ ID NO: 28), ELKTPLGDTTHTCPRCP (EPKSCDTPPPCPRCP)$_3$ (SEQ ID NO: 29), ESKYGPPCPSCP (SEQ ID NO: 30), DKTHTCPPCP (SEQ ID NO: 47), VECPPCP (SEQ ID NO: 48), AVECPPCP (SEQ ID NO: 49), DTTHTCPRCP (SEQ ID NO: 50), or PPCPSCP (SEQ ID NO: 51).

In one embodiment the first disulfide-linked polypeptide and/or the second disulfide-linked polypeptide comprises a CH2 domain and/or a CH3 domain of human origin. In one embodiment the CH2 domain and the CH3 of human origin is of a human antibody of the class IgG or IgE. In one embodiment the CH2 domain and the CH3 domain is of a human antibody of the subclass IgG1, or IgG2, or IgG3, or IgG4. In one embodiment the CH2 domain comprises the amino acid sequence of SEQ ID NO: 31. In one embodiment the CH2 domain is of a human antibody of the subclass IgG1 or IgG2 and comprises at least one mutation in E233, L234, L235, G236, D265, D270, N297, E318, K320, K322, A327, P329, A330, and/or P331 (numbering according to the EU index of Kabat). In one embodiment the CH2 domain 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 CH2 domain is of a human antibody of the subclass IgG1 with the mutations L234A and L235A and/or P329G. In one embodiment the CH2 domain is of a human antibody of the subclass IgG4 with the mutation S228P and/or L235E. In one embodiment the CH2 domain comprises the amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 33. In one embodiment the CH3 domain comprises the amino acid sequence of SEQ ID NO: 34.

In one embodiment the first disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 35 and the second disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 36.

In one embodiment the first and the second disulfide-linked polypeptide comprise the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38.

In one embodiment the first disulfide-linked polypeptide or the second disulfide-linked polypeptide is consisting of the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38.

In one embodiment the first disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 39 and the second disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 40.

In one embodiment the polypeptide chains, which are linked by one or more disulfide bonds, are linked by two, or three, or four disulfide bonds.

In one embodiment the complex is characterized in that the fusion polypeptide comprises in N- to C-terminal direction

(i) a virus-derived peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 01 to SEQ ID NO: 09,
(ii) a first linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 16, 17, 18, 21, 22, and 23.
(iii) a β2-microglobulin that has an amino acid sequence of SEQ ID NO: 10 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions,
(iv) a second linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 16, 17, 18, 21, 22, and 23.
(v) the extracellular domains α1, α2 and α3 of a class I MHC molecule that has an amino acid sequence of SEQ ID NO: 11 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions, and
(vi) a third linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 12, 16, 17, 18, 21, 22, and 23.

In one embodiment the first disulfide-linked polypeptide and the second disulfide-linked polypeptide further comprise

- a human IgG1 CH2 domain comprising an amino acid sequence selected from SEQ ID NO: 31, 32, and 33, and
- a human IgG1 CH3 domain comprising an amino acid sequence selected from SEQ ID NO: 34, 35, and 36.

In one embodiment the complex is characterized in that it comprises

- one fusion polypeptide that comprises in N- to C-terminal direction

(i) a virus-derived peptide that has an amino acid sequence selected from SEQ ID NO: 01 to SEQ ID NO: 09,
(ii) a first linker peptide that has an amino acid sequence selected from SEQ ID NO: 16, 17, 18, 21, 22, and 23.
(iii) a β2-microglobulin that has an amino acid sequence of SEQ ID NO: 10 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions,

In one embodiment the first and second disulfide-linked polypeptide chain comprise the same antibody heavy chain hinge region polypeptide.

In one embodiment the virus-derived polypeptide comprises the amino acid sequence of SEQ ID NO: 01, the first linker peptide comprises the amino acid sequence of SEQ ID NO: 21, the second linker peptide comprises the amino acid sequence of SEQ ID NO: 22, the third linker peptide comprises the amino acid sequence of SEQ ID NO: 12, the human IgG1 CH2 domain comprises the amino acid sequence of SEQ ID NO: 32 or 33, and the human IgG1 CH3 domain of one disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 35 and the human IgG1 CH3 domain of the other disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 36.

In one embodiment the complex is characterized in that it comprises

- one fusion polypeptide that comprises in N- to C-terminal direction
  - (i) a virus-derived peptide that has an amino acid sequence selected from SEQ ID NO: 01 to SEQ ID NO: 09,
  - (ii) a first linker peptide that has an amino acid sequence selected from SEQ ID NO: 16, 17, 18, 21, 22, and 23.
  - (iii) a β2-microglobulin that has an amino acid sequence of SEQ ID NO: 10 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions,
  - (iv) a second linker peptide that has an amino acid sequence selected from SEQ ID NO: 16, 17, 18, 21, 22, and 23.
  - (v) the extracellular domains α1, α2 and α3 of a class I MHC molecule that has an amino acid sequence of SEQ ID NO: 11 or is a variant thereof comprising of from 1 to 10 amino acid exchanges, additions, and/or deletions, and
  - (vi) a third linker peptide that has an amino acid sequence selected from SEQ ID NO: 12, 16, 17, 18, 21, 22, and 23,

and

- two polypeptide chains, which are linked by one or more disulfide bonds,

  wherein the first disulfide-linked polypeptide chain comprises in N- to C-terminal direction
  - (i) an immunoglobulin light or heavy chain variable domain,

(ii) an immunoglobulin light or heavy chain constant domain,

(iii) an antibody heavy chain hinge region polypeptide comprising an amino acid sequence selected from SEQ ID NO: 24 to SEQ ID NO: 30 and SEQ ID NO: 47-51,

(iv) a human IgG1 CH2 domain comprising an amino acid sequence selected from SEQ ID NO: 31, 32, and 33, and

(v) a human IgG1 CH3 domain comprising an amino acid sequence selected from SEQ ID NO: 34, 35, and 36,

and the second disulfide-linked polypeptide chain comprises an antibody heavy chain hinge region polypeptide comprising an amino acid sequence selected from SEQ ID NO: 24 to SEQ ID NO: 30 and SEQ ID NO: 47-51,

wherein the fusion polypeptide is

- covalently bound either to the C-terminus or the N-terminus of the first disulfide-linked polypeptide chain, or
- covalently bound to the N-terminus of an antibody variable domain that is the complementary heavy or light chain variable domain to that comprised in the first disulfide-linked polypeptide chain, or
- covalently bound to the C-terminus of an antibody constant domain that is the complementary heavy or light chain constant domain to that comprised in the first disulfide-linked polypeptide chain.

In one embodiment the virus-derived polypeptide comprises the amino acid sequence of SEQ ID NO: 01, the first linker peptide comprises the amino acid sequence of SEQ ID NO: 21, the second linker peptide comprises the amino acid sequence of SEQ ID NO: 22, the third linker peptide comprises the amino acid sequence of SEQ ID NO: 12, the human IgG1 CH2 domain comprises the amino acid sequence of SEQ ID NO: 32 or 33, and the human IgG1 CH3 domain of one disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 35 and the human IgG1 CH3 domain of the other disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 36.

In one embodiment the complex is characterized in that it comprises

- one fusion polypeptide that comprises in N- to C-terminal direction
  (i) a virus-derived peptide that has an amino acid sequence selected from SEQ ID NO: 01 to SEQ ID NO: 09,

- covalently bound to the C-terminus of an antibody constant domain that is the complementary heavy or light chain constant domain to that comprised in the first disulfide-linked polypeptide chain.

In one embodiment the virus-derived polypeptide comprises the amino acid sequence of SEQ ID NO: 01, the first linker peptide comprises the amino acid sequence of SEQ ID NO: 21, the second linker peptide comprises the amino acid sequence of SEQ ID NO: 22, the third linker peptide comprises the amino acid sequence of SEQ ID NO: 12, the human IgG1 CH2 domain comprises the amino acid sequence of SEQ ID NO: 32 or 33, and the human IgG1 CH3 domain of one disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 35 and the human IgG1 CH3 domain of the other disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 36.

In one embodiment

- the first linker peptide comprises the amino acid sequence of SEQ ID NO: 21, and/or
- the second linker peptide comprises the amino acid sequence of SEQ ID NO: 22, and/or
- the third linker peptide comprises the amino acid sequence of SEQ ID NO: 12, and/or
- the human IgG1 CH2 domain comprises the amino acid sequence of SEQ ID NO: 32 or 33, and/or
- the human IgG1 CH3 domain of one disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 35 and the human IgG1 CH3 domain of the other disulfide-linked polypeptide comprises the amino acid sequence of SEQ ID NO: 36.

In one embodiment the virus-derived peptide is selected from the group comprising SEQ ID NO: 01 to SEQ ID NO: 09, SEQ ID NO: 52 to SEQ ID NO: 112, or is a variant thereof comprising of from 1 to 3 amino acid exchanges, additions, and/or deletions.

One aspect as reported herein is a nucleic acid encoding the complex 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.

One aspect as reported herein is a host cell comprising the nucleic acid as reported herein.

As reported herein is a method of producing a complex as reported herein comprising culturing the host cell as reported herein so that the complex is produced.

In one embodiment the complex is recovered from the cells or the cultivation medium and thereby the complex is produced.

As reported herein is an immunoconjugate comprising the complex as reported herein and a cytotoxic agent.

One aspect as reported herein is a pharmaceutical formulation comprising the complex 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 complex as reported herein for use as a medicament.

One aspect as reported herein is the complex as reported herein for use in treating cancer or a chronic viral infection.

One aspect as reported herein is the complex 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 complex as reported herein for use in removal cancer cells or virus infected cells.

One aspect as reported herein is the use of the complex as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for treatment of cancer or a chronic 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 removal cancer cells or virus infected cells.

As reported herein is a method of treating an individual having cancer or a chronic virus infection comprising administering to the individual an effective amount of the complex as reported herein.

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

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 complex as reported herein to attract virus-specific cytotoxic T-cells of an individual to a target.

As reported herein is a method of removal cancer cells or virus infected cells in an individual comprising administering to the individual an effective amount of the complex as reported herein to remove/disintegrate cancer cells or virus infected cells.

Detailed Description of the Invention

Short description of the figures

Figure 1 Annotated scheme of the complexes as reported herein.

Figure 2 Exemplary polypeptides comprised in the complex as reported herein: fusion polypeptides were N-terminally fused to either an antibody light chain or to an antibody heavy chain hinge region comprising polypeptide.

Figure 3 Western blot of a SDS polyacrylamide gel of cell culture supernatant of HEK 293 cells transfected with the corresponding expression plasmids. Staining was performed with peroxidase conjugated polyclonal rabbit anti-human κ-light chain antibody and polyclonal rabbit anti-human IgG antibody conjugated to horseradish peroxidase.
Lanes: 1: two-armed peptide-β2-microglobulin-HLA-A0201-IgG-Fc; 2: one-armed peptide-β2-microglobulin-HLA-A0201-