polypeptide derivatives that are connected to the PK-modulating entity with uncertain stoichiometries and/or at undefined positions. Additionally currently used polypeptide modification-technologies often result in strongly reduced or even complete loss of biological activity of the therapeutic polypeptide. In addition, it is difficult to predict pharmacological properties and/or possible degradation routes of the chemical conjugates.

US 5,804,371 reports hapten-labeled peptides and their use in an immunological method of detection. A digoxigenin-labeled peptide (Bradykinin) and its application to chemiluminoenzyme immunoassay of Bradykinin in inflamed tissues are reported by Decarie A., et al. (Peptides 15 (1994) 511-518).

In WO 2004/065569 multi-functional antibodies are reported.

Summary ~~of the Invention~~

It has been found that by the covalent coupling of a haptenylated compound to an anti-hapten antibody a stabilization and PK-property improvement of the compound can be achieved.

One aspect as reported herein is a conjugate comprising an antigen and an antibody that specifically binds to the antigen wherein a covalent bond is between the antigen and an amino acid residue in a variable region of the antibody.

~~One aspect as reported herein~~ The disclosure provides for ~~is~~ a conjugate comprising an antigen and an antibody that specifically binds to the antigen characterized by a covalent bond between the antigen and an amino acid residue in the CDR2 of the antibody, whereby the CDR2 is determined according to Kabat.

It has been found that any antigen can be used in the conjugates and methods as reported herein upon derivatization with a universal linker which comprises the functional residue for the formation of the covalent bond between the antigen and an amino acid residue in the CDR2 of the antibody. The location of the functional group in the universal linker has the advantage that it is not necessary to re-engineer the synthesis and the position of the functional group in the CDR2 of the antibody.

One aspect as reported herein is a conjugate comprising a hapten compound and an antibody that specifically binds to the hapten (anti-hapten antibody) wherein a covalent bond is between the hapten and an amino acid residue in a variable region of the antibody.

The disclosure provides for ~~One aspect as reported herein is~~ a conjugate comprising a haptenylated compound and an antibody that specifically binds to the hapten of the haptenylated compound (anti-hapten antibody) characterized by a covalent bond between the haptenylated compound and an amino acid residue in the CDR2 of the antibody, whereby the CDR2 is determined according to Kabat.

In one embodiment of all aspects the CDR2 is the heavy chain CDR2.

In one embodiment of all aspects the conjugate comprises a therapeutic or detectable moiety. In one embodiment the therapeutic or detectable moiety is covalently conjugated to the antigen or the hapten.

In one embodiment the antigen or hapten is conjugated to a polypeptide consisting of 5 to 60 amino acid residues. In one embodiment the polypeptide comprises 10 to 50 amino acid residues. In one embodiment the polypeptide comprises 12 to 40 amino acid residues. In one embodiment the polypeptide comprises 12 to 30 amino acids residues.

In one embodiment the antigen or hapten is conjugated to a detectable label.

In one embodiment the antigen or the hapten is conjugated to the polypeptide, or to the detectable label, or to the payload via a linker. In one embodiment the linker is a non-peptidic linker.

One aspect as reported herein is an antibody that has in the light and/or the heavy chain a cysteine residue in the CDR2. The ~~whereby the~~ CDRs ~~are~~ may be determined according to Kabat.

In one embodiment the cysteine residue is in the heavy chain CDR2.

In one embodiment the cysteine residue in the heavy chain CDR2 of the antibody is at position 52, or position 52a, or position 52b, or position 52c, or position 52d, or position 53 according to the heavy chain variable domain numbering of Kabat.

In one embodiment the cysteine residue in the heavy chain CDR2 of the antibody is at position 52a, or position 52b, or position 52c, or position 53 according to the heavy chain variable domain numbering of Kabat.

In one embodiment the cysteine residue in the heavy chain CDR2 of the antibody is at position 52b or at position 53 according to the heavy chain variable domain numbering of Kabat.

In one embodiment the antibody has in exactly one heavy chain variable domain a cysteine residue at position 52b or position 53.

In one embodiment the hapten is biotin, or theophylline, or digoxigenin, or carborane, or fluorescein.

In one embodiment the antibody is a humanized or human antibody.

In one embodiment the antibody is a full length antibody, or a Fab, or a scFv, or a scFv conjugated to an Fc-region.

In one embodiment the cysteine forms a disulfide bond with an isolated cysteine residue or an isolated homocysteine residue

One ~~aspect~~ embodiment as reported herein is an immunoconjugate comprising the conjugate as reported herein and a cytotoxic agent.

One aspect as reported herein is a pharmaceutical formulation comprising the conjugate as reported herein or the antibody as reported herein and a pharmaceutically acceptable carrier.

The conjugate as reported herein for use as a medicament.

The conjugate as reported herein for the treatment of cancer.

The conjugate as reported herein for the treatment of diabetes.

The conjugate as reported herein for the treatment of adiposities.

The conjugate as reported herein for the treatment of an inflammatory disease.

The conjugate as reported herein for the treatment of a metabolic disease.

The conjugate as reported herein for the treatment of a viral disease.

One ~~aspect~~ embodiment as reported herein is the use of a conjugate as reported herein in the manufacture of a medicament.

One embodiment ~~aspect~~ as reported herein is the use of a conjugate as reported herein as diagnostic agent.

One embodiment ~~aspect~~ as reported herein is the use of a conjugate as reported herein comprising a therapeutic polypeptide to increase the stability of the therapeutic polypeptide.

One embodiment ~~aspect~~ as reported herein is the use of a conjugate as reported herein comprising a therapeutic polypeptide to increase the activity of the therapeutic polypeptide.

One embodiment ~~aspect~~ as reported herein is the use of a conjugate as reported herein comprising a therapeutic polypeptide to increase the in vivo half-life of the therapeutic polypeptide.

One embodiment ~~aspect~~ as reported herein is the use of a conjugate as reported herein in the treatment of a disease.

One embodiment ~~aspect~~ as reported herein is a method of treating an individual having a disease comprising administering to the individual an effective amount of a conjugate as reported herein.

One embodiment ~~aspect~~ as reported herein is a method of treating a disease in an individual comprising administering to the individual an effective amount of the conjugate as reported herein.

In one embodiment the disease is cancer.

In one embodiment the disease is diabetes.

In one embodiment the disease is adipositas.

One embodiment ~~aspect~~ as reported herein is a method of producing a conjugate as reported herein comprising the combination of an antibody comprising a first reactive group and an antigen that has a second reactive group whereby the alpha carbon atom of the amino acid residue that bears the first reactive group is about 10 to 11 Angstrom apart from the atom of the antigen to which the linker is fused.

One embodiment ~~aspect~~ as reported herein is a method of producing a conjugate as reported herein comprising the steps of

- combining in solution an antibody that specifically binds to a hapten and comprises a reactive group at one amino acid residue in the CDR2 with a haptenylated compound comprising a reactive group, wherein the haptenylated compound comprises a payload, such as a peptide consisting of 5 to 60 amino acids or a detectable label, and
- recovering of the conjugate from the solution.

One embodiment ~~aspect~~ as reported herein is a method for producing an antibody for the formation of a conjugate as reported herein, comprising the step of

- cultivating a cell comprising a nucleic acid encoding the antibody, and

- recovering the antibody from the cell or the cultivation medium,

wherein in the antibody the residue in the heavy chain CDR2 is mutated to cysteine that has in the X-ray structure of the non-covalent complex of the antibody and its antigen or a haptenylated compound a distance of 10 to 11 Angstrom between the alpha-carbon atom of the amino acid residue in the antibody CDR2 and the atom of the hapten to which the linker is connected or to an antigen atom between which the covalent bond is to be formed.

One embodiment ~~aspect~~ as reported herein is a method for identifying a position in an antibody CDR2 that can be mutated to cysteine for the formation of a covalent bond between the residue in the antibody CDR2 and the bound antigen or haptenylated compound comprising the step of

- providing a crystal structure of the non-covalent complex of the antibody and the antigen or haptenylated compound, whereby the antigen or haptenylated compound comprises a linker sequence, and

- identifying an amino acid residue in the CDR2 of the antibody and in the linker sequence with a distance of 10 to 11 Angstrom between the alpha-carbon atoms of the amino acid residue in the antibody CDR2 and the atom in the antigen to which the linker is fused,

wherein the identified position is the position in an antibody CDR2 that can be mutated to cysteine for the formation of a covalent bond between the residue in the antibody CDR2 and the bound antigen or haptenylated compound.

One embodiment ~~aspect~~ as reported herein is a bispecific antibody for targeted delivery of a haptenylated compound to a target cell, wherein the bispecific antibody comprises a first binding site that specifically binds to the haptenylated compound and a second binding specificity that specifically binds to a cell surface marker of the cell.

Description of the Figures

Figure 1: Procedure for digoxigenylation (conjugation of digoxigenin to) of peptides (Figure 1A). Examples of a digoxigenylated label