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

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.~~

The disclosure provides for 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 a cysteine residue at position 52b or at position 53 according to the heavy chain variable domain numbering of Kabat of the antibody and the hapten, wherein the hapten is selected from the group of haptens comprising biotin, theophylline, digoxigenin, carborane, and fluoresceinand an amino acid residue in a variable region of the antibody.

The disclosure provides for 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 CDRs 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 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 embodiment as reported herein is the use of a conjugate as reported herein in the manufacture of a medicament.

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

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

Patent Claims

~~1. 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.~~

21. A conjugate comprising a hapten and an antibody that specifically binds to the hapten (anti-hapten antibody) wherein a covalent bond is between a cysteine residue at position 52b or at position 53 according to the heavy chain variable domain numbering of Kabat of the antibody and the hapten ~~and an amino acid residue in a variable region of the antibody~~, wherein the hapten is selected from the group of haptens comprising biotin, theophylline, digoxigenin, carborane, and fluorescein.

~~3. The conjugate according to claim 1 or 2, characterized in that the amino acid residue in a variable region is in the heavy chain CDR2.~~

~~4. The conjugate according to any one of the preceding claims, characterized in that the covalent bond is between a cysteine residue in the heavy chain CDR2 of the antibody and the antigen or hapten.~~

~~5. The conjugate according to claim 4, characterized in that 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.~~

62. The conjugate according to ~~any one of the preceding~~ claims 1, characterized in that the covalent bond is a disulfide bond.

73. The conjugate according to ~~any one of the preceding~~ claims 1 or 2, characterized in that the antibody is a bispecific antibody comprising a first binding specificity to a first antigen or a first hapten and a second binding specificity to a second antigen or a second hapten.

84. The conjugate according to claim 73, characterized in that the first binding specificity is to a hapten and a second binding specificity is to a non-hapten antigen.

95. The conjugate according to any one of the preceding claims, characterized in that the antibody is a full length antibody.

106. The conjugate according to any one of the preceding claims, characterized in that the antibody is a humanized antibody or a human antibody.

117. The conjugate according to any one of the preceding claims, characterized in that the conjugate further comprises a therapeutic or detectable moiety.

~~12. The conjugate according to any one of the preceding claims, characterized in that the hapten is selected from the group of haptens comprising biotin, theophylline, digoxigenin, carborane, and fluorescein.~~

~~13. An antibody that has in the light and/or the heavy chain a cysteine residue in the CDR2.~~

~~14. The antibody according to claim 13, characterized in that 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.~~

~~15~~8. A pharmaceutical formulation comprising the conjugate according to any one of claims 1 to ~~12~~ 7 ~~or the antibody according to claim 13 or 14~~ and a pharmaceutically acceptable carrier.