scaffolds with controlled serum pharmacokinetics. Methods and compositions related to peptides and proteins with C-terminal elements cross-reference to related applications is reported in WO 2009/105671. In WO 2007/038658 antibody-drug conjugates and methods of use are reported. Compositions and methods for targeted biological delivery of molecular carriers are reported in WO 2004/062602. In WO 2002/072141 targeted ligands are reported.

In WO 2009/037659 magnetic detection of small entities is reported. Homogeneous analyte detection is reported in WO 2006/137932. In US 2008/0044834 a three-component biosensor for detecting macromolecules and other analytes is reported. The design and synthesis of bispecific reagents is reported in WO 95/05399.

**Summary** ~~of the Invention~~

It has been found that for the targeted delivery of an effector moiety a complex comprising polypeptide and polynucleotide components is especially useful. The effector moiety, the polypeptide component and the polynucleotide component of the complex are non-covalently bound to each other. This allows a modular production of the individual components of the complex. Due to the modular architecture of the complex individual components can be change without the need to change the other components of the complex. This allows for an easy and efficient assembly of a multitude of complex variants e.g. for the provision of a library.

There is provided ~~Thus, one aspect as reported herein is~~ a complex comprising

a) a first polypeptide
   i) that specifically binds to a first target, and
   ii) that is conjugated to a first member of a first binding pair,
b) a second polypeptide
   i) that specifically binds to a second target, and
   ii) that is conjugated to a first member of a second binding pair, and
c) a polynucleotide linker
   i) that is conjugated to the second member of the first binding pair, and
   ii) that is conjugated to the second member of the second binding pair.

One aspect as reported herein is a complex comprising

a) a first polypeptide that specifically binds to a first target and that is conjugated to a first member of a first binding pair,
b) a second polypeptide that specifically binds to a second target and that is conjugated to a first member of a second binding pair, and
c) a ss-L-DNA-linker conjugated to the second member of the first binding pair and conjugated to the second member of the second binding pair.

There is also provided~~Another aspect as reported herein is~~ a complex that is an intermediate during the production of the above complex. This complex comprises

a) a polypeptide

i) that specifically binds to a target, and

ii) that is conjugated to a first member of a binding pair,

b) a polynucleotide linker that is conjugated to the second member of the binding pair.

Another aspect as reported herein is a complex comprising

a) a polypeptide that specifically binds to a target and that is conjugated to a first member of a binding pair,

b) a ss-L-DNA-linker conjugated to the second member of the binding pair, and

c) an effector moiety conjugated to a polynucleotide that is complementary to at least a part of the ss-L-DNA-linker.

The following are embodiments of the disclosure~~all aspects as reported herein~~.

In one embodiment the complex is a non-covalent complex.

In one embodiment the complex further comprises an effector moiety that is conjugated to a polynucleotide that is complementary to at least a part of the polynucleotide linker.

In one embodiment the complex further comprises a further polypeptide i) that specifically binds to a second target, and ii) that is conjugated to a first member of a second binding pair, and the polynucleotide linker is conjugated to the second member of the second binding pair.

In one embodiment the complex further comprises an effector moiety conjugated to a polynucleotide that is i) complementary to at least a part of the polynucleotide that is conjugated to the first effector moiety and ii) not complementary to the polynucleotide linker.

In one embodiment the first target and/or the second target is/are a cell surface protein.

In one embodiment the polypeptide is a monovalent binding polypeptide. In one embodiment the monovalent binding polypeptide is an antibody or antibody fragment.

In one embodiment the first and second polypeptide bind to the same target and to non-overlapping epitopes thereon.

In one embodiment the polynucleotide linker comprises of from 8 to 1000 nucleotides. In one embodiment the polynucleotide linker comprises of from 10 to 500 nucleotides.

In one embodiment the members of the binding pairs are selected from the group consisting of leucine zipper domain dimers and hybridizing nucleic acid sequences.

In one embodiment the polynucleotide linker is enantiomeric DNA. In one embodiment the enantiomeric DNA is L-DNA. In one embodiment the L-DNA is single stranded L-DNA (ss-L-DNA).

In one embodiment the effector moiety is selected from the group consisting of a binding moiety, a labeling moiety, and a biologically active moiety.

In one embodiment the polynucleotide linker is conjugated to the member of the binding pair at its first or second terminus.

In one embodiment the polynucleotide linker is conjugated to two second members of two binding pairs, whereby the second member of the first binding pair is conjugated to the first terminus of the polynucleotide linker and the second member of the second binding pair is conjugated to the second terminus of the polynucleotide linker.

There is also provided~~One aspect as reported herein is~~ a complex as reported herein wherein the first polypeptide is the FAB' fragment of the anti-HER2 antibody 2C4, the second polypeptide is the FAB' fragment of the anti-HER2 antibody 4D5, the members of the binding pairs are each hybridizing nucleic acids, and the polynucleotide linker comprises 60 to 100 L-DNA nucleotides.

In one embodiment the FAB' fragment of the anti-HER2 antibody 2C4 comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 35, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37, and the FAB' fragment of the anti-HER2 antibody 4D5 comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 27, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 29.

In one embodiment the first and second member of the first binding pair comprise the nucleic acid sequences of SEQ ID NO: 05 and SEQ ID NO: 08, respectively.

In one embodiment the first and second member of the second binding pair comprise the nucleic acid sequences of SEQ ID NO: 06 and SEQ ID NO: 07, respectively.

In one embodiment the FAB' fragment of the anti-HER2 antibody 2C4 comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 39, (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 40, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 41, and the FAB' fragment of the anti-HER2 antibody 4D5 comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 31, (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 32, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 33.

In one embodiment the FAB' fragment of the anti-HER2 antibody 4D5 comprises a heavy chain variable domain with the amino acid sequence of SEQ ID NO: 26 and/or a light chain variable domain with the amino acid sequence of SEQ ID NO: 30.

In one embodiment the FAB' fragment of the anti-HER2 antibody 2C4 comprises a heavy chain variable domain with the amino acid sequence of SEQ ID NO: 34 and/or a light chain variable domain with the amino acid sequence of SEQ ID NO: 38.

In one embodiment first and/or the second polypeptide of the complex further comprises independently of each other one or more of a CH1 domain of human IgG1 class, or of human IgG2 class, or of human IgG3 class, or of human IgG4 class, and light chain constant domain of human kappa class, or of human lambda class.

There is also provided~~Another aspect as reported herein is~~ a method of producing a complex comprising the following components

a) a first polypeptide
   i) that specifically binds to a first target, and
   ii) that is conjugated to a first member of a first binding pair,
b) a second polypeptide
   i) that specifically binds to a second target, and
   ii) that is conjugated to a first member of a second binding pair, and
c) a polynucleotide linker
   i) that is conjugated to the second member of the first binding pair, and
   ii) that is conjugated to the second member of the second binding pair,

comprising the steps of:

a) synthesizing the first polypeptide that specifically binds to a first target and that is conjugated to a first member of a first binding pair,

b) synthesizing the second polypeptide that specifically binds to a second target and that is conjugated to a first member of a second binding pair,

c) synthesizing the polynucleotide linker that is conjugated to the second member of the first binding pair and that is conjugated to the second member of the second binding pair, and

d) forming the complex by combining the synthesized components.

Another aspect as reported herein is a method of producing a complex comprising the components

a) a first polypeptide that specifically binds to a first target and that is conjugated to a first member of a first binding pair,

b) a second polypeptide that specifically binds to a second target and that is conjugated to a first member of a second binding pair, and

c) a ss-L-DNA-linker conjugated to the second member of the first binding pair and conjugated to the second member of the second binding pair,

comprising the steps of: a) synthesizing the first polypeptide specifically binding to a first target which is conjugated to a first member of a first binding pair, and synthesizing the second polypeptide specifically binding to a second target which is conjugated to a first member of a second binding pair, respectively, and b) synthesizing the ss-L-DNA-linker conjugated at its first terminus to the second member of the first binding pair and conjugated at its second terminus to the second member of the second binding pair, and c) forming the polypeptide-polynucleotide-complex by hybridizing the synthesized components.

There is also provided~~Also an aspect as reported herein is~~ a method of producing a complex comprising the components

a) a polypeptide

i) that specifically binds to a target, and

ii) that is conjugated to a first member of a binding pair,

b) a polynucleotide linker that is conjugated to the second member of the binding pair, and

c) an effector moiety that is conjugated to a polynucleotide that is complementary to at least a part of the polynucleotide linker,

comprising the steps of:

a) synthesizing the polypeptide that specifically binds to a target and that is conjugated to a first member of a binding pair,

b) synthesizing the polynucleotide linker that is conjugated to the second member of the binding pair,

c) synthesizing the effector moiety that is conjugated to a polynucleotide that is complementary to at least a part of the polynucleotide linker, and

d) forming the complex by combining the synthesized components.

Another aspect as reported herein is a method of producing a complex comprising the components

a) a polypeptide that specifically binds to a target and that is conjugated to a first member of a binding pair,

b) a ss-L-DNA-linker conjugated to the second member of the binding pair, and

c) an effector moiety conjugated to a polynucleotide that is complementary to at least a part of the polynucleotide linker,

comprising the steps of: a) synthesizing the polypeptide specifically binding to a target and conjugated to a first member of a binding pair, and synthesizing an effector moiety conjugated to a polynucleotide that is complementary to at least a part of the ss-L-DNA-linker, respectively, b) synthesizing the ss-L-DNA-linker conjugated at its first terminus to the second member of the binding pair, and c) forming the polypeptide-polynucleotide-complex by hybridizing the synthesized components.

Another aspect as reported herein is a pharmaceutical formulation comprising the complex as reported herein and optionally a pharmaceutically acceptable carrier.

A further aspect as reported herein is a complex as reported herein for use as a medicament.

There is also provided ~~Also an aspect as reported herein is~~ the complex as reported herein for use in treating cancer.

There is also provided~~A further aspect as reported herein is~~ the complex as reported herein for use in inhibiting growth of HER2 positive cancer cells.

Another 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. In one embodiment the medicament is for inhibiting growth of HER2 positive cancer cells.

There is also provided~~An aspect as reported herein is~~ a method of treating an individual having cancer comprising administering to the individual an effective amount of the complex as reported herein.

There is also provided~~An aspect as reported herein is~~ a method for inhibiting the growth of HER2 positive cancer cells in an individual comprising administering to the individual an effective amount of the complex as reported herein to inhibit the growth of HER2 positive cancer cells.

There is also provided~~An aspect as reported herein is~~ a complex that comprises at least one antibody fragment that binds to human ErbB2 and that blocks ligand activation of an ErbB receptor, as well as a composition comprising the complex and a pharmaceutically acceptable carrier as well as the complex as reported herein further comprising a cytotoxic agent.

Herein is reported a method of treating cancer in an individual, wherein the cancer is characterized by overexpression of the ErbB2 receptor, comprising administering to the individual a therapeutically effective amount of a complex as reported herein wherein the complex comprises an antibody or antibody fragment that binds to ErbB2.

Herein is also reported a method of treating cancer in an individual, wherein the cancer is not characterized by overexpression of the ErbB2 receptor, comprising administering to the individual a therapeutically effective amount of the complex as reported herein wherein the complex comprises an antibody or an antibody fragment that binds to ErbB2 and blocks ligand activation of an ErbB receptor.

In addition, herein is reported a method of treating hormone independent cancer in a human comprising administering to the human a therapeutically effective amount of the complex as reported herein wherein the complex comprises an antibody or an antibody fragment that binds to ErbB2 and blocks ligand activation of an ErbB receptor.