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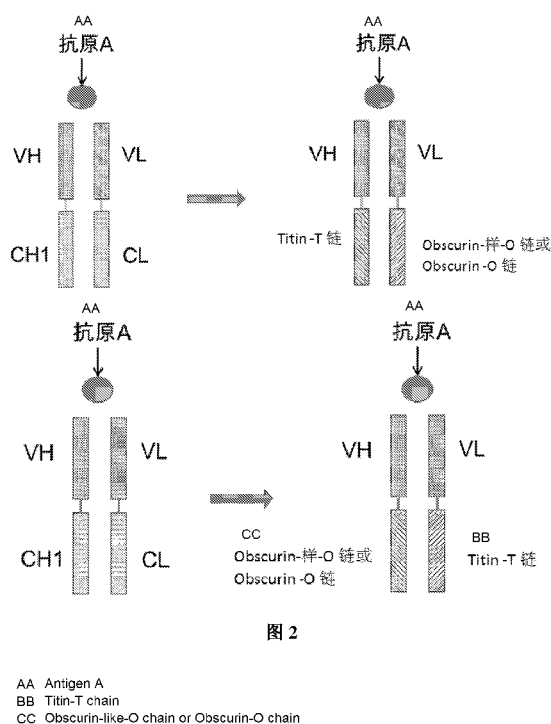
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(54) Title: NEW POLYPEPTIDE COMPLEX

(54) 发明名称: 新型多肽复合物



(57) Abstract: The present disclosure relates to a new polypeptide complex. Specifically, the present disclosure relates to a domain-engineered antibody. At least one of the constant region domains CH1 and/or CL of the antibody is replaced, and the domain CH1/CL is replaced by a Titin T chain/Ob-scurin-O chain or by a Titin T chain/Ob-scurin-like-O chain.

(57) 摘要: 本披露涉及新型多肽复合物。具体地, 本披露涉及一种结构域改造的抗体, 所述抗体的至少一个恒定区结构域CH1和/或CL被替代, 所述结构域CH1/CL被Titin T链/Ob-scurin-O链或被Titin T链/Ob-scurin-样-O链替代。

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NEW POLYPEPTIDE COMPLEX

The present application claims priority to the Chinese Patent Application (Application No. CN202010020878.7) filed on Jan. 09, 2020.

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TECHNICAL FIELD

The present disclosure relates to the field of antibody pharmaceuticals, and specifically comprises a novel antibody in which CH1 and CL structures are substituted and use thereof.

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BACKGROUND

The statements herein merely provide background information related to the present disclosure and may not necessarily constitute the prior art.

With the continuous improvement of antibody humanization technology, monoclonal antibodies have been developed rapidly in recent years. Various monoclonal antibodies have been used to treat major diseases such as malignant tumors and autoimmune diseases. However, the immune escape of tumors is often accompanied by a variety of different mechanisms, and a single monoclonal antibody can only bind to one specific target, which can greatly reduce the therapeutic effect of the monoclonal antibody.

The bispecific antibody (BsAb) is an artificial antibody formed by combining antibodies targeting two different antigens or two different epitopes together by using a genetic engineering means. Different from the monoclonal antibody, the bispecific antibody has the ability to target two different epitopes simultaneously, and can play special biological functions, such as immune cell recruitment, receptor co-stimulation or co-inhibition, multivalent virus neutralization, etc., and are expected to obtain better clinical therapeutic effects than single monoclonal antibodies, even antibody combinations.

A wide variety of recombinant bispecific antibodies have been developed, such as tetravalent bispecific antibodies formed by fusion of, for example, an IgG antibody and a single-chain domain (see Coloma, M.J., et al., *Nature Biotech.* 15 (1997) 159–163; Morrison, S.L., *Nature Biotech.* 25 (2007) 1233–1234). There are other bispecific forms, such as DVD-Ig, CrossMab and BiTE (Spiess et al., *Molecular Immunology*, 67 (2), pp. 95–106 (2015)).

Various structural models for bispecific antibodies have also been disclosed, for example, the introduction of the mutation "knobs-into-holes" into the Fc region (Ridgway et al., *Protein Engineering*, 9 (7), pp. 617–21 (1996)); the introduction of electrostatic design (Gunasekaran et al., *Journal of Biological Chemistry*, 285, (25), pp. 19637–19646, (2010)), or the introduction of negative state design (Kreudenstein et al., *mAbs*, 5 (5), pp. 646–654 (2013); Leaver-Fay et al., *Structure*, 24 (4), pp. 641–651 (2016)), the exchange of CH1 and CL domains (CrossMab platform) (Schaefer et al., *Proceedings of the National Academy of Sciences of the United States of America*, 108 (27), pp. 11187–11192 (2011)), and fusion with the TCR constant region (WO2019057122A1).

SUMMARY

However, in the preparation of a bispecific antibody, a random combination of different polypeptide chains results in a variety of different products, only one of which is desired, and the resulting byproducts comprise an antibody lacking a light chain, a half-antibody, a heavy chain polymer, light-heavy-chain mispairing, and the like, causing significant challenges to the development of downstream processes. Therefore, the present disclosure provides a novel domain-engineered polypeptide complex.

In some embodiments, the present disclosure provides a polypeptide complex, which comprises a first antigen-binding moiety comprising:

A) a first polypeptide, comprising a first heavy chain variable domain (VH1) from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a Titin-T chain, and

a second polypeptide, comprising a first light chain variable domain (VL1) from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a domain capable of interacting with a Titin-T chain;

or,

B) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a domain capable of interacting with a Titin-T chain, and

a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a Titin-T chain;

or,

C) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising an Obscurin-O chain or an Obscurin-like-O chain, and

a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a domain capable of interacting with an Obscurin-O chain or an Obscurin-like-O chain;

or,

D) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a domain capable of interacting with an Obscurin-O chain or an Obscurin-like-O chain, and

a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising an Obscurin-O chain or an Obscurin-like-O chain;

wherein the first antigen-binding moiety specifically binds to a first antigen, and the first domain and the second domain are capable of forming a dimer.

In some embodiments, for the aforementioned polypeptide complex, the domain capable of interacting with the Obscurin-O chain or the Obscurin-like-O chain is the Titin-T chain, and the domain capable of interacting with the Titin-T chain is the Obscurin-O chain or

the Obscurin-like-O chain.

In some embodiments, for the aforementioned polypeptide complex, the VH1 and the VL1 of the first antigen-binding moiety form a first antigen-binding site specifically binding to the first antigen.

- 5 In some embodiments, the C-terminus of the VH1 is operably linked to an N-terminus of the first domain.

In some embodiments, the C-terminus of the VL1 is operably linked to an N-terminus of the second domain.

- 10 In some embodiments, for the aforementioned polypeptide complex, the first domain and the second domain form a dimer through natural inter-chain bonds and/or non-natural inter-chain bonds.

- 15 In some embodiments, the first domain and the second domain form a dimer through natural inter-chain bonds; in some embodiments, one or more residues at positions selected from the group consisting of 7–15, 19–24, 26, 55, 59 and 60 on the Titin-T chain and one or more residues at positions selected from the group consisting of 3–6, 9, 41, 73, 75 and 80–90 on the Obscurin-O chain are linked to each other, or one or more residues selected from the group consisting of positions 1, 7–10, 13–16, 19–26, 59–60 and 96 on the Titin-T chain and one or more residues selected from the group consisting of positions 4–5, 10, 12–13, 74, 76, 78 and 82–91 on the Obscurin-like-O chain are linked to each other; the residue position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the residue position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the residue position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

- 25 In some embodiments, for any one of the aforementioned polypeptide complexes, the first domain and the second domain form a dimer through at least one non-natural inter-chain bonds.

In some embodiments, the non-natural inter-chain bond is formed between a particular mutated residue of the first domain and a particular mutated residue of the second domain.

- 30 In some embodiments, at least one of the particular mutated residue of the first domain and the particular mutated residue of the second domain is a cysteine residue.

In some embodiments, the non-natural inter-chain bond is a disulfide bond; in some embodiments, the dimer comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 non-natural inter-chain bonds.

- 35 In some embodiments, for the aforementioned polypeptide complex, the particular mutated residue of the first domain and the particular mutated residue of the second domain are located at a contact interface of the first domain and the second domain.

- 40 In some embodiments, the particular mutated residue of the aforementioned first domain and the particular mutated residue of the second domain have mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and

39, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some specific embodiments, the aforementioned first mutated residue and the aforementioned second mutated residue have mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8C, 20C, 22C, 25S, 26C and 39T, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3C, 9C, 25S, 76S and 88C; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8C, 20C, 22C, 25S, 26C and 39T, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6E, 26S, 74C, 77S, 84C and 86C. In some embodiments, the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has an 88C mutation; the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-O chain has a 3C mutation; the Titin-T chain has 25S, 39T and 26C mutations, and the Obscurin-O chain has a 9C mutation; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S and 88C mutations; the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-O chain has 25S, 76S and 3C mutations; the Titin-T chain has 25S, 39T and 26C mutations, and the Obscurin-O chain has 25S, 76S and 9C mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-like-O chain has 6E and 74C mutations; the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-like-O chain has 6E and 84C mutations; the Titin-T chain has 25S, 39T and 22C mutations, and the Obscurin-like-O chain has 6E and 86C mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-like-O chain has 6E, 26S, 77S and 74C mutations; the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-like-O chain has 6E, 26S, 77S and 84C mutations; or

the Titin-T chain has 25S, 39T and 22C mutations, and the Obscurin-like-O chain has 6E, 26S, 77S and 86C mutations;

the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some specific embodiments, the aforementioned first mutated residue and the aforementioned second mutated residue have mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, the particular mutated residue of the aforementioned first domain and the particular mutated residue of the second domain have mutations on positions selected from the group consisting of: the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has an A88C mutation; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has an A3C mutation; the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has an R9C mutation; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S and A88C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has C25S, C76S and A3C mutations; the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has C25S, C76S and R9C mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has C6E and V74C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E and G84C mutations; the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain has C6E and A86C mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and V74C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and G84C mutations; the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and A86C mutations. The mutation position

in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, the aforementioned first domain and the aforementioned second domain are selected from the group consisting of the following Titin-T chain/Obscurin-O chain, or Titin-T chain/Obscurin-like-O chain: the Titin-T chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and/or the Obscurin-O chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88 on the basis of SEQ ID NO: 33; or the Titin-T chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and/or the Obscurin-like-O chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34.

In some embodiments, the aforementioned first domain and the aforementioned second domain are selected from the group consisting of: a Titin-T chain/Obscurin-O chain, and a Titin-T chain/Obscurin-like-O chain. The Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T on the basis of SEQ ID NO: 32, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C on the basis of SEQ ID NO: 33; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T on the basis of SEQ ID NO: 32, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C on the basis of SEQ ID NO: 34. The mutation position in the Titin-T chain is a natural sequence numbering position of the sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 34.

In some embodiments, the aforementioned first domain and the aforementioned second domain are selected from the group consisting of: a Titin-T chain/Obscurin-O chain, and a Titin-T chain/Obscurin-like-O chain. The Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an A88C mutation on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an A3C mutation on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A26C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an R9C mutation on the

basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and A88C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and A3C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A26C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and R9C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E and V74C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E and G84C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and T22C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E and A86C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S, C77S and V74C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S, C77S and G84C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and T22C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S, C77S and A86C mutations on the basis of SEQ ID NO: 34. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, for the aforementioned polypeptide complex, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62. In some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7R and 7K, 62K and 62H, and 11L; most preferably, the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 7K and 62K mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 7K and 62H mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 11L and 62K mutations; or the Titin-T chain has 25S, 39T and 8C mutations and the Obscurin-O chain has 25S, 76S, 88C, 11L and 62H mutations; the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33.

In some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, K11L, T62K and T62H; in some embodiments, the Titin-T chain has C25S, C39T, and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62K mutations; the Titin-

T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62H mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62K mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62H mutations. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33.

In some embodiments, for the aforementioned polypeptide complex, the Obscurin-O chain is an Obscurin-O chain having one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62 on the basis of SEQ ID NO: 45; in some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, K11L and T62K and T62H on the basis of SEQ ID NO: 45; in some embodiments, the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62K mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62H mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62K mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62H mutations on the basis of SEQ ID NO: 45. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33.

In some embodiments, for the aforementioned polypeptide complex, the first domain and the second domain have one or more amino acid residue mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

In some embodiments, for the aforementioned polypeptide complex, the first domain and the second domain are selected from the group consisting of the following Titin-T chain/Obscurin-O chain: the Titin-T chain is a polypeptide having one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 35,

and the Obscurin-O chain is a polypeptide having one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 50. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

In some embodiments, the aforementioned first domain and the aforementioned second domain have one or more residue mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3W, 11I, 13L, 22M, 40S, 42K, 45S, 47E, 49G, 56S, 58E, 66S and 66K, 70R, 75V, 77S, 79T, 81R, 82M, 83D and 84L, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2E, 11K, 12S, 13Y, 14T, 17E, 20L, 22M and 22S, 30D, 32P, 34E, 36T, 41K, 42L, 44I, 45T, 53L, 58V, 62E, 67Q and 67T, 69S, 89L, 92E, 94G and 97G. In some embodiments, the Titin-T chain has 66S and 77S amino acid mutations, and/or the Obscurin-O chain has 11K, 12S, 13Y, 14T and 22S amino acid mutations; the Titin-T chain has 66K, 70R, 79T and 81R amino acid mutations, and/or the Obscurin-O chain has 2E, 17E, 30D, 32P, 34E, 36T, 44I, 45T, 58V, 62E, 67Q, 69S and 97G amino acid mutations; the Titin-T chain has 3W, 11I, 13L, 22M and 82M amino acid mutations, and/or the Obscurin-O chain has 20L, 22M and 53L amino acid mutations; the Titin-T chain has 11I, 66K, 79T and 81R amino acid mutations, and/or the Obscurin-O chain has 41K, 45T, 67Q, 69S and 89L amino acid mutations; the Titin-T chain has 40S, 42K, 45S, 47E, 49G, 56S, 58E, 75V, 83D, and 84L amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E, and 94G amino acid mutations; the Titin-T chain has 47E, 49G, 56S, 58E and 75V amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E and 94G amino acid mutations; the Titin-T chain has 56S, 58E and 75V amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E and 94G amino acid mutations; or the Titin-T chain has 56S, 58E, 66S and 77S amino acid mutations, and/or the Obscurin-O chain has 12S, 13Y, 22S, 42L, 45T, 67Q, 69S, 92E and 94G amino acid mutations; the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

In some embodiments, the aforementioned first domain and the aforementioned second domain have one or more residue mutations on positions selected from the group consisting of: the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L,

L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

- 5 In some embodiments, the aforementioned first domain and the aforementioned second domain are selected from the group consisting of the following Titin-T chain/Obscurin-O chain: the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L
10 on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G on the basis of SEQ ID NO: 35. The mutation position in the Titin-T chain is a natural
15 sequence numbering position of a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position of a sequence SEQ ID NO: 50.

- In some embodiments, the aforementioned Titin-T chain has M66S and T77S amino acid mutations, and/or the Obscurin-O chain has L11K, A12S, F13Y, V14T and T22S amino
20 acid mutations; the Titin-T chain has M66K, K70R, S79T and G81R amino acid mutations, and/or the Obscurin-O chain has G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S and A97G amino acid mutations; the Titin-T chain has P3W, S11I, I13L, T22M and N82M amino acid mutations, and/or the Obscurin-O chain has D20L, T22M and A53L amino acid mutations; the Titin-T chain has S11I,
25 M66K, S79T and G81R amino acid mutations, and/or the Obscurin-O chain has Q41K, A45T, A67Q, G69S and V89L amino acid mutations; the Titin-T chain has G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D and F84L amino acid mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; the Titin-T chain has Q47E, Q49G, N56S, D58E and L75V amino acid
30 mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; the Titin-T chain has N56S, D58E and L75V amino acid mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; or the Titin-T chain has N56S, D58E, M66S and T77S amino acid mutations, and/or the Obscurin-O chain has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E
35 and D94G amino acid mutations. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

- In some embodiments, the aforementioned first domain and the aforementioned second
40 domain are selected from the group consisting of the following Titin-T chain/Obscurin-O chain: the Titin-T chain has M66S and T77S amino acid mutations on the basis of SEQ

ID NO: 35, and/or the Obscurin-O chain has L11K, A12S, F13Y, V14T and T22S amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has M66K, K70R, S79T and G81R amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S and A97G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has P3W, S11I, I13L, T22M and N82M amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has D20L, T22M and A53L amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has S11I, M66K, S79T and G81R amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q41K, A45T, A67Q, G69S and V89L amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D and F84L amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has Q47E, Q49G, N56S, D58E and L75V amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has N56S, D58E and L75V amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; or the Titin-T chain has N56S, D58E, M66S and T77S amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50. The mutation position in the Titin-T chain is a natural sequence numbering position of a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position of a sequence SEQ ID NO: 50.

In some embodiments, for the aforementioned polypeptide complex, the VH1 is operably linked to the first domain through a first linking domain, and the VL1 is operably linked to the second domain through a second linking domain.

In some embodiments, the aforementioned first and/or second linking domain is selected from the group consisting of: an N-terminal fragment of the Titin-T chain, an N-terminal fragment of the Obscurin-O chain and an N-terminal fragment of the Obscurin-like-O chain, and a $(G_xS)_y$ linker, wherein X is selected from the group consisting of integers from 1 to 5 (for example, 1, 2, 3, 4 or 5), and Y is selected from the group consisting of integers from 1 to 6 (for example, 1, 2, 3, 4, 5 or 6).

In some embodiments, the aforementioned first and/or second linking domain is selected from the group consisting of: "KAGIR", "DQPQF", $(G_4S)_1$ and $(G_4S)_2$.

In some embodiments, for the aforementioned polypeptide complex, when the first domain is a Titin-T chain, the first linking domain is a KAGIR polypeptide; when the second domain is an Obscurin-O chain, the second linking domain is a DQPQF polypeptide. In other embodiments, when the second domain is a Titin-T chain, the second linking domain is a KAGIR polypeptide, and when the first domain is an

Obscurin-O chain, the first linking domain is a DQPQF polypeptide.

In some embodiments of the polypeptide complex, wherein,

(A) the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 and/or 5 amino acid residues of KAGIR added at the N-terminus on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L and/or a KAGIR amino acid residue added at the N-terminus; and/or

(B) the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 and/or a KAGIR amino acid residue added at the N-terminus on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G and/or a DQPQF amino acid residue added at the N-terminus; or

the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C;

the mutation position in the Titin-T chain is a natural sequence numbering position of the sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 34.

In some embodiments of the polypeptide complex, wherein (A) the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 32; more preferably, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 35, and preferably has one or more amino acid mutations on

positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L; the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 35, and/or

- 5 (B) the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88 on the basis of SEQ ID NO: 33, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 33;
- 10 preferably, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62 on the basis of SEQ ID NO: 45, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, T62K and T62H, and K11L, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID
- 15 NO: 45; more preferably, the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 50, and preferably has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D,
- 20 T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 50; or
- the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO:
- 25 34, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C, and the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of SEQ ID NO: 34.

- In some embodiments of the polypeptide complex, wherein the Titin-T chain comprises
- 30 a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33,
- 35 42–58, 77–86; or the Titin-T chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-like-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a polypeptide having a sequence having at least 80% sequence
- 40 identity to any one of SEQ ID NOs: 34, 59–64. Wherein, the at least 80% sequence identity refers to, for example, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,

- 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity. In some embodiments, the aforementioned Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 68, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 80.
- 5 In other embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 73, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 83.
- In other embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a
- 10 sequence set forth in SEQ ID NO: 84.
- In other embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86.
- In other embodiments, the Titin-T chain comprises a polypeptide having a sequence set
- 15 forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86.
- In other embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 75, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86.
- 20 In some embodiments, the Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO: 68, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 80; the Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO: 73, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 83; the Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO:
- 25 76, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 84; the Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 86; the Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 86; or the
- 30 Titin-T chain is a polypeptide having a sequence set forth in SEQ ID NO: 75, and the Obscurin-O chain is a polypeptide having a sequence set forth in SEQ ID NO: 86.
- In some embodiments, for the aforementioned polypeptide complex, the first antigen is selected from the group consisting of: a foreign antigen, an endogenous antigen, an autoantigen, a neoantigen, a viral antigen and a tumor antigen.
- 35 In some embodiments, disclosed is a multispecific polypeptide complex, comprising: a first polypeptide complex, being any one of the aforementioned polypeptide complexes and specifically binding to a first antigen, and
- a second polypeptide complex, comprising a second antigen-binding moiety and specifically binding to a second antigen.
- 40 In some embodiments, the first polypeptide complex and the second polypeptide complex bind to two different antigens.

In some embodiments, the first polypeptide complex and the second polypeptide complex bind to two different epitopes on the same antigen.

In some embodiments, the multispecific polypeptide complex is a multispecific polypeptide complex, and more preferably, the multispecific polypeptide complex is a bispecific antibody.

In some embodiments, the second polypeptide complex of the multispecific polypeptide complex comprises a second heavy chain variable domain (VH2) and a second light chain variable domain (VL2). Mismatching between the VH1 of the first polypeptide complex and the VL2 of the second polypeptide complex, and/or between the VH2 of the second polypeptide complex and the VL1 of the first polypeptide complex is less susceptible to happen. In some embodiments, the VH2 and the VL2 of the second antigen-binding moiety form a second antigen-binding site specifically binding to the second antigen.

In some embodiments, for the aforementioned multispecific polypeptide complex, the second antigen-binding moiety of the second polypeptide complex comprises:

a third polypeptide, comprising a VH2 from an N-terminus to a C-terminus, the VH2 being operably linked to a third domain comprising a CH1, and

a fourth polypeptide, comprising a VL2 from an N-terminus to a C-terminus, the VL2 being operably linked to a fourth domain comprising a CL.

In some embodiments, the C-terminus of VH2 is linked to the N-terminus of CH1, and the C-terminus of VL2 is linked to the N-terminus of CL.

In some embodiments, for the aforementioned multispecific polypeptide complex, the first polypeptide complex further comprises an operably-linked first dimerization domain, and the second polypeptide complex further comprises an operably-linked second dimerization domain, the first dimerization domain and the second dimerization domain being bound together.

In some embodiments, a C-terminus of the first domain of the first polypeptide complex is operably linked to an N-terminus of the first dimerization domain, and a C-terminus of the third domain of the second polypeptide complex is operably linked to an N-terminus of the second dimerization domain.

In some embodiments, the aforementioned first dimerization domain and the aforementioned second dimerization domain are bound to form a dimer by a means of an antibody hinge region or a portion thereof, a linker, a disulfide bond, a hydrogen bond, an electrostatic interaction, a salt bridge, a hydrophobic-hydrophilic interaction, or a combination thereof.

In some embodiments, the aforementioned first dimerization domain and the aforementioned second dimerization domain are bound to form a dimer by an antibody hinge region or a portion thereof, and preferably a hinge region of IgG1, IgG2 or IgG4 or a portion thereof. In some embodiments, the hinge region of IgG1, IgG2, IgG3 or IgG4 or a portion thereof is preferred to form a dimer.

In some embodiments, for the aforementioned multispecific polypeptide complex, the first dimerization domain and/or the second dimerization domain further comprises an

antibody CH2 domain and/or an antibody CH3 domain.

In some embodiments, for the aforementioned multispecific polypeptide complex, the antibody CH2 domain and/or the antibody CH3 domain is derived from IgG1, IgG2 or IgG4. In some embodiments, the antibody CH2 domain and/or the antibody CH3 domain is derived from IgG1, IgG2, IgG3 or IgG4.

In some embodiments, for the aforementioned multispecific polypeptide complex, the first polypeptide sequentially comprises VH1-L1-T chain-L2-CH2-CH3 from an N-terminus to a C-terminus, the second polypeptide sequentially comprises VL1-L3-O chain or VL1-L4-OL chain from an N-terminus to a C-terminus, the third polypeptide sequentially comprises VH2-CH1-CH2-CH3 from an N-terminus to a C-terminus, and the fourth polypeptide sequentially comprises VL1-CL from an N-terminus to a C-terminus; or the first polypeptide sequentially comprises VH1-L2-O chain-L3-CH2-CH3 or VH1-L4-OL chain-L5-CH2-CH3 from an N-terminus to a C-terminus, the second polypeptide sequentially comprises VL1-L1-T chain from an N-terminus to a C-terminus, the third polypeptide sequentially comprises VH2-CH1-CH2-CH3 from an N-terminus to a C-terminus, and the fourth polypeptide sequentially comprises VL2-CL from an N-terminus to a C-terminus; the L1 to L5 are spacers (also known as linking domains) which may or may not be present. Preferably, the spacer is selected from the group consisting of: an N-terminal fragment of a Titin-T chain, an N-terminal fragment of an Obscurin-O chain, an N-terminal fragment of an Obscurin-like-O chain, and a linker (e.g., (G_xS)_y linker), wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6. Most preferably, the spacer is selected from the group consisting of: "KAGIR", "DQPQF", (G₄S)₁ and (G₄S)₂.

In some embodiments, for the aforementioned multispecific polypeptide complex, the first dimerization domain and the second dimerization domain are not identical and are bound in a manner that prevents homodimerization and/or favors heterodimerization.

In some embodiments, the aforementioned first dimerization domain and the aforementioned second dimerization domain are bound to form a dimer by a means of knob-into-hole, a hydrophobic interaction, an electrostatic interaction, a hydrophilic interaction or a flexibility increase.

In some embodiments, the aforementioned first dimerization domain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 2, and the second dimerization domain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 3; or the first dimerization domain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 3, and the second dimerization domain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 2.

In some embodiments, the present disclosure provides a domain engineered antibody in which at least one constant region domain CH1 and at least one constant region domain CL are substituted, wherein,

the domain CH1 is substituted with a Titin-T chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain;

the domain CL is substituted with the Titin-T chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain;

5 the domain CH1 is substituted with an Obscurin-O chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Obscurin-O chain;

the domain CL is substituted with the Obscurin-O chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the

10 Obscurin-O chain;

the domain CH1 is substituted with an Obscurin-like-O chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Obscurin-like-O chain; or

the domain CL is substituted with the Obscurin-like-O chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the

15 Obscurin-like-O chain.

In some embodiments, for the aforementioned domain engineered antibody, the domain capable of interacting with the Obscurin-O chain or the Obscurin-like-O chain is the Titin-T chain, and the domain capable of interacting with the Titin-T chain is the Obscurin-O

20 chain or the Obscurin-like-O chain.

In some embodiments, the antibody comprises a heavy chain variable region VH1 and a light chain variable region VL1, the VH1 and the VL1 forming a primary binding site specifically binding to an antigen thereof; a C-terminus of the VH1 is operably linked to an N-terminus of the Titin-T chain, a C-terminus of the VL1 is operably linked to an N-

25 terminus of the Obscurin-O chain or the Obscurin-like-O chain, or the C-terminus of the VL1 is operably linked to the N-terminus of the Titin-T chain, and the C-terminus of the VH1 is operably linked to the N-terminus of the Obscurin-O chain or the Obscurin-like-O chain.

In some embodiments, the present disclosure provides a Fab fragment of a domain engineered antibody in which a constant region domain CH1 and a constant region domain CL are substituted, wherein,

30 the domain CH1 is substituted with a Titin-T chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain; or

the domain CL is substituted with the Titin-T chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain; or

35 the domain CH1 is substituted with an Obscurin-O chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Obscurin-O chain; or

the domain CL is substituted with the Obscurin-O chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the

40 Obscurin-O chain; or

the domain CH1 is substituted with the Obscurin-like-O chain, and the domain CL is substituted with a domain capable of having an inter-protein interaction with the Obscurin-like-O chain; or

the domain CL is substituted with the Obscurin-like-O chain, and the domain CH1 is substituted with a domain capable of having an inter-protein interaction with the Obscurin-like-O chain.

In some embodiments, for the aforementioned Fab fragment, the domain having an inter-protein interaction with the Titin-T chain is the Obscurin-O chain or the Obscurin-like-O chain; the domain having an inter-protein interaction with the Obscurin-O chain or the Obscurin-like-O chain is the Titin-T chain.

In some embodiments, the Fab comprises a heavy chain variable region VH1 and a light chain variable region VL1, the VH1 and the VL1 forming a primary binding site specifically binding to an antigen thereof; a C-terminus of the VH1 is operably linked to an N-terminus of the Titin-T chain, a C-terminus of the VL1 is operably linked to an N-terminus of the Obscurin-O chain or the Obscurin-like-O chain, or the C-terminus of the VL1 is operably linked to the N-terminus of the Titin-T chain, and the C-terminus of the VH1 is operably linked to the N-terminus of the Obscurin-O chain or the Obscurin-like-O chain.

In some embodiments, the present disclosure provides a domain engineered antibody comprising the aforementioned Fab fragment.

In some embodiments, the present disclosure provides a bispecific antibody comprising a first heavy chain and a first light chain specifically binding to a first antigen and further comprising a second heavy chain and a second light chain specifically binding to a second antigen, wherein,

a CH1 domain of the first heavy chain is substituted with a Titin-T chain, and a CL domain of the first light chain is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain; or

the CL domain of the first light chain is substituted with the Titin-T chain, and the CH1 domain of the first heavy chain is substituted with a domain capable of having an inter-protein interaction with the Titin-T chain; or

the domain CH1 of the first heavy chain is substituted with the Obscurin-O chain, and the domain CL of the first light chain is substituted with a domain capable of having an inter-protein interaction with the Obscurin-O chain; or

the domain CL of the first light chain is substituted with the Obscurin-O chain, and the domain CH1 of the first heavy chain is substituted with a domain capable of having an inter-protein interaction with the Obscurin-O chain; or

the domain CH1 of the first heavy chain is substituted with the Obscurin-like-O chain, and the domain CL of the first light chain is substituted with a domain capable of having an inter-protein interaction with the Obscurin-like-O chain; or

the domain CL of the first light chain is substituted with the Obscurin-like-O chain, and the domain CH1 of the first heavy chain is substituted with a domain capable of having

an inter-protein interaction with the Obscurin-like-O chain.

The bispecific antibody binds to a first antigen and a second antigen which are not identical, or binds to two different epitopes on the same antigen.

In specific embodiments, mispairing between the first heavy chain and the second light chain, and between the first light chain and the second heavy chain is less susceptible to happen.

In some embodiments, for the aforementioned bispecific antibody, the domain having an inter-protein interaction with the Titin-T chain is the Obscurin-O chain or the Obscurin-like-O chain; the domain having an inter-protein interaction with the Obscurin-O chain or the Obscurin-like-O chain is the Titin-T chain.

In some embodiments, the first heavy chain comprises a first heavy chain variable region (VH1), and the first light chain comprises a first light chain variable region (VL1), the VH1 and the VL1 forming an antigen-binding site specifically binding to a first antigen, wherein a C-terminus of the VH1 is operably linked to an N-terminus of the Titin-T chain, a C-terminus of the VL1 is operably linked to an N-terminus of the Obscurin-O chain or the Obscurin-like-O chain, or the C-terminus of the VL1 is operably linked to the N-terminus of the Titin-T chain, and the C-terminus of the VH1 is operably linked to the N-terminus of the Obscurin-O chain or the Obscurin-like-O chain.

In some embodiments, for the aforementioned bispecific antibody, the second heavy chain comprises a second heavy chain variable region (VH2) from an N-terminus to a C-terminus operably linked to the CH1; the second light chain comprises a second light chain variable region (VL2) from an N-terminus to a C-terminus operably linked to the CL.

In some embodiments, for the aforementioned bispecific antibody, the VH2 and the VL2 form an antigen-binding site specifically binding a second antigen, and the C-terminus of the VH2 is operably linked to the N-terminus of the CH1; the C-terminus of the VL2 is operably linked to the N-terminus of the CL.

In some embodiments, for the aforementioned bispecific antibody, the bispecific antibody structural model is selected from the group consisting of F(ab)₂, scFv-Fab, (scFv)₂-Fab, KiH, CrossMAb, Triomab quadroma, FcΔAdp, ART-Ig, BiMAb, Biclomics, BEAT, DuoBody, Azymetric, XmaB, 2:1 TCBs, 1Fab-IgG TDB, FynomAb, two-in-one/DAF, scFv-Fab-IgG, DART-Fc, LP- DART, CODV-Fab-TL, HLE-BiTE, F(ab)₂-CrossMAb, IgG-(scFv)₂, Bs4Ab, DVD-Ig, Tetravalent-DART-Fc, (scFv)₄-Fc, CODV-Ig, mAb2, F(ab)₄-CrossMAb, IgG and Fab-IgG, and the like.

In some embodiments, for the aforementioned bispecific antibody, C-termini of the first heavy chain and the second heavy chain comprise a CH2 domain and/or a CH3 domain.

In some embodiments, the aforementioned CH1, CH2 and CH3 domains are derived from IgG1, IgG2 or IgG4. In some embodiments, the aforementioned CH1, CH2 and CH3 domains are derived from IgG1, IgG2, IgG3 or IgG4. In some embodiments, the aforementioned first heavy chain and the aforementioned second heavy chain are bound to form a dimer by a means of an antibody hinge region or a portion thereof, a linker, a

disulfide bond, a hydrogen bond, an electrostatic interaction, a salt bridge, a hydrophobic-hydrophilic interaction, or a combination thereof.

In some embodiments, for the aforementioned bispecific antibody, the first heavy chain sequentially comprises VH1-L1-T chain-L2-CH2-CH3 from an N-terminus to a C-terminus, and the first light chain sequentially comprises VL1-L3-O chain or VL1-L4-OL chain from an N-terminus to a C-terminus; the second heavy chain sequentially comprises VH2-CH1-CH2-CH3 from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL2-CL from an N-terminus to a C-terminus; or the first light chain sequentially comprises VL1-L1-T chain from an N-terminus to a C-terminus, and the first heavy chain sequentially comprises VH1-L2-O chain-L3-CH2-CH3 or VH1-L4-OL chain-L5-CH2-CH3 from an N-terminus to a C-terminus; the second heavy chain sequentially comprises VH2-CH1-CH2-CH3 from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL2-CL from an N-terminus to a C-terminus;

wherein L1 to L5 are spacers which may or may not be present. Preferably, the spacer is an N-terminal fragment of a Titin-T chain, an N-terminal fragment of an Obscurin-O chain, an N-terminal fragment of an Obscurin-like-O chain or a linker, for example, a $(G_xS)_y$ linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6; preferably, the spacer is selected from the group consisting of: "KAGIR", "DQPQF", $(G_4S)_1$ and $(G_4S)_2$.

In some embodiments, for the aforementioned bispecific antibody, the CH2 and the CH3 of the first heavy chain are not identical to the CH2 and the CH3 of the second heavy chain and are bound in a manner that prevents homodimerization and/or favors heterodimerization.

In some embodiments, the aforementioned first heavy chain and the aforementioned second heavy chain are bound to form a dimer by a means of knob-into-hole, a hydrophobic interaction, an electrostatic interaction, a hydrophilic interaction or a flexibility increase.

In some embodiments, the aforementioned first heavy chain and the aforementioned second heavy chain are bound by knob-into-hole to form a dimer. In some embodiments, the CH2-CH3 domain of the aforementioned first heavy chain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 2, and the CH2-CH3 domain of the second heavy chain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 3; or the CH2-CH3 domain of the first heavy chain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 3, and the CH2-CH3 domain of the second heavy chain has amino acid residues at positions 104 to 330 of a sequence set forth in SEQ ID NO: 2.

In some embodiments, for the aforementioned bispecific antibody, the first heavy chain sequentially comprises VH1-L1-T chain-L2-knob-Fc from an N-terminus to a C-terminus, the first light chain sequentially comprises VL1-L3-O chain or VL1-L4-OL chain from an N-terminus to a C-terminus, the second heavy chain sequentially comprises

VH2-CH1-hole-Fc from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL1-CL from an N-terminus to a C-terminus; or the first heavy chain sequentially comprises VH1-L1-T chain-L2-hole-Fc from an N-terminus to a C-terminus, the first light chain sequentially comprises VL1-L3-O chain or VL1-L4-OL chain from an N-terminus to a C-terminus, the second heavy chain sequentially comprises VH2-CH1-knob-Fc from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL2-CL from an N-terminus to a C-terminus; or the first light chain sequentially comprises VL1-L1-T chain from an N-terminus to a C-terminus, the first heavy chain sequentially comprises VH1-L2-O chain-L3-knob-Fc or VH1-L4-OL chain-L5-knob-Fc from an N-terminus to a C-terminus, the second heavy chain sequentially comprises VH2-CH1-hole-Fc from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL2-CL from an N-terminus to a C-terminus; the first light chain sequentially comprises VL1-L1-T chain from an N-terminus to a C-terminus, the first heavy chain sequentially comprises VH1-L2-O chain-L3-hole-Fc or VH1-L4-OL chain-L5-hole-Fc from an N-terminus to a C-terminus, the second heavy chain sequentially comprises VH2-CH1-knob-Fc from an N-terminus to a C-terminus, and the second light chain sequentially comprises VL2-CL from an N-terminus to a C-terminus;

the L1 to L5 are spacers which may or may not be present. Preferably, the spacer is an N-terminal fragment of a Titin-T chain, an N-terminal fragment of an Obscurin-O chain, an N-terminal fragment of an Obscurin-like-O chain or a linker, for example, a $(G_xS)_y$ linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6; preferably, the spacer is selected from the group consisting of: "KAGIR", "DQPQF", $(G_4S)_1$ and $(G_4S)_2$.

In some embodiments, for any one of the aforementioned domain engineered antibody, the Fab fragment of a domain engineered antibody, or the bispecific antibody, the domain having an inter-protein interaction with a Titin-T chain is an Obscurin-O chain or an Obscurin-like-O chain; the domain having an inter-protein interaction with an Obscurin-O chain or an Obscurin-like-O chain is a Titin-T chain. For any one of the aforementioned domain engineered antibody, or the Fab fragment of a domain engineered antibody, or the bispecific antibody, the operable linkage is a linkage of two polypeptide sequences through a spacer or a direct linkage of two polypeptides.

In some embodiments, for the aforementioned domain engineered antibody, or the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain, are bound through natural inter-chain bonds and/or unnatural inter-chain bonds to form a dimer.

In some embodiments, the first domain and the second domain form a dimer through natural inter-chain bonds, and one or more residues at positions selected from the group consisting of 7-15, 19-24, 26, 55, 59 and 60 on the Titin-T chain and one or more residues at positions selected from the group consisting of 3-6, 9, 41, 73, 75, and 80-90 on the

Obscurin-O chain are linked to each other, or one or more residues selected from the group consisting of positions 1, 7–10, 13–16, 19–26, 59–60 and 96 on the Titin-T chain and one or more residues selected from the group consisting of positions 4–5, 10, 12–13, 74, 76, 78 and 82–91 on the Obscurin-like-O chain are linked to each other. the residue position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the residue position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the residue position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain, form a dimer through at least one non-natural inter-chain bonds. In some embodiments, the non-natural inter-chain bond is a disulfide bond; in some embodiments, the dimer comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 non-natural inter-chain bonds.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, wherein, the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86.

In some embodiments, the Titin-T chain/Obscurin-O chain, or the Titin-T chain/Obscurin-like-O chain, is as follows:
the Titin-T chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and/or the Obscurin-O chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88 on the basis of SEQ ID NO: 33; or
the Titin-T chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and/or the Obscurin-like-O chain is a polypeptide having one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, wherein, the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8C, 20C, 22C, 25S, 26C and 39T, and/or the Obscurin-O

chain has one or more amino acid residue mutations on positions selected from the group consisting of 3C, 9C, 25S, 76S and 88C; or
the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8C, 20C, 22C, 25S, 26C and 39T, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6E, 26S, 74C, 77S, 84C and 86C;
5 more preferably, the non-natural inter-chain bond is located at a mutation position selected from the group consisting of the following:
the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has a 88C
10 mutation;
the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-O chain has a 3C mutation;
the Titin-T chain has 25S, 39T and 26C mutations, and the Obscurin-O chain has a 9C mutation;
15 the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S and 88C mutations;
the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-O chain has 25S, 76S and 3C mutations;
the Titin-T chain has 25S, 39T and 26C mutations, and the Obscurin-O chain has 25S,
20 76S and 9C mutations;
the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-like-O chain has 6E and 74C mutations;
the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-like-O chain has 6E and 84C mutations;
25 the Titin-T chain has 25S, 39T and 22C mutations, and the Obscurin-like-O chain has 6E and 86C mutations;
the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-like-O chain has 6E, 26S, 77S and 74C mutations;
the Titin-T chain has 25S, 39T and 20C mutations, and the Obscurin-like-O chain has 6E,
30 26S, 77S and 84C mutations; or
the Titin-T chain has 25S, 39T and 22C mutations, and the Obscurin-like-O chain has 6E, 26S, 77S and 86C mutations;
the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is
35 a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.
In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, wherein,
40 the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the

Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the
5 Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C; the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation
10 position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, the aforementioned Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T on the basis of SEQ ID NO: 32, and/or the Obscurin-O chain has
15 one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C on the basis of SEQ ID NO: 33; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T on the basis of SEQ ID NO: 32, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on
20 positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C on the basis of SEQ ID NO: 34. The mutation position in the Titin-T chain is a natural sequence numbering position of the sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence
25 numbering position of the sequence SEQ ID NO: 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, wherein,
the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has an A88C mutation;

30 the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has an A3C mutation;

the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has an R9C mutation;

the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has
35 C25S, C76S and A88C mutations;

the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has C25S, C76S and A3C mutations;

the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has C25S, C76S and R9C mutations;

40 the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has C6E and V74C mutations;

the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E and G84C mutations;

the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain has C6E and A86C mutations;

5 the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and V74C mutations;

the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and G84C mutations;

the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain

10 has C6E, C26S, C77S and A86C mutations;

the mutation position in the Titin-T chain is a natural sequence position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence position relative to a sequence SEQ ID NO:

15 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an A88C mutation on the basis of SEQ ID NO: 33; the Titin-T chain has C25S,

20 C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an A3C mutation on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A26C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has an R9C mutation on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and

25 A88C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and A3C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has C25S, C39T and A26C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S and R9C mutations on the basis of SEQ ID NO: 33; the Titin-T chain has

30 C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E and V74C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E and G84C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and T22C mutations on the basis of SEQ ID NO: 32, and the

35 Obscurin-like-O chain has C6E and A86C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S, C77S and V74C mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and V20C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S, C77S and G84C

40 mutations on the basis of SEQ ID NO: 34; the Titin-T chain has C25S, C39T and T22C mutations on the basis of SEQ ID NO: 32, and the Obscurin-like-O chain has C6E, C26S,

C77S and A86C mutations on the basis of SEQ ID NO: 34. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Obscurin-O chain further has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62. In some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7R and 7K, 62K and 62H, and 11L; most preferably, the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 7K and 62K mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 7K and 62H mutations; the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 11L and 62K mutations; or the Titin-T chain has 25S, 39T and 8C mutations, and the Obscurin-O chain has 25S, 76S, 88C, 11L and 62H mutations. In some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, K11L, T62K and T62H; in some embodiments, the Titin-T chain has C25S, C39T, and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62K mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62H mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62K mutations; or the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62H mutations. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Obscurin-O chain is an Obscurin-O chain having one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62 on the basis of SEQ ID NO: 45; in some embodiments, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, K11L and T62K and T62H on the basis of SEQ ID NO: 45; in some embodiments, the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62K mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62H mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ

ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62K mutations on the basis of SEQ ID NO: 45; the Titin-T chain has C25S, C39T and A8C mutations on the basis of SEQ ID NO: 32, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62H mutations on the basis of SEQ ID NO: 45. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97. In some embodiments, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3W, 11I, 13L, 22M, 40S, 42K, 45S, 47E, 49G, 56S, 58E, 66S and 66K, 70R, 75V, 77S, 79T, 81R, 82M, 83D and 84L, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2E, 11K, 12S, 13Y, 14T, 17E, 20L, 22M and 22S, 30D, 32P, 34E, 36T, 41K, 42L, 44I, 45T, 53L, 58V, 62E, 67Q and 67T, 69S, 89L, 92E, 94G and 97G. More preferably, the Titin-T chain has 66S and 77S amino acid mutations, and/or the Obscurin-O chain has 11K, 12S, 13Y, 14T and 22S amino acid mutations; the Titin-T chain has 66K, 70R, 79T and 81R amino acid mutations, and/or the Obscurin-O chain has 2E, 17E, 30D, 32P, 34E, 36T, 44I, 45T, 58V, 62E, 67Q, 69S and 97G amino acid mutations; the Titin-T chain has 3W, 11I, 13L, 22M and 82M amino acid mutations, and/or the Obscurin-O chain has 20L, 22M and 53L amino acid mutations; the Titin-T chain has 11I, 66K, 79T and 81R amino acid mutations, and/or the Obscurin-O chain has 41K, 45T, 67Q, 69S and 89L amino acid mutations; the Titin-T chain has 40S, 42K, 45S, 47E, 49G, 56S, 58E, 75V, 83D, and 84L amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E, and 94G amino acid mutations; the Titin-T chain has 47E, 49G, 56S, 58E and 75V amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E and 94G amino acid mutations; the Titin-T chain has 56S, 58E and 75V amino acid mutations, and/or the Obscurin-O chain has 42L, 45T, 67T, 69S, 92E and 94G amino acid mutations; or the Titin-T chain has 56S, 58E, 66S and 77S amino acid mutations, and/or the Obscurin-O chain has 12S, 13Y, 22S, 42L, 45T, 67Q, 69S, 92E and 94G amino acid mutations. the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50. In some embodiments, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L, and/or the Obscurin-O chain has one or more

amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G. In some embodiments, the Titin-T chain has M66S and T77S amino acid mutations, and/or the Obscurin-O chain has L11K, A12S, F13Y, V14T and T22S amino acid mutations; the Titin-T chain has M66K, K70R, S79T and G81R amino acid mutations, and/or the Obscurin-O chain has G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S and A97G amino acid mutations; the Titin-T chain has P3W, S11I, I13L, T22M and N82M amino acid mutations, and/or the Obscurin-O chain has D20L, T22M and A53L amino acid mutations; the Titin-T chain has S11I, M66K, S79T and G81R amino acid mutations, and/or the Obscurin-O chain has Q41K, A45T, A67Q, G69S and V89L amino acid mutations; the Titin-T chain has G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D and F84L amino acid mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; the Titin-T chain has Q47E, Q49G, N56S, D58E and L75V amino acid mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; the Titin-T chain has N56S, D58E and L75V amino acid mutations, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations; or the Titin-T chain has N56S, D58E, M66S and T77S amino acid mutations, and/or the Obscurin-O chain has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G amino acid mutations. the mutation position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 50.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain is a polypeptide having one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 35, and the Obscurin-O chain is a polypeptide having one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 50. The mutation position in the Titin-T chain is a natural sequence numbering position of a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position of a sequence SEQ ID NO: 50. In some embodiments, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E,

D94G and A97G on the basis of SEQ ID NO: 35. In some embodiments, the Titin-T chain has M66S and T77S amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has L11K, A12S, F13Y, V14T and T22S amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has M66K, K70R, S79T and G81R amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S and A97G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has P3W, S11I, I13L, T22M and N82M amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has D20L, T22M and A53L amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has S11I, M66K, S79T and G81R amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q41K, A45T, A67Q, G69S and V89L amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D and F84L amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has Q47E, Q49G, N56S, D58E and L75V amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; the Titin-T chain has N56S, D58E and L75V amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has Q42L, A45T, A67T, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; or the Titin-T chain has N56S, D58E, M66S and T77S amino acid mutations on the basis of SEQ ID NO: 35, and/or the Obscurin-O chain has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G amino acid mutations on the basis of SEQ ID NO: 50; the mutation position in the Titin-T chain is a natural sequence numbering position of a sequence SEQ ID NO: 35; the mutation position in the Obscurin-O chain is a natural sequence numbering position of a sequence SEQ ID NO: 50.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody or the Fab fragment of a domain engineered antibody, N-termini of the Titin-T chain, the Obscurin-O chain or the Obscurin-like-O chain are operably linked to the VH or the VL through a linking domain. In some embodiments, the linking domain is selected from the group consisting of: an N-terminal fragment of the Titin-T chain, an N-terminal fragment of the Obscurin-O chain, an N-terminal fragment of the Obscurin-like-O chain, and a $(G_xS)_y$ linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6. In some embodiments, the linking domain is selected from the group consisting of: "KAGIR", "DQPQF", $(G_4S)_1$ and $(G_4S)_2$.

In some embodiments, the Titin-T chain is linked to the VH or the VL through a KAGIR polypeptide, and/or the Obscurin-O chain is linked to the VL or the VH through a DQPQF polypeptide.

In some embodiments, for the aforementioned polypeptide complex, wherein,

- (A) the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 and/or a KAGIR amino acid residue added at the N-terminus on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L and/or a KAGIR amino acid residue added at the N-terminus; and/or
- (B) the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 and/or a DQPQF amino acid residue added at the N-terminus on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G and/or a DQPQF amino acid residue added at the N-terminus; or
- the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C;
- the mutation position in the Titin-T chain is a natural sequence numbering position of the sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 34;
- preferably, wherein,
- (A) the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 32; more preferably, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 35, and preferably has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V,

T77S, S79T, G81R, N82M, E83D and F84L; the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 35, and/or

(B) the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88 on the basis of SEQ ID NO: 33, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 33; preferably, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62 on the basis of SEQ ID NO: 45, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, T62K and T62H, and K11L, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 45; more preferably, the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 50, and preferably has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 50; or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C, and the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of SEQ ID NO: 34.

In some embodiments, for the aforementioned domain engineered antibody, the bispecific antibody, or the Fab fragment of a domain engineered antibody, the Titin-T chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86; or the Titin-T chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-like-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64. Wherein, the at least 80% sequence identity refers to, for example, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%

sequence identity.

In some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 68, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 80; the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 73, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 83; the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 84; the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86; the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86; or the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 75, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86.

In some embodiments, the aforementioned bispecific antibody is a bispecific antibody selected from the group consisting of any one of the following A–G:

A. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 89 or a sequence having at least 85% sequence identity to SEQ ID NO: 89, the first light chain has a sequence set forth in SEQ ID NO: 90 or a sequence having at least 85% sequence identity to SEQ ID NO: 90, the second heavy chain has a sequence set forth in SEQ ID NO: 87 or a sequence having at least 85% sequence identity to SEQ ID NO: 87, and the second light chain has a sequence set forth in SEQ ID NO: 88 or a sequence having at least 85% sequence identity to SEQ ID NO: 88;

B. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 93 or a sequence having at least 85% sequence identity to SEQ ID NO: 93, the first light chain has a sequence set forth in SEQ ID NO: 94 or a sequence having at least 85% sequence identity to SEQ ID NO: 94, the second heavy chain has a sequence set forth in SEQ ID NO: 91 or a sequence having at least 85% sequence identity to SEQ ID NO: 91, and the second light chain has a sequence set forth in SEQ ID NO: 92 or a sequence having at least 85% sequence identity to SEQ ID NO: 92;

C. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 97 or a sequence having at least 85% sequence identity to SEQ ID NO: 97, the first light chain has a sequence set forth in SEQ ID NO: 98 or a sequence having at least 85% sequence identity to SEQ ID NO: 98, the second heavy chain has a sequence set forth in SEQ ID NO: 95 or a sequence having at least 85% sequence identity to SEQ ID NO: 95, and the second light chain has a sequence set forth in SEQ ID NO: 96 or a sequence having at least 85% sequence identity to SEQ ID NO: 96;

D. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 99 or a sequence having at least 85% sequence identity to SEQ ID NO: 99, the first light chain has a sequence set forth in SEQ ID NO: 100 or a sequence having at least 85%

- sequence identity to SEQ ID NO: 100, the second heavy chain has a sequence set forth in SEQ ID NO: 101 or a sequence having at least 85% sequence identity to SEQ ID NO: 101, and the second light chain has a sequence set forth in SEQ ID NO: 96 or a sequence having at least 85% sequence identity to SEQ ID NO: 96;
- 5 E. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 102 or a sequence having at least 85% sequence identity to SEQ ID NO: 102, the first light chain has a sequence set forth in SEQ ID NO: 100 or a sequence having at least 85% sequence identity to SEQ ID NO: 100, the second heavy chain has a sequence set forth in SEQ ID NO: 95 or a sequence having at least 85% sequence identity to SEQ ID NO: 95,
- 10 and the second light chain has a sequence set forth in SEQ ID NO: 96 or a sequence having at least 85% sequence identity to SEQ ID NO: 96;
- F. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 103 or a sequence having at least 85% sequence identity to SEQ ID NO: 103, the first light chain has a sequence set forth in SEQ ID NO: 104 or a sequence having at least 85% sequence identity to SEQ ID NO: 104, the second heavy chain has a sequence set forth in SEQ ID NO: 95 or a sequence having at least 85% sequence identity to SEQ ID NO: 95,
- 15 and the second light chain has a sequence set forth in SEQ ID NO: 96 or a sequence having at least 85% sequence identity to SEQ ID NO: 96;
- G. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 107 or a sequence having at least 85% sequence identity to SEQ ID NO: 107, the first light chain has a sequence set forth in SEQ ID NO: 108 or a sequence having at least 85% sequence identity to SEQ ID NO: 108, the second heavy chain has a sequence set forth in SEQ ID NO: 109 or a sequence having at least 85% sequence identity to SEQ ID NO: 109, and the second light chain has a sequence set forth in SEQ ID NO: 110 or a sequence
- 20 having at least 85% sequence identity to SEQ ID NO: 110;
- H. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 122 or a sequence having at least 85% sequence identity to SEQ ID NO: 122, the first light chain has a sequence set forth in SEQ ID NO: 123 or a sequence having at least 85% sequence identity to SEQ ID NO: 123, the second heavy chain has a sequence set forth in SEQ ID NO: 116 or a sequence having at least 85% sequence identity to SEQ ID NO: 116, and the second light chain has a sequence set forth in SEQ ID NO: 117 or a sequence
- 30 having at least 85% sequence identity to SEQ ID NO: 117;
- I. the first heavy chain of the bispecific antibody has a sequence set forth in SEQ ID NO: 118 or a sequence having at least 85% sequence identity to SEQ ID NO: 118, the first light chain has a sequence set forth in SEQ ID NO: 119 or a sequence having at least 85% sequence identity to SEQ ID NO: 119, the second heavy chain has a sequence set forth in SEQ ID NO: 124 or a sequence having at least 85% sequence identity to SEQ ID NO: 124, and the second light chain has a sequence set forth in SEQ ID NO: 125 or a sequence
- 35 having at least 85% sequence identity to SEQ ID NO: 125;
- 40 wherein, the at least 85% sequence identity refers to, for example, at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%

sequence identity.

In some embodiments, the present disclosure provides a method for preparing a multispecific antibody, which comprises substituting a CH1/CL of an antibody with a Titin-T chain and an Obscurin-O chain, or a Titin-T chain and an Obscurin-like-O chain.

5 In some embodiments of the method for preparing a multispecific antibody, the multispecific antibody of the present disclosure has reduced mispairing between light chains and heavy chains as compared to a wild-type in which a CH1/CL is not substituted with a Titin-T chain/Obscurin-O chain, or a Titin-T chain/Obscurin-like-O chain.

In some embodiments, the present disclosure further provides a multispecific antibody
10 obtained by the aforementioned method for preparing a multispecific antibody. In some embodiments, the multispecific antibody comprises a heavy chain variable region (VH1) and a light chain variable region (VL1), the VH1 and the VL1 forming an antigen binding site specifically binding to a first antigen; a C-terminus of the VH1 is operably linked to an N-terminus of the Titin-T chain, a C-terminus of the VL1 is operably linked to an N-terminus of the Obscurin-O chain or the Obscurin-like-O chain, or the C-terminus of the
15 VL1 is operably linked to the N-terminus of the Titin-T chain, and the C-terminus of the VH1 is operably linked to the N-terminus of the Obscurin-O chain or the Obscurin-like-O chain.

In some embodiments, for the method for preparing a multispecific antibody, the Titin-T
20 chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86; or the Titin-T chain comprises a polypeptide
25 having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-like-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a polypeptide having a
30 sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64.

In some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 68, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 80; in some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 73, and the Obscurin-O chain
35 comprises a polypeptide having a sequence set forth in SEQ ID NO: 83; in some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 84; in some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 76, and the Obscurin-O chain
40 comprises a polypeptide having a sequence set forth in SEQ ID NO: 86; in some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in

SEQ ID NO: 75, and the Obscurin-O chain comprises a polypeptide having a sequence set forth in SEQ ID NO: 86.

In some embodiments, wherein,

(A) the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 and/or 5 amino acid residues of KAGIR added at the N-terminus on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L and/or 5 amino acid residues of KAGIR added at the N-terminus; and/or

(B) the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 and/or a DQPQF amino acid residue added at the N-terminus on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G and/or a DQPQF amino acid residue added at the N-terminus; or

the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C;

the mutation position in the Titin-T chain is a natural sequence numbering position of the sequence SEQ ID NO: 32; the mutation position in the Obscurin-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 33; the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of the sequence SEQ ID NO: 34;

preferably, wherein,

(A) the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the basis of SEQ ID NO: 32, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 32; more preferably, the Titin-T chain has one or more amino acid mutations on positions selected from the group consisting of 3, 11, 13, 22, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79,

81, 82, 83 and 84 on the basis of SEQ ID NO: 35, and preferably has one or more amino acid mutations on positions selected from the group consisting of P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S, M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L; the mutation position in the Titin-T chain is a natural sequence numbering position of SEQ ID NO: 35, and/or

(B) the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88 on the basis of SEQ ID NO: 33, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 33; preferably, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62 on the basis of SEQ ID NO: 45, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, T62K and T62H, and K11L, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 45; more preferably, the Obscurin-O chain has one or more amino acid mutations on positions selected from the group consisting of 2, 11, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 62, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 50, and preferably has one or more amino acid mutations on positions selected from the group consisting of G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, K62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G, and the mutation position in the Obscurin-O chain is a natural sequence numbering position of SEQ ID NO: 50; or

the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34, and preferably has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C, and the mutation position in the Obscurin-like-O chain is a natural sequence numbering position of SEQ ID NO: 34.

In some embodiments, the present disclosure provides a conjugate comprising any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody or the bispecific antibody, or the multispecific antibody.

In some embodiments, the present disclosure provides a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, or having a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86, or having a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64; preferably, the polypeptide can be used to substitute a CH1 and/or a CL of an antibody. More preferably, the polypeptide is a

Titin-T chain and an Obscurin-O chain, or a Titin-T chain and an Obscurin-like-O chain, and the single-sided CH1 and CL of the bispecific antibody are substituted with the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain. After the substitution, the mispairing between the first heavy chain and the second light chain, or between the first light chain and the second heavy chain, is less susceptible to happen.

In some embodiments, the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L and/or 5 amino acid residues of KAGIR added at the N-terminus; the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 and/or a DQPQF amino acid residue added at the N-terminus on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G and/or a DQPQF amino acid residue added at the N-terminus; the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO:34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C.

Disclosed is a polypeptide for use in substituting a CH1 and/or a CL of an antibody, a CH1 and/or a CL of an antigen-binding fragment, or a CH1 and/or a CL of a polypeptide complex, wherein the polypeptide has a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76; or the polypeptide has a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86; or the polypeptide has a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64; preferably, the polypeptide is a Titin-T chain and an Obscurin-O chain, or a Titin-T chain and an Obscurin-like-O chain. More preferably, after the single-sided CH1 and CL of the bispecific antibody are substituted with the

polypeptide, the mispairing between the first heavy chain and the second light chain, or between the first light chain and the second heavy chain, is less susceptible to happen.

In some embodiments, the present disclosure provides a Titin-T chain, an Obscurin-O chain, and/or an Obscurin-like-O chain, wherein the Titin-T chain has a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and the Obscurin-O chain has a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86; the Obscurin-like-O chain has a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64. In some embodiments, the Titin-T chain/Obscurin-O chain, or Titin-T chain/Obscurin-like-O chain, may be used to substitute a CH1 and/or a CL of an antibody.

In some embodiments, the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L; the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G; the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C.

In some embodiments, the present disclosure further discloses use of a Titin-T chain and an Obscurin-O chain, or a Titin-T chain and an Obscurin-like-O chain, in the reduction of mispairing of a light/heavy chain of a multispecific antibody; in some embodiments, the Titin-T chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs:

33, 42–58, 77–86 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86; or the Titin-T chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, and/or the Obscurin-like-O chain comprises a polypeptide having a sequence set forth in any one of SEQ ID NOs: 34, 59–64 or a polypeptide having a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59–64. In some embodiments, for the aforementioned use of a Titin-T chain and an Obscurin-O chain, or a Titin-T chain and an Obscurin-like-O chain, in the reduction of mispairing of a light/heavy chain of a multispecific antibody, the Titin-T chain has a sequence set forth in SEQ ID NO: 32 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 8, 20, 22, 25, 26, 39, 3, 11, 13, 40, 42, 45, 47, 49, 56, 58, 66, 70, 75, 77, 79, 81, 82, 83 and 84 and/or 5 amino acid residues of KAGIR added at the N-terminus on the basis of SEQ ID NO: 32; preferably, the Titin-T chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C, C39T, P3W, S11I, I13L, T22M, G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, M66S and M66K, K70R, L75V, T77S, S79T, G81R, N82M, E83D and F84L and/or 5 amino acid residues of KAGIR added at the N-terminus; the Obscurin-O chain has a sequence set forth in SEQ ID NO: 33 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 3, 9, 25, 76, 88, 7, 11, 62, 2, 12, 13, 14, 17, 20, 22, 30, 32, 34, 36, 41, 42, 44, 45, 53, 58, 67, 69, 89, 92, 94 and 97 and/or a DQPQF amino acid residue added at the N-terminus on the basis of SEQ ID NO: 33; preferably, the Obscurin-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S, A88C, L7K and L7R, T62K and T62H, G2E, L11K, A12S, F13Y, V14T, V17E, D20L, T22M and T22S, N30D, T32P, Q34E, S36T, Q41K, Q42L, V44I, A45T, A53L, L58V, T62E, A67Q and A67T, G69S, V89L, Q92E, D94G and A97G and/or a DQPQF amino acid residue added at the N-terminus; the Obscurin-like-O chain has a sequence set forth in SEQ ID NO: 34 or further has a sequence having one or more amino acid mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the basis of SEQ ID NO: 34; preferably, the Obscurin-like-O chain has a sequence having one or more amino acid mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C.

In some embodiments, the multispecific antibody comprises a heavy chain variable region (VH1) and a light chain variable region (VL1), the VH1 and the VL1 forming an antigen binding site specifically binding to a first antigen; a C-terminus of the VH1 is operably linked to an N-terminus of the Titin-T chain, a C-terminus of the VL1 is operably linked to an N-terminus of the Obscurin-O chain or the Obscurin-like-O chain, or the C-terminus of the VL1 is operably linked to the N-terminus of the Titin-T chain, and the C-terminus of the VH1 is operably linked to the N-terminus of the Obscurin-O chain or the Obscurin-

like-O chain.

In some embodiments, the present disclosure provides a nucleic acid molecule encoding any one of the aforementioned polypeptide complex, or the multispecific polypeptide complex, or the domain engineered antibody, or the Fab fragment of a domain engineered antibody, or the bispecific antibody, or the polypeptide, or the multispecific antibody.

In some embodiments, the present disclosure provides a vector comprising the aforementioned nucleic acid molecule.

In some embodiments, the present disclosure provides a host cell obtained by transformation (transduction or transfection) with the aforementioned vector, wherein the host cell is selected from the group consisting of prokaryotic cells and eukaryotic cells, preferably eukaryotic cells, and more preferably mammalian cells. In some embodiments, the host cell does not include any animal or plant cells capable of developing into a whole individual, such as human embryonic stem cells, fertilized eggs, or germ cells.

In some embodiments, the host cell is a eukaryotic cell, and more preferably a mammalian cell including, but not limited to, CHO, 293, NSO, and a cell in which gene editing can be performed to alter the glycosylation modification of an antibody or an antigen-binding fragment thereof, thereby altering the ADCC function of the antibody or the antigen binding fragment thereof, e.g., knocking out genes such as FUT8 or GnT-III. In some embodiments, the mammalian cell does not include a human cell.

In some embodiments, the present disclosure provides a method for preparing any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, or the polypeptide, or the multispecific antibody, which comprises the following steps:

culturing the aforementioned host cell followed by purification and recovery of the polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody or the polypeptide, or the multispecific antibody.

In some embodiments, the present disclosure provides a pharmaceutical composition comprising any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the nucleic acid, the multispecific antibody, or the conjugate, and one or more pharmaceutically acceptable carriers, excipients or diluents. Preferably, the unit dose of the pharmaceutical composition may contain 0.01 wt% to 99 wt% of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the multispecific antibody or the conjugate, or the unit dose of the pharmaceutical composition contains the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the multispecific antibody or the conjugate in an amount of preferably 0.1–2000 mg, and more preferably

1–1000 mg.

In some embodiments, the present disclosure provides use of any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the pharmaceutical composition, the nucleic acid molecule or the multispecific antibody in the preparation of a medicament for the treatment or prevention of a disease or condition. In some embodiments, the disease or condition is a tumor, an inflammatory disease, an autoimmune disease or an infectious disease. In some embodiments, the disease or condition is a bone-related disease, such as a disease or disorder of osteoporosis, osteopenia or osteoarthritis, rheumatoid arthritis, periodontal disease or multiple myeloma. In some embodiments, the tumor is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia and lymphoid malignancies. In some embodiments, the tumor is selected from the group consisting of: squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), neuroglioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), primary mediastinal large B-cell lymphoma, mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), large B-cell lymphoma rich in T-cells/histiocytes, multiple myeloma, myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), gastrointestinal (tract) cancer, kidney cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, gastric cancer, bone cancer, Ewing's sarcoma, cervical cancer, brain cancer, gastric cancer, bladder cancer, hepatoma, breast cancer, colon cancer, hepatocellular carcinoma (HCC), clear cell renal cell carcinoma (RCC), head and neck cancer, laryngeal cancer, hepatobiliary cancer, central nervous system cancer, esophageal cancer, malignant pleural mesothelioma, systemic light chain amyloidosis, lymphoplasmacytic lymphoma, myelodysplastic syndrome, myeloproliferative tumors, neuroendocrine tumors, Merkel cell carcinoma, testicular cancer, and skin cancer. In some embodiments, the inflammatory disease is selected from the group consisting of: rheumatoid arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, multiple sclerosis, type I diabetes, hepatitis (e.g., hepatitis B, hepatitis A, hepatitis C), myocarditis, Sjogren's syndrome, autoimmune hemolytic anemia after transplant rejection, bullus pemphigoid, Graves' disease, Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), myasthenia gravis, pemphigus and pernicious anemia. In some embodiments, the immune disease may be selected from the group consisting of: rheumatoid arthritis, psoriasis, joint psoriasis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, arteriosclerosis, leukocyte adhesion-

deficient disease, multiple sclerosis, Raynaud's syndrome, Sjogren's syndrome, juvenile diabetes, Reiter's disease, Behcet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathy, immune-mediated thrombocytopenic symptoms (such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura),

5 hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, HIV and herpes virus related diseases, severe acute respiratory syndrome, choreoretinitis and immunological diseases caused by virus infection (such as

10 diseases caused or mediated by B cell infection by Epstein-Barr Virus (EBV)).

In some embodiments, the present disclosure provides a method for treating or preventing a disease or condition, which comprises administering to a subject a prophylactically or therapeutically effective amount of any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment

15 of a domain engineered antibody, the bispecific antibody, the pharmaceutical composition, the nucleic acid molecule or the multispecific antibody. In some embodiments, the disease or condition is a tumor, an inflammatory disease, an autoimmune disease or an infectious disease. In some embodiments, the disease or condition is a bone-related disease, such as a disease or disorder of osteoporosis,

20 osteopenia or osteoarthritis, rheumatoid arthritis, periodontal disease or multiple myeloma. In some embodiments, the tumor is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia and lymphoid malignancies. In some embodiments, the tumor is selected from the group consisting of: squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer (NSCLC), head

25 and neck squamous cell carcinoma (HNSCC), neuroglioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), primary mediastinal large B-cell lymphoma, mantle cell lymphoma (MCL), small lymphocytic lymphoma

30 (SLL), large B-cell lymphoma rich in T-cells/histiocytes, multiple myeloma, myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), gastrointestinal (tract) cancer, kidney cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma

35 multiforme, gastric cancer, bone cancer, Ewing's sarcoma, cervical cancer, brain cancer, gastric cancer, bladder cancer, hepatoma, breast cancer, colon cancer, hepatocellular carcinoma (HCC), clear cell renal cell carcinoma (RCC), head and neck cancer, laryngeal cancer, hepatobiliary cancer, central nervous system cancer, esophageal cancer, malignant pleural mesothelioma, systemic light chain amyloidosis, lymphoplasmacytic

40 lymphoma, myelodysplastic syndrome, myeloproliferative tumors, neuroendocrine tumors, Merkel cell carcinoma, testicular cancer, and skin cancer. In some embodiments,

the inflammatory disease is selected from the group consisting of: rheumatoid arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, multiple sclerosis, type I diabetes, hepatitis (e.g., hepatitis B, hepatitis A, hepatitis C), myocarditis, Sjogren's syndrome, autoimmune hemolytic anemia after transplant rejection, bullus pemphigoid, Graves' disease, Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), myasthenia gravis, pemphigus and pernicious anemia. In some embodiments, the immune disease may be selected from the group consisting of: rheumatoid arthritis, psoriasis, joint psoriasis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, arteriosclerosis, leukocyte adhesion-deficient disease, multiple sclerosis, Raynaud's syndrome, Sjogren's syndrome, juvenile diabetes, Reiter's disease, Behcet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathy, immune-mediated thrombocytopenic symptoms (such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura), hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Osler-Weber's syndrome, chronic renal failure, acute infectious mononucleosis, HIV and herpes virus related diseases, severe acute respiratory syndrome, choreoretinitis and immunological diseases caused by virus infection (such as diseases caused or mediated by B cell infection by Epstein-Barr Virus (EBV)).

In some embodiments, the present disclosure provides any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the pharmaceutical composition, the nucleic acid molecule or the multispecific antibody for use as a medicament. In some embodiments, the medicament is used for treating or preventing a disease or condition. In some embodiments, the disease or condition is a tumor, an inflammatory disease, an autoimmune disease or an infectious disease. In some embodiments, the disease or condition is a bone-related disease, such as a disease or disorder of osteoporosis, osteopenia or osteoarthritis, rheumatoid arthritis, periodontal disease or multiple myeloma. In some embodiments, the tumor is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia and lymphoid malignancies. In some embodiments, the tumor is selected from the group consisting of: squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), neuroglioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), primary mediastinal large B-cell lymphoma, mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), large B-cell lymphoma rich in T-cells/histiocytes, multiple myeloma, myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), gastrointestinal (tract) cancer, kidney cancer, ovarian cancer, liver cancer,

lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, gastric cancer, bone cancer, Ewing's sarcoma, cervical cancer, brain cancer, gastric cancer, bladder cancer, hepatoma,

5 breast cancer, colon cancer, hepatocellular carcinoma (HCC), clear cell renal cell carcinoma (RCC), head and neck cancer, laryngeal cancer, hepatobiliary cancer, central nervous system cancer, esophageal cancer, malignant pleural mesothelioma, systemic light chain amyloidosis, lymphoplasmacytic lymphoma, myelodysplastic syndrome, myeloproliferative tumors, neuroendocrine tumors, Merkel cell carcinoma, testicular

10 cancer, and skin cancer. In some embodiments, the inflammatory disease is selected from the group consisting of: rheumatoid arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, multiple sclerosis, type I diabetes, hepatitis (e.g., hepatitis B, hepatitis A, hepatitis C), myocarditis, Sjogren's syndrome, autoimmune hemolytic anemia after transplant rejection, bullus pemphigoid, Graves' disease, Hashimoto's thyroiditis,

15 systemic lupus erythematosus (SLE), myasthenia gravis, pemphigus and pernicious anemia. In some embodiments, the immune disease may be selected from the group consisting of: rheumatoid arthritis, psoriasis, joint psoriasis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis,

20 glomerulonephritis, eczema, asthma, arteriosclerosis, leukocyte adhesion-deficient disease, multiple sclerosis, Raynaud's syndrome, Sjogren's syndrome, juvenile diabetes, Reiter's disease, Behcet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathy, immune-mediated thrombocytopenic symptoms (such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura),

25 hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, HIV and herpes virus related diseases, severe acute respiratory syndrome, choreoretinitis and immunological diseases caused by virus infection (such as

30 diseases caused or mediated by B cell infection by Epstein-Barr Virus (EBV)). In some embodiments, the present disclosure provides a detection method, which comprises a step of contacting a sample to be tested with any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody or

35 the multispecific antibody. In some embodiments, the present disclosure provides a reagent for use in detection or assay, wherein the reagent comprises any one of the aforementioned polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody or the

40 multispecific antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A and FIG. 1B are structure diagrams of an interaction interface between a Titin-T domain and an Obscurin-O domain or between a Titin-T chain domain and an Obscurin-like-O chain domain;

5 FIG. 2 is a schematic diagram of Fab with substituted CH1 and CL;

FIG. 3 is a schematic structural diagram of an IgG monospecific antibody with substituted double-sided CH1 and CL;

FIG. 4 is a schematic structural diagram of an IgG bispecific antibody with substituted single-sided CH1 and CL;

10 FIG. 5 is a schematic structural diagram of a DI-1 bispecific antibody;

FIGs. 6A to 6C are DI-1 mass spectrometry diagrams. FIG. 6A is an LC1/LC2 mass spectrogram, and FIG. 6B is an HC1/HC2 mass spectrogram; FIG. 6C is an LC1+LC2+HC1+HC2 mass spectrogram;

15 FIG. 7 is schematic structural diagrams of molecule structures with mispairing of light/heavy chains of an antibody;

FIG. 8 is a schematic structural diagram of a BU5 bispecific antibody;

FIGs. 9A to 9C are BU5 mass spectrometry diagrams;

FIG. 10 is an experimental result graph of osteoclast differentiation in an DI-1 bispecific antibody;

20 FIG. 11 is an experimental result graph of TF1 cell proliferation in a DI-1 bispecific antibody;

FIG. 12 is schematic structural diagrams of bispecific antibodies HJ-1, HJ-2, HJ-3 and HJ-4;

25 FIGs. 13A to 13D are mass spectrometry diagrams of four-chain co-expression of bispecific antibodies HJ-1, HJ-2, HJ-3 and HJ-4;

FIGs. 14A to 14B are mass spectrometry diagrams of three-chain co-expression of HJ-1-H1, HJ-1-H2 and HJ-1-L2 for the bispecific antibody HJ-1;

FIGs. 15A to 15B are mass spectrometry diagrams of three-chain co-expression of HJ-3-H1, HJ-3-H2 and HJ-3-L2 for the bispecific antibody HJ-3; and

30 FIGs. 16A to 16B are interactions between residues.

DETAILED DESCRIPTION

35 In order that the present disclosure may be more readily understood, certain technical and scientific terms are specifically defined below. Unless otherwise specifically defined herein, all other technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the present disclosure belongs.

The three-letter codes and one-letter codes for amino acids used herein are as described in *J.biol.chem.*, 243, p 3558 (1968).

40 An "antibody (Ab)" is typically an immunoglobulin (Ig), and a naturally-occurring intact antibody is a tetrapeptide chain structure composed of two identical heavy chains and two

identical light chains linked by inter-chain disulfide bonds. The heavy chain constant regions of an immunoglobulin differ in their amino acid composition and arrangement, and thus in their antigenicity. Accordingly, immunoglobulins can be classified into five classes, namely, IgM, IgD, IgG, IgA and IgE, with their corresponding heavy chains being μ chains, δ chains, γ chains, α chains and ϵ chains, respectively. The same class of Ig can be classified into different subclasses according to the differences of amino acid composition of the hinge region and the number and position of disulfide bonds of heavy chains, for example, IgG can be classified into IgG1, IgG2, IgG3 and IgG4. As light chains are classified into κ chains or λ chains according to the difference of constant regions, antibodies can be classified into two types. Each of the five classes of Ig may have either κ chains or λ chains. According to the difference of individual amino acids in the constant region of the λ chain, the λ chain can be classified into four subtypes of $\lambda 1$, $\lambda 2$, $\lambda 3$ and $\lambda 4$.

Antibodies disclosed herein include antibodies or antigen-binding fragments thereof, including antibodies or antigen-binding fragments thereof that have been engineered on the basis of immunoglobulins while retaining the antigen binding ability; the antibodies or antigen-binding fragments thereof include monospecific antibodies, and multispecific antibodies (e.g., bispecific antibodies), and further include monovalent antibodies, or multivalent antibodies (e.g., bivalent antibodies). An antigen-binding fragment of an antibody, for example, may be an antigen-binding fragment comprising at least one VH-CH1 and at least one VL-CL structure, wherein the VH and VL structures are capable of being close to each other based on inter-chain interactions and retaining the antigen binding ability. In some embodiments, the antigen-binding fragment of the antibody is a monovalent Fab fragment (Fab1 fragment), a divalent Fab fragment (F(ab)2), a trivalent Fab fragment (F(ab)3), a multivalent (two or more) Fab fragment, or other monospecific, bispecific or multispecific antigen-binding fragments comprising at least one Fab fragment.

The "domain engineered antibody" described herein refers to an antibody formed after the CH1 and/or CL of the antibody has been substituted with other domains or peptide fragments, which can be used to substitute the CH1/CL domain of the antibody and generally has intermolecular interactions; alternative domain combinations include, but are not limited to, an IL13RA1 Fibronectin type-III 3 domain/IL4R Fibronectin type-III domain, an IL6ST Fibronectin type-III 2 domain/IL6R Fibronectin type-III 2 domain, an HFE Ig-like C1-type domain/B2M Ig-like C1-type domain, a CD1B Ig-like domain/B2M Ig-like C1-type domain, an Obscurin Ig-like 1 domain/Titin Ig-like 152 domain or an Obscurin-like Ig-like 1 domain/Titin Ig-like 152 domain. In some embodiments, the domain engineered antibody is a monospecific antibody, a bispecific antibody or a multispecific antibody; in some embodiments, the domain engineered antibody is a monovalent antibody, a bivalent antibody or a multivalent antibody; in some embodiments, the domain engineered antibody is a whole antibody or an antigen-binding fragment thereof; in some embodiments, the antibody antigen-binding fragment is a Fab

fragment, which may be a monovalent Fab fragment (Fab1 fragment), a divalent Fab fragment (F(ab)2), a trivalent Fab fragment (F(ab)3) or a multivalent (two or more) Fab fragment. Illustratively, a schematic structural diagram of a Fab fragment of an antibody with a CH1 and CL substituted with a Titin-T chain/Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain is shown in FIG. 2; a schematic structural diagram of the antibody with the CH1 and CL substituted with the Titin-T chain/Obscurin-O chain or with the Titin-T chain/Obscurin-like-O chain is shown in FIG. 3; a schematic structural diagram of the bispecific antibody with one-side CH1 and CL substituted with the Titin-T chain/Obscurin-O chain or with the Titin-T chain/Obscurin-like-O chain is shown in FIG. 4. Other antibodies with at least one CH1 and at least one CL substituted with a Titin-T chain/Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain is, for example, a bivalent antibody with one-side CH1 and CL substituted with a Titin-T chain/Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain, a bispecific antibody with both-side CH1 and CL substituted with a Titin-T chain/Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain, a F(ab)2 fragment with two CH1/CL substituted with a Titin-T chain/an Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain, or a F(ab)3 fragment with 1 or 2 or 3 CH1/CL substituted with a Titin-T chain/Obscurin-O chain or with a Titin-T chain/Obscurin-like-O chain.

"Titin" is a large sarcomeric protein with a complex molecular folding structure. It is known to have the functions of linking thick myofilaments to a Z-wire, maintaining the integrity and stability of myofibrils, and the like. Titin is the third most abundant protein in skeletal muscle fibers, with a molecular weight of 2700 kDa (more than 25000 amino acids) and a length of 1 μ m, which is about half of the sarcomere.

A "Titin Ig-like 152 domain" is an Ig-like domain on a Titin protein named as the Titin Ig-like 152 domain, which is capable of binding to an Obscurin Ig-like 1 domain or an Obscurin-like Ig-like 1 domain through intermolecular interactions to form a dimeric complex (available from the RCSB PDB database).

"Titin-T chain" or "T chain" refers to a peptide fragment of 78–118 amino acids in length comprising a Titin Ig-like 152 domain in a Titin protein or a functional variant thereof, wherein the Titin-T chain is capable of binding to the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain through intermolecular interactions to form a complex. The functional variant of the T chain is obtained through the mutation on partial amino acids of a wild-type T chain, but still has a peptide fragment of a complex formed by binding to the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain through intermolecular interactions. In the present disclosure, the Titin-T chain can be used to substitute the CH1 or CL domain of an antibody without affecting the binding of the VH and VL of the antibody and the binding of the antibody to an epitope. The partial amino acids of the Titin-T chain can be mutated so long as the Titin-T chain is still capable of associating with the Obscurin Ig-like 1 domain to form a complex. For example, amino acids of a suitable length are added or truncated at the C-terminus and/or the N-terminus of the Titin Ig-like 152 domain; for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid

residues can be added or truncated; for example, 5 "KAGIR" amino acids of the Titin protein immediately adjacent to the N-terminus of the Titin Ig-like 152 domain are added at the N-terminus of the Titin Ig-like 152 domain; a linker sequence of a suitable length (e.g., (G_xS)_y linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6, such as, "G₄S" or "(G₄S)₂") can also be added at the N-terminus and/or the C-terminus of the Titin Ig-like 152 domain to allow the N-terminus of the Titin Ig-like 152 domain to be linked to the VH and/or VL of the antibody through the linker sequence. Other mutations can also be made on amino acids of the Titin Ig-like 152 domain, for example, certain amino acids may be mutated to increase inter-chain disulfide bonds, improving complex stability. In some embodiments of the present disclosure, the Titin-T chain is a polypeptide having a sequence set forth in any one of SEQ ID NOs: 32, 35–41, 65–76 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 32, 35–41, 65–76, wherein the polypeptide is capable of associating with an Obscurin-O chain or an Obscurin-like-O chain to form a complex.

"Obscurin" is a protein encoded by the OBSCN gene and belongs to the giant sarcosine signaling protein family. Obscurin is expressed in cardiac and skeletal muscle and plays an important role in the organization of myofibrils during sarcomere assembly. Obscurin is the major cytoplasmic ligand of sarcoplasmic reticulin sANK1, which can prevent the degradation of sANK1 (Lange S et al., *Molecular Biology of the Cell.*, 23 (13): 2490–504); Obscurin acts as a signaling link between sarcoplasmic reticulum domain and sarcoplasmic reticulum domain (Bagnato P et al., *The Journal of Cell Biology.*, 160 (2): 245–53); Obscurin participates in the formation of new sarcomere during myofibril assembly (Borisov AB, et al., *Biochemical and Biophysical Research Communications.*, 310 (3): 910–918).

The "Obscurin Ig-like 1 domain" is a stretch of Ig-like domain in an Obscurin protein named as the Obscurin Ig-like 1 domain, which is capable of binding to a Titin Ig-like 152 domain through intermolecular interactions to form a complex (available from the RCSB PDB database).

"Obscurin-O chain" or "O chain" refers to a peptide fragment of 87–117 amino acids in length comprising an Obscurin Ig-like 1 domain in an Obscurin protein or a functional variant thereof, wherein the Obscurin-O chain is capable of binding to the Titin Ig-like 152 domain through intermolecular interactions to form a complex. The functional variant of the Obscurin-O chain is obtained through the mutation on partial amino acids of a wild type O chain, but still has a peptide fragment of a complex formed by binding to the Titin Ig-like 152 domain through intermolecular interactions. In the present disclosure, the Obscurin-O chain may substitute the CH1 or CL domain of an antibody without affecting the binding of the VH and VL of the antibody and the binding of the antibody to an epitope. The partial amino acids of the Obscurin-O chain can be mutated so long as the Obscurin-O chain is capable of associating with the Titin Ig-like 152 domain to form a complex. For example, amino acids of a suitable length are added or truncated at the C-

terminus and/or the N-terminus of the Obscurin-O domain, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are added or truncated; for example, 5 "DQPQF" amino acids of the wild-type Obscurin protein immediately adjacent to the N-terminus of the Obscurin Ig-like 1 domain are added at the N-terminus of the Obscurin-O domain. A linker sequence of a suitable length (e.g., (G_xS)_y linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6, such as, "G₄S" or "(G₄S)₂") can also be added at the N-terminus and/or the C-terminus of the Obscurin-O domain to allow the N-terminus of the Obscurin-O domain to be linked to the VH and/or VL of the antibody through the linker sequence. Other mutations can also be made on partial amino acids of the Obscurin Ig-like 1 domain, for example, certain amino acids may be mutated to increase inter-chain disulfide bonds, thereby improve antibody stability, and the like. In some embodiments of the present disclosure, the Obscurin-O chain is a polypeptide having a sequence set forth in any one of SEQ ID NOs: 33, 42–58, 77–86 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 33, 42–58, 77–86, wherein the polypeptide is capable of associating with the Titin-T chain to form a complex.

"Obscurin-like 1" is a protein encoded by the OBSL1 gene located in SPEG of human chromosome 2q35 and is closely related to Obscurin. Alternative splicing of "Obscurin-like 1" produces multiple isoforms with a predicted molecular weight ranging from 130 kD to 230 kD (Geisler SB et al., (2007), *Genomics*, 89 (4): 521–31).

The "Obscurin-like Ig-like 1 domain" is a stretch of Ig-like domain in an Obscurin-like 1 protein named as the Obscurin-like Ig-like 1 domain, which is capable of binding to a Titin Ig-like 152 domain through natural intermolecular interactions to form a complex (available from the RCSB PDB database).

"Obscurin-like-O chain" or "OL chain" refers to a peptide fragment of 78–118 amino acids in length comprising an Obscurin-like Ig-like 1 domain in an Obscurin-like 1 protein or a functional variant thereof. The Obscurin-like-O chain is capable of binding to the Titin Ig-like 152 domain through intermolecular interactions to form a complex. The functional variant of the Obscurin-like-O chain is obtained through the mutation on partial amino acids of a wild-type OL chain, but still has a peptide of a complex formed by binding to the Titin Ig-like 152 domain through interactions. In the present disclosure, the Obscurin-like-O chain may substitute the CH1 or CL domain of an antibody without affecting the binding of the VH and VL of the antibody and the binding of the antibody to an epitope. The partial amino acids of the Obscurin-like-O chain can be mutated so long as the Obscurin-like-O chain is capable of associating with the Titin Ig-like 152 domain to form a complex. In some embodiments, for example, amino acids of a suitable length are added or truncated at the C-terminus and/or the N-terminus of the Obscurin-O domain, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are added or truncated. A linker sequence of a suitable length (e.g., (G_xS)_y linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6, such as, "G₄S" or "(G₄S)₂") can also be added at the N-terminus

and/or the C-terminus of the Obscurin-like-O domain to allow the N-terminus of the Obscurin-like-O domain to be linked to the VH and/or VL of the antibody through the linker sequence. Other mutations can also be made on partial amino acids of the Obscurin-like Ig-like 1 domain, for example, certain amino acids may be mutated to increase inter-chain disulfide bonds, thereby improve antibody stability, and the like. In some embodiments of the present disclosure, the Obscurin-like-O chain is a polypeptide having a sequence set forth in any one of SEQ ID NOs: 34, 59-64 or a sequence having at least 80% sequence identity to any one of SEQ ID NOs: 34, 59-64, wherein the polypeptide is capable of associating with the Titin-T chain to form a complex.

In addition, partial amino acids in the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain may be mutated so long as it still enables the Titin Ig-like 152 domain and the Obscurin Ig-like 1 domain, or the Titin Ig-like 152 domain and the Obscurin-like Ig-like 1 domain, to be associated with each other to form a complex. In some embodiments, amino acids of a suitable length (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids of the wild-type protein immediately adjacent to a domain) may be added or truncated at the C-terminus and/or the N-terminus of the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain so long as it still enables the Titin Ig-like 152 domain and the Obscurin Ig-like 1 domain, or the Titin Ig-like 152 domain and the Obscurin-like Ig-like 1 domain, to be associated with each other to form a complex. For example, 5 "KAGIR" amino acids of the wild-type Titin protein immediately adjacent to the N-terminus of the Titin Ig-like 152 domain are added to the N-terminus of the Titin Ig-like 152 domain; or 5 "DQPQF" amino acids of the wild-type Obscurin protein immediately adjacent to the N-terminus of the Obscurin Ig-like 1 domain are added at the N-terminus of the Obscurin Ig-like 1 domain. In some embodiments, a linker sequence of a suitable length (e.g., (G_xS)_y linker, wherein X is selected from the group consisting of integers from 1 to 5, and Y is selected from the group consisting of integers from 1 to 6, such as, "G₄S" or "(G₄S)₂ ") may be added at the N-terminus and/or the C-terminus of the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain to allow the N-terminus of the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain to be linked to the VH or VL of the antibody through a linker sequence. In some embodiments, other mutations can also be made on partial amino acids of the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain so long as it still enables the Titin Ig-like 152 domain and the Obscurin Ig-like 1 domain, or the Titin Ig-like 152 domain and the Obscurin-like Ig-like 1 domain to be interacted with each other to form a complex, for example, partial amino acids are mutated to increase inter-chain disulfide bonds, thereby improving antibody stability, and the like.

The "Fab fragment" refers to a fragment capable of binding to an antigen that can be produced by enzymatic treatment of a monoclonal antibody and comprises light chain (VL-CL) and heavy chain (VH-CH1) structures.

The "domain engineered Fab fragment" refers to a polypeptide fragment of a Fab

fragment of an antibody in which a CL and/or CH1 have been substituted with other domains or peptide fragments, and still retains the interaction between VH and VL and retains the binding ability of the antibody to the antigen. In some embodiments, the domain engineered Fab fragment may be part of a multivalent antibody or multivalent polypeptide complex. In other embodiments, the domain engineered Fab fragment is a single protein molecule. The Fab fragment may be a monovalent Fab fragment (Fab fragment 1), a bivalent Fab fragment (F(ab)2), a trivalent Fab fragment (F(ab)3) or a multivalent (two or more) Fab fragment. Exemplarily, the schematic diagram of the Fab fragment with substituted CH1 and CL is shown in FIG. 2.

The term "specific antibody" or "specific polypeptide complex" refers to an antibody or polypeptide complex capable of specifically binding to a target antigen or an epitope thereof. Antibodies are classified into monospecific antibodies, bispecific antibodies, trispecific antibodies, tetraspecific antibodies, ..., multispecific (binding to two or more different target antigens or different epitopes thereof) antibodies according to the number of different target antigens or different epitopes thereof to which the antibodies bind. Polypeptide complexes are classified into monospecific polypeptide complexes, bispecific polypeptide complexes, trispecific polypeptide complexes, tetraspecific polypeptide complexes, ..., multispecific (binding to two or more different target antigens or different epitopes thereof) polypeptide complexes according to the number of different target antigens or different epitopes thereof to which the polypeptide complexes bind. For example, a "bispecific antibody" refers to an antibody (including an antibody or an antigen-binding fragment thereof, such as, a single chain antibody) capable of specifically binding to two different antigens or two different epitopes of the same antigen. Bispecific antibodies of various structures have been disclosed in the prior art; the bispecific antibodies can be classified into IgG-like bispecific antibodies and antibody-fragment-type bispecific antibodies according to the integrity of IgG molecules; the bispecific antibodies can be classified into bivalent, trivalent, tetravalent or higher-valent bispecific antibodies in configuration according to the number of the antigen-binding regions; the bispecific antibodies can be classified into symmetric bispecific antibodies and asymmetric bispecific antibodies according to whether their structures are symmetric or asymmetric. Among them, the bispecific antibodies based on antibody fragments, such as Fab fragments lacking Fc fragments, formed by binding 2 or more Fab fragments in one molecule, have low immunogenicity, small molecular weight and high tumor tissue permeability, and typical antibody structures of this type comprise bispecific antibodies, such as F(ab)₂, scFv-Fab and (scFv)₂-Fab; IgG-like bispecific antibodies (e.g., having Fc fragments) have relatively large molecular weight, and the Fc fragments facilitate later purification of the antibody and increase their solubility and stability, and the Fc fragments may further bind to the receptor FcRn and increase the serum half-life of the antibody, and typical structural models of bispecific antibodies comprise bispecific antibodies such as KiH, CrossMAb, Triomab quadroma, FcΔAdp, ART-Ig, BiMAb, Biclomics, BEAT, DuoBody, Azymetric, XmaB, 2:1 TCBs, 1Fab-IgG TDB, FynomAb,

two-in-one/DAF, scFv-Fab-IgG, DART-Fc, LP- DART, CODV-Fab-TL, HLE-BiTE, F(ab)₂-CrossMAb, IgG-(scFv)₂, Bs4Ab, DVD-Ig, Tetravalent-DART-Fc, (scFv)₄-Fc, CODV-Ig, mAb2 and F(ab)₄-CrossMAb (see Aran F. Labrijn et al., *Nature Reviews Drug Discovery*, volume 18, pages 585–608 (2019); Chen S1 et al., *J Immunol Res.*, Feb. 11, 2019; 2019: 4516041).

The term "monovalent", "divalent", "trivalent" or "multivalent" refers to the presence of a specified number of antigen binding sites in an antibody or a polypeptide complex. For example, the "monovalent antibody" refers to the presence of one antigen binding site in an antibody, the "monovalent polypeptide complex" refers to the presence of one antigen binding site in a polypeptide complex; the "bivalent antibody" refers to the presence of two antigen binding sites in an antibody, and the "bivalent polypeptide complex" refers to the presence of two antigen binding sites in a polypeptide complex; the "trivalent antibody" refers to the presence of three antigen binding sites in an antibody, and the "trivalent polypeptide complex" refers to the presence of three antigen binding sites in a polypeptide complex; the "multivalent antibody" refers to the presence of multiple (e.g., three or more) antigen binding sites in an antibody, and the "multivalent polypeptide complex" refers to the presence of multiple (e.g., two or more) antigen binding sites in a polypeptide complex.

The term "polypeptide", "peptide" or "protein" is used interchangeably in the present disclosure and refers to a polymer of amino acid residues, or a collection of polymers of multiple amino acid residues. These terms are used to describe amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally-occurring amino acid, as well as naturally-occurring amino acid polymers and non-naturally-occurring amino acid polymers. A polypeptide sequence is generally described as having an amino terminus (N-terminus) at the left end and having a carboxyl terminus (C-terminus) at the right end. The "polypeptide complex" disclosed herein refers to a complex comprising one or more polypeptides that are associated with implementing certain functions. In some embodiments, the polypeptide complex is an antibody or an antigen-binding fragment thereof capable of specifically binding to an antigen.

The term "binding region" or "binding site" or "binding domain" for an antigen refers to a region or portion of a specific protein molecule (e.g., an antibody molecule) that is capable of specifically binding to an antigen, and the antigen binding region can be a portion of a ligand binding domain that is capable of directly binding to an antigen, or can be a domain that comprises a variable region of an antibody that is capable of directly binding to an antigen.

The term "operably linked" or "operable linkage" means that two or more biological sequences are linked in a manner such that they function in the intended manner, regardless of the presence or absence of a spacer (also referred to as a linker or a linker sequence). When used to describe polypeptides, the term means that two polypeptide sequences are linked in such a manner that the linked product has the desired biological function, with or without a spacer between these two sequences. For example, an antibody

variable region can be operably linked to a constant region to form a stable product with antigen binding activity. The term may also be used to describe polynucleotides. For example, when a polynucleotide encoding a polypeptide is operably linked to a regulatory sequence (e.g., a promoter sequence, an enhancer sequence or a silencer sequence), the term means that the polynucleotide sequence is linked in a manner that allows for the regulated expression of the polypeptide by the polynucleotide.

The term "dimerization domain" refers to a polypeptide domain capable of promoting association to form a dimer. In some embodiments, the first dimerization domain may be associated with the second dimerization domain. The association may be bound or linked or bonded by any suitable means, for example, through a linker, a disulfide bond, a hydrogen bond, an electrostatic interaction, a salt bridge, a hydrophobic-hydrophilic interaction, or a combination thereof. Exemplary dimerization domains include, but are not limited to, antibody hinge regions, antibody CH2 domains, antibody CH3 domains and other suitable protein monomers or polypeptides capable of dimerizing and interacting with each other. The hinge regions, CH2 and CH3 may be derived from any antibody isotype, e.g., IgG1, IgG2, IgG3 and IgG4.

The term "interaction domain" refers to a domain of a polypeptide that is capable of facilitating the interaction or association of two or more homologous or heterologous polypeptides. For example, interaction domains are dimerization domains that facilitate association with each other to form a dimer. An inter-protein interaction domain is a domain of a polypeptide that interacts or associates between two or more proteins, for example, an Obscurin-like Ig-like 1 domain in an Obscurin-like protein that is capable of forming a complex with a Titin Ig-like 152 domain of a Titin protein through intermolecular interactions. In some embodiments, the domain that interacts with the Titin-T chain is an Obscurin-O chain or an Obscurin-like-O chain.

The term "dimer" refers to a structure formed by covalent or non-covalent interactions of two molecules (e.g., polypeptides or proteins). The homodimer or homodimerization is formed from two identical molecules while the heterodimer or heterodimerization is formed from two different molecules. Two molecules can form a dimer through natural inter-chain bonds, and can also form a dimer through unnatural inter-chain bonds. In some embodiments of the present disclosure, the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain, may form a dimer through natural inter-chain bonds. It is well known to those skilled in the art that, for two domains associated with each other to form a dimer, contact interface residues within 6 angstroms between the first domain and the second domain (especially residues within 4.5 angstroms) play a critical role in maintaining the association of these two domains (Yan, Changhui et al., *"Characterization of protein-protein interfaces"*, the Protein Journal, vol., 27,1 (2008): 59–70). Through analysis of the complex formed by associating the Titin-T chain with the Obscurin-O chain or associating the Titin-T chain with the Obscurin-like-O chain by the MOE (molecular operating environment) system (see FIG. 1A and FIG. 1B), it has been found that one or more of residues at positions 7–15, 19–24, 26, 55, 59 and 60 on

the Titin-T chain and one or more of residues at positions 3–6, 9, 41, 73, 75 and 80–90 on the Obscurin-O chain interact with each other, and one or more of residues at positions 1, 7–10, 13–16, 19–26, 59–60 and 96 on the Titin-T chain and one or more of residues at positions 4–5, 10, 12–13, 74, 76, 78 and 82–91 on the Obscurin-like-O chain interact with each other (see FIG. 16A and FIG. 16B), wherein the contact interface residues at these sites are separated at a distance within 4.5 angstroms, playing a critical role in maintaining the association of these two domains. In addition, in some other embodiments, the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain, may form a dimer through non-natural inter-chain bonds, wherein the dimer comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more non-natural inter-chain bonds. A disulfide bond can be formed between the Titin-T chain and the Obscurin-O chain or between the Titin-T chain and the Obscurin-like-O chain by mutating partial amino acids on the Titin-T chain, the Obscurin-O chain or the Obscurin-like-O chain, thereby stabilizing the dimer. In some embodiments, the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 6, 26, 74, 77, 84 and 86. In some embodiments, the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of A3C, R9C, C25S, C76S and A88C; or the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of A8C, V20C, T22C, C25S, A26C and C39T, and/or the Obscurin-like-O chain has one or more amino acid residue mutations on positions selected from the group consisting of C6E, C26S, C77S, V74C, G84C and A86C. In some embodiments, the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has an A88C mutation; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has an A3C mutation; the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has an R9C mutation; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S and A88C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-O chain has C25S, C76S and A3C mutations; the Titin-T chain has C25S, C39T and A26C mutations, and the Obscurin-O chain has C25S, C76S and R9C mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has C6E and V74C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E and G84C mutations; the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain has C6E and A86C mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-like-O chain has

C6E, C26S, C77S and V74C mutations; the Titin-T chain has C25S, C39T and V20C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and G84C mutations; the Titin-T chain has C25S, C39T and T22C mutations, and the Obscurin-like-O chain has C6E, C26S, C77S and A86C mutations. In some embodiments, the Obscurin-O chain further has one or more amino acid residue mutations on positions selected from the group consisting of 7, 11 and 62; preferably, the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of L7K and L7R, K11L, T62K and T62H; most preferably, the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62K mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, L7K and T62H mutations; the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62K mutations; or the Titin-T chain has C25S, C39T and A8C mutations, and the Obscurin-O chain has C25S, C76S, A88C, K11L and T62H mutations. The mutation position in the Titin-T chain is a natural sequence numbering position relative to a T.0 chain (SEQ ID NO: 32); the mutation position in the Obscurin-O chain is a natural sequence numbering position relative to an O.0 chain (SEQ ID NO: 33); the mutation position in the Obscurin-like-O chain is a natural sequence numbering position relative to an OL.0 chain (SEQ ID NO: 34).

In the present disclosure, "mispairing" means that two or more homologous or heterologous polypeptides are interacted or associated together to form an undesired dimer or multimer mispairing. "Mispairing is less susceptible to happen" means, for example, that when polypeptides A1, B1 and B2 are co-expressed, if the desired amount of A1-B1 dimer expression is greater than the amount of A1-B2 dimer, preferential mispairing between A1-B1 is considered to happen, i.e., mispairing between A1-B2 is less susceptible to happen. In some embodiments of the present disclosure, in the multispecific polypeptide complex, mispairing between VH1 of the first polypeptide complex and VL2 of the second polypeptide complex is less susceptible to happen, and/or mispairing between VL1 of the first polypeptide complex and VH2 of the second polypeptide complex is less susceptible to happen. However, preferential mispairing between VH1-VL1 and preferential mispairing between VH2-VL2 are considered.

The "disulfide bond" refers to a covalent bond formed between sulfur atoms in the structure R-S-S-R'. The amino acid cysteine comprises a thiol group which may form a disulphide bond with a second thiol group, for example with a thiol group of another cysteine residue. Disulfide bonds can be formed between the thiol groups of two cysteine residues located on two polypeptide chains, respectively, thereby forming an inter-chain bridge or an inter-chain bond.

Electrostatic interactions are non-covalent interactions and play a critical role in protein folding, stability, flexibility and function, including ionic interactions, hydrogen bonding and halogen bonding. Electrostatic interactions may be formed in polypeptides, for example, between Lys and Asp, between Lys and Glu, between Glu and Arg, or between

Glu and Trp on a first chain and Arg, Val or Thr on a second chain.

Salt bridges are close-range electrostatic interactions, primarily from the anionic carboxylate of Asp or Glu and from the cationic ammonium of Lys or the guanidino group of Arg, which are pairs of oppositely charged residues in close spatial proximity in the native protein structure. Charged and polar residues in the hydrophobic interface can act as hot spots for binding. Among them, residues having ionizable side chains, such as His, Tyr and Ser, can also participate in the formation of salt bridges.

The hydrophilic interaction means that molecules with polar groups have large affinity to water and can form transient bonding with water through hydrogen bonds. The

hydrophobic interaction is a non-covalent interaction between non-polar molecules. These non-polar molecules (e.g., some neutral amino acid residues, also known as hydrophobic residues) have a tendency to aggregate with each other in an aqueous environment and keep away from water. For example, hydrophobic interactions may be formed between one or more of Val, Tyr and Ala in the first chain and one or more of Val, Leu and Trp in the second chain, or His and Ala in the first chain and Thr and Phe in the second chain. (See Brinkmann et al., 2017).

The term "hydrogen bond" is formed by electrostatic attraction between two polar groups when a hydrogen atom is covalently bonded to a highly electronegative atom, such as, nitrogen, oxygen or fluorine. Hydrogen bonds can be formed between backbone oxygens (e.g., chalcogen groups) and amide hydrogens (nitrogen groups) of two residues of a polypeptide, for example, a hydrogen bond can be formed between a nitrogen group in Asn and an oxygen group in His, or an oxygen group in Asn and a nitrogen group in Lys. The interactions between hydrogen bonds are stronger than Van der Waals interactions, but weaker than interactions between covalent or ionic bonds, and are critical for maintaining secondary and tertiary structures. For example, an α -helix is formed when the spacing of amino acid residues occurs regularly between positions i and $i+4$, and a sheet of twisted folds formed by peptide fragments of 3–10 amino acids in length when two peptides are linked through at least two or three backbone hydrogen bonds is a β -sheet.

As used herein, "knob-into-hole" refers to an interaction between two polypeptides, one of which has a bulge (i.e., a "knob") due to the presence of amino acid residues with bulky side chains (e.g., tyrosine or tryptophan). The other polypeptide has a cavity (i.e., a "hole") in which small side-chain amino acid residues (e.g., alanine or threonine) are present, and a bulge can be positioned in the cavity to facilitate the interaction of the two polypeptides to form a heterodimer or a complex. Methods for producing polypeptides with bulges into the holes are known in the art and can be found in Patents US5731169, WO1996027011, etc.

"Non-natural inter-chain bonds" refer to inter-chain bonds not found in wild-type polypeptide polymers. For example, a non-natural inter-chain bond may be formed between a mutated amino acid residue of one polypeptide and a wild-type amino acid residue or a mutated amino acid residue of another polypeptide. In certain embodiments,

at least one non-natural inter-chain bond is a "disulfide bond" formed following amino acid mutation. In some embodiments of the present disclosure, non-natural inter-chain bonds between the Titin-T chain and the Obscurin-O chain, or the Titin-T chain and the Obscurin-like-O chain, are formed by mutation on one or more amino acid residues on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the Titin-T chain, and/or positions selected from the group consisting of 3, 9, 25, 76 and 88 on the Obscurin-O chain, or formed by mutation on one or more amino acid residues on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39 on the Titin-T chain, and/or positions selected from the group consisting of 6, 26, 74, 77, 84 and 86 on the Obscurin-like-O chain.

The term "contact interface" refers to a specific region on polypeptides where the polypeptides are in contact with or interacted with each other. The contact interface comprises one or more amino acid residues, and when an interaction occurs, amino acid residues of the contact interface on a polypeptide are capable of interacting with the corresponding amino acid residues with which they are in contact. The amino acid residues of the contact interface may be in a continuous or discontinuous sequence. For example, when the interface is three-dimensional, amino acid residues within the interface can be separated at different positions on the linear sequence.

The "linking domain" or "spacer" refers to a border or a border region where two polypeptide sequences are fused or combined. For example, the linking domain may comprise at least a portion of a C-terminal fragment from the first fusion polypeptide that is fused to at least a portion of an N-terminal fragment from the second fusion polypeptide, with or without other spacers therebetween. For example, the spacer may be rich in glycine and proline residues, such as a spacer having a single or repeated sequence consisting of threonine/serine and glycine, GGGGS, TGGGG, SGGGG, or a tandem repeat thereof (e.g., 2, 3, 4, 5 or more repeats). In certain embodiments, the spacer comprises a GGGGS or 2 or more tandem repeats thereof.

A natural intact antibody comprises two heavy chains and two light chains. Each heavy chain consists of a variable region ("HCVR", VH) and first, second and third constant regions (CH1, CH2 and CH3), second (CH2) and third (CH3) constant regions of the antibody constitute the "Fc", and the N-terminus of CH2 may or may not comprise a hinge region portion of the antibody which is rich in proline, including inter-chain disulfide bonds; while each light chain consists of a variable region ("LCVR", VL) and a constant region (CL). A portion near the N-terminus of the heavy and light chains has a variable sequence of about 110 amino acids is a variable region (Fv region); a portion near the C-terminus has a relatively stable sequence of the remaining amino acids is a constant region. The variable region includes 3 hypervariable regions (HVRs) and 4 framework regions (FRs) with relatively conserved sequences. The 3 hypervariable regions, which determine the specificity of the antibody, are also known as complementarity determining regions (CDRs). Each of the light chain variable region (VL) and the heavy chain variable region (VH) is composed of 3 CDR regions and 4 FR regions, and the sequence from the

amino terminus to the carboxyl terminus is FR1–CDR1–FR2–CDR2–FR3–CDR3–FR4. The 3 CDR regions of the light chain refer to LCDR1, LCDR2 and LCDR3; the 3 CDR regions of the heavy chain refer to HCDR1, HCDR2 and HCDR3.

The antibodies disclosed herein may, for example, be antibodies derived from animals (e.g., antibodies of murine, avian, rabbit, camel and monkey), chimeric antibodies, humanized antibodies and fully human antibodies. The antibodies disclosed herein include, in addition to full-length antibodies, antigen-binding fragments binding to an antigen.

The term "murine antibody" used herein refers to a monoclonal antibody to an antigen prepared according to the knowledge and skill in the art. During the preparation, a test subject is injected with an antigen, and then hybridoma of antibodies expressing the desired sequence or functional properties is isolated. In a preferred embodiment of the present disclosure, the murine antibody or an antigen-binding fragment thereof may further comprise a light chain constant region of a murine κ and λ chain or a variant thereof, or further comprises a heavy chain constant region of murine IgG1, IgG2 or IgG3 or a variant thereof.

The term "chimeric antibody" is an antibody formed by fusion of the variable region of an antibody of another first species to the constant region of an antibody of a second species. For example, the establishment of a human-mouse chimeric antibody comprises establishing a hybridoma secreting a mouse-derived specific monoclonal antibody, cloning a variable region gene from a mouse hybridoma cell, then cloning a constant region gene of a human antibody as required, linking the mouse variable region gene and the human constant region gene into a chimeric gene and then inserting the chimeric gene into an expression vector, and finally expressing a chimeric antibody molecule in a eukaryotic system or a prokaryotic system. In a preferred embodiment of the present disclosure, the light chain of the chimeric antibody further comprises a light chain constant region of human κ and λ chains or variants thereof. The heavy chain of the antigen chimeric antibody further comprises a heavy chain constant region of human IgG1, IgG2, IgG3 or IgG4 or a variant thereof, and preferably comprises a heavy chain constant region of human IgG1, IgG2 or IgG4, or an IgG1, IgG2 or IgG4 variant using an amino acid mutation (e.g., L234A and/or L235A mutation, and/or S228P mutation).

The term "humanized antibody", also known as CDR-grafted antibody, refers to an antibody produced by grafting murine CDR sequences into a human antibody variable region framework, i.e., a different type of human germline antibody framework sequence.

Such the antibody can overcome the heterogeneous reaction induced by the chimeric antibody because of carrying a large amount of mouse protein components. Such the framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. Germline DNA Sequences for human heavy and light chain variable region genes can be obtained from the "VBase" human germline sequence database and found in Kabat, E.A. et al., 1991, *Sequences of Proteins of Immunological Interest*, 5th edition. To avoid decreased immunogenicity and

decreased activity at the same time, the human antibody variable region framework sequences may be minimally reversely-mutated or back-mutated to retain activity. The humanized antibodies disclosed herein also include humanized antibodies formed after further affinity maturation mutations on the CDRs from yeast display.

5 In one embodiment of the present disclosure, the antibody or antigen-binding fragment thereof may further comprise a light chain constant region of a human or murine κ and λ chain or a variant thereof, or further comprise a heavy chain constant region of a human or murine IgG1, IgG2, IgG3 or IgG4 or a variant thereof, and preferably comprises a heavy chain constant region of human IgG1, IgG2 or IgG4, or an IgG1, IgG2 or IgG4
10 variant using an amino acid mutation (e.g., L234A and/or L235A mutation, and/or S228P mutation).

The "conventional variants" of the human antibody heavy chain constant region and the human antibody light chain constant region, including the same, in the present disclosure refer to variants of the heavy chain constant region or light chain constant region that
15 have been disclosed in the prior art and derived from human without altering the structure and function of the antibody variable region, and exemplary variants include variants of the heavy chain constant region of IgG1, IgG2, IgG3 or IgG4 with the heavy chain constant region having site-directed engineering and amino acid substitution, and specifically, substitutions comprise such as YTE mutations known in the prior art, L234A
20 and/or L235A mutations, S228P mutations, and/or mutations that obtain a knob-into-hole structure (such that the heavy chain of the antibody has a combination of knob-Fc and hole-Fc), all of which have been confirmed to give the antibody new properties without altering the function of the antibody variable region.

The "human antibody" (HuMAb) and "fully human antibody" can be used
25 interchangeably and can be either a human derived antibody or an antibody obtained from a transgenic organism that is "engineered" to produce specific human antibodies in response to antigenic challenge and can be produced by any method known in the art. The transgenic organism can synthesize human antibodies, and the organism can be used to produce human antibody-secreting hybridomas. A human antibody can also be an
30 antibody in which the heavy and light chains are encoded by nucleotide sequences derived from one or more human DNA sources. Fully human antibodies can also be constructed by gene or chromosome transfection methods and phage display techniques, or by in-vitro activated B cells, all of which are known in the art.

The terms "full-length antibody", "intact antibody", "complete antibody" and "whole
35 antibody" are used interchangeably herein and refer to a substantially intact form of an antibody, as distinguished from antigen-binding fragments defined below. The term especially refers to antibodies in which the light and heavy chains comprise constant regions. The "antibody" disclosed herein encompasses a "full-length antibody" and an antigen-binding fragment thereof.

40 In some embodiments, a full-length antibody disclosed herein includes a full-length antibody formed by a light chain having a light chain variable region linked to a light

chain constant region and a heavy chain having a heavy chain variable region linked to a heavy chain constant region. Those skilled in the art can select light chain constant regions and heavy chain constant regions derived from different antibodies according to actual needs, such as light chain constant regions and heavy chain constant regions of human antibodies.

The term "antigen-binding fragment" of an antibody refers to one or more fragments of an antibody that retain the ability to bind to an antigen (e.g., an antigen). It has been shown that fragments of full-length antibodies can be used to perform the antigen binding function of the antibody. Examples of binding fragments encompassed in the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region, (iii) an Fd fragment consisting of the VH and CH1 domains; (iv) an Fv fragment consisting of the VH and VL domains of a single arm of an antibody; (v) dsFv, a stable antigen-binding fragment formed by inter-chain disulfide bonds from VH and VL; and (vi) diabodies, bispecific antibodies and multispecific antibodies comprising scFv, dsFv, Fab and other fragments. Furthermore, although the two domains of the Fv fragment, VL and VH, are encoded by separate genes, they can be linked by a synthetic linker using a recombinant method, such that it is capable of generating a single protein chain in which the VL and VH regions are paired to form monovalent molecules (referred to as single chain Fv (scFv); see, e.g., Bird et al., (1988) *Science*, 242: 423–426; and Huston et al., (1988) *Proc.Natl.Acad.Sci USA* 85: 5879–5883). Such single chain antibodies are also included in the term "antigen-binding fragment" of an antibody. Such antibody fragments are obtained using conventional techniques known to those skilled in the art, and the fragments are screened for utility in the same manner as for intact antibodies. Antigen-binding moieties may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact immunoglobulins. The antibodies can be antibodies of different types, for example, an IgG (e.g., IgG1, IgG2, IgG3 or IgG4 subtype), IgA1, IgA2, IgD, IgE or IgM antibody.

F(ab')₂ is an antibody fragment having a molecular weight of about 100,000 and having antigen binding activity and comprising two Fab regions linked at the hinge position, which is obtained by enzymatically digesting the lower portion of two disulfide bonds in the IgG hinge region.

Fab' is an antibody fragment having a molecular weight of about 50,000 and having antigen-binding activity, which is obtained by cleaving the disulfide bonds in the hinge region of the above-mentioned F(ab')₂. Fab' disclosed herein can be produced by treating F(ab')₂ disclosed herein that specifically recognizes an antigen with a reducing agent such as dithiothreitol.

In addition, the Fab' can be produced by inserting DNA encoding the Fab' fragment of the antibody into a prokaryotic expression vector or a eukaryotic expression vector and introducing the vector into a prokaryote or a eukaryote to express the Fab'.

The term "single chain antibody", "single chain Fv" or "scFv" refers to a molecule comprising an antibody heavy chain variable domain (or region; VH) and an antibody light chain variable domain (or region; VL) linked by a linker. Such scFv molecules may have the general structure: NH₂–VL–linker–VH–COOH or NH₂–VH–linker–VL–COOH. A suitable linker in the prior art consists of repeated GGGGS amino acid sequences or variants thereof, for example using variants of 1–4 repeats (Holliger et al., (1993), *Proc. Natl. Acad. Sci. USA* 90: 6444–6448). Other linkers useful in the present disclosure are described in Alfthan et al., (1995), *Protein Eng.*, 8: 725–731, Choi et al., (2001), *Eur.J.Immunol.*, 31: 94–106, Hu et al., (1996), *Cancer Res.*, 56: 3055–3061, Kipriyanov et al., (1999), *J.Mol.Biol.*, 293: 41–56 and Roovers et al., (2001), *Cancer Immunol.*

Diabodies are antibody fragments in which an scFv or Fab is dimerized, and are antibody fragments having bivalent antigen binding activity. In the divalent antigen binding activity, the two antigens may be the same or different.

The diabodies disclosed herein can be produced by the following steps: obtaining cDNA encoding VH and VL of the antibodies disclosed herein, constructing DNA encoding scFv, inserting the DNA into an expression vector, and then introducing the expression vector into a prokaryote or a eukaryote to express the diabodies.

The dsFv is obtained by linking polypeptides in which one amino acid residue in each of VH and VL is substituted with a cysteine residue via a disulfide bond between cysteine residues. The amino acid residue substituted with a cysteine residue may be selected based on the prediction of the three-dimensional structure of the antibody according to a known method (*Protein Engineering*, 7, 697 (1994)).

The full-length antibody, the antigen-binding fragment, the bispecific antibody, the multispecific antibody, the polypeptide, the polypeptide complex or the multispecific polypeptide complex disclosed herein can be produced by the following steps: obtaining cDNA encoding an antibody of the present disclosure, constructing DNA encoding a dsFv, inserting the DNA into an expression vector, and then introducing the expression vector into a prokaryote or eukaryote to express the dsFv.

The term "amino acid difference" or "amino acid mutation" refers to the presence of an amino acid change or mutation in a variant protein or polypeptide as compared to the original protein or polypeptide, including the occurrence of 1, 2, 3 or more amino acid insertions, deletions or substitutions on the basis of the original protein or polypeptide.

The term "antibody framework" or "FR region" refers to a portion of a variable domain VL or VH that serves as a scaffold for the antigen-binding loops (CDRs) of the variable domain. It is essentially a variable domain without CDRs. The term "complementarity determining region", "CDR" or "hypervariable region" refers to one of the 6 hypervariable regions within the variable domain of an antibody which primarily contribute to antigen binding. Typically, there are three CDRs (HCDR1, HCDR2 and HCDR3) per heavy chain variable region and three CDRs (LCDR1, LCDR2 and LCDR3) per light chain variable region. Any of a variety of well-known protocols may be used to determine the amino

acid sequence boundaries of the CDRs, including the "Kabat" numbering scheme (see Kabat et al., (1991), *"Sequences of Proteins of Immunological Interest"*, 5th edition, Public Health Service, National Institutes of Health, Bethesda, MD), "Chothia" numbering scheme (see Al-Lazikani et al., (1997) JMB 273: 927–948) and
5 ImMunoGenTics (IMGT) numbering scheme (Lefranc M.P., Immunologist, 7, 132–136 (1999); Lefranc, M.P. et al., *Dev. Comp. Immunol.*, 27, 55–77 (2003)), etc.

The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody specifically binds (e.g., a specific site on an antigen molecule). Epitopes typically comprise at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15
10 contiguous or non-contiguous amino acids in a unique spatial conformation. See, e.g., *Epitope Mapping Protocols in Methods in Molecular Biology*, volume 66, G.E.Morris, Ed. (1996).

The term "specific binding", "selective binding", "selectively binds" or "specifically binds" refers to the binding of an antibody to an epitope on a predetermined antigen.
15 Typically, the antibody binds with an affinity (KD) of less than about 10^{-7} M, e.g., less than about 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M or less.

The term "KD" refers to the dissociation equilibrium constant for a particular antibody-antigen interaction. Typically, an antibody disclosed herein binds to an antigen with a dissociation equilibrium constant (KD) of less than about 10^{-7} M, e.g., less than about 10^{-8} M or 10^{-9} M, for example, the affinity of an antibody to an antigen in the present
20 disclosure is determined by FACS method for KD values.

The term "competition", when used in the context of antigen binding proteins that compete for the same epitope (e.g., neutralizing antigen binding proteins or neutralizing antibodies), refers to competition between the antigen binding proteins, as determined by
25 the following assay: in such assay, the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) to be detected prevents or inhibits (e.g., reduces) specific binding of a reference antigen binding protein (e.g., ligand or reference antibody) to a common antigen. Numerous types of competitive binding assays are available for determining whether an antigen binding protein competes with another, such
30 as, solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahli et al., 1983, *Methods in Enzymology* 9: 242–253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., 1986, *J.Immunol.*, 137: 3614–3619), solid phase direct labeling assay, solid phase direct labeling sandwich assay (see, e.g., Harlow and Lane, 1988, *Antibodies, A Laboratory Manual* (antibody, Lab Manual), Cold Spring Harbor Press); solid phase
35 direct labeling RIA with I-125 label (see, e.g., Morel et al., 1988, *Molec.Immunol.*, 25: 7–15); solid phase direct biotin-avidin EIA (see, e.g., Cheung et al., 1990, *Virology*, 176: 546–552); and direct-labeled RIA (Moldenhauer et al., 1990, *Scand.J.Immunol.*, 32: 77–82). Typically, the assay involves the use of purified antigen bound to a solid surface or
40 cell carrying either an unlabeled test antigen binding protein or a labeled reference antigen binding protein. Competitive inhibition is measured by measuring the amount of label

that binds to a solid surface or cell in the presence of the measured antigen binding protein. Typically, the measured antigen binding protein is present in excess. Antigen binding proteins identified by competitive assays (competing antigen binding proteins) include an antigen binding protein binding to the same epitope as a reference antigen binding protein and an antigen binding protein binding to a proximal epitope sufficiently close to the binding epitope of the reference antigen binding protein, wherein the two epitopes sterically hinder binding from occurring. Additional details regarding methods for determining competitive binding are provided in the examples herein. Typically, when a competing antigen binding protein is present in excess, it will inhibit (e.g., reduce) at least 40%–45%, 45%–50%, 50%–55%, 55%–60%, 60%–65%, 65%–70%, 70%–75% or 75% or more of specific binding of a reference antigen binding protein to a common antigen. In certain instances, the term "nucleic acid molecule" as used herein refers to DNA molecules and RNA molecules in which binding is inhibited by at least 80%–85%, 85%–90%, 90%–95%, 95%–97% or 97% or more. The nucleic acid molecule may be single-stranded or double-stranded, and preferably double-stranded DNA or single-stranded mRNA or modified mRNA. A nucleic acid is "effectively linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, a promoter or enhancer is effectively linked to a coding sequence if it affects the transcription of the coding sequence.

The term "expression vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In one embodiment, the vector is a "plasmid" which refers to a circular double-stranded DNA loop to which additional DNA fragments can be linked. In another embodiment, the vector is a viral vector, wherein additional DNA fragments may be linked to the viral genome. The vectors disclosed herein are capable of autonomous replication in a host cell into which they have been introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors) or being integrated into the genome of a host cell upon introduction into the host cell and thereby replicated along with the host genome (e.g., non-episomal mammalian vectors).

Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art, such as Cold Spring Harbor Antibody Technical Guide, Chapters 5–8 and 15. For example, a mouse may be immunized with an antigen, and the resulting antibody can be renatured, purified and amino acid sequenced using conventional methods. Antigen-binding fragments can likewise be prepared using conventional methods. The antibody or antigen-binding fragment disclosed herein is genetically engineered to incorporate one or more human FR regions in a non-human CDR region. Human FR germline sequences can be obtained from the website of ImMunoGeneTics (IMGT) by aligning the IMGT human antibody variable region germline gene database with MOE software, or from Immunoglobulin Journal, 2001 ISBN 012441351.

The term "host cell" refers to a cell into which an expression vector has been introduced. Host cells may include bacterial, microbial, plant or animal cells. Bacteria susceptible to

transformation include members of the species *enterobacteria*, such as strains of *Escherichia coli* or *Salmonella*; *Bacillus* such as *Bacillus subtilis*; *Pneumococcus*; *Streptococcus* and *Haemophilus influenzae*. Suitable microorganisms include *Saccharomyces cerevisiae* and *Pichia pastoris*. Suitable animal host cell lines include

5 CHO (Chinese hamster ovary cell lines), 293 cells and NS0 cells.

Engineered antibodies or antigen-binding fragments disclosed herein may be prepared and purified using conventional methods. For example, cDNA sequences encoding the heavy and light chains can be cloned and recombined into an expression vector. The recombinant expression vector can stably transfect CHO cells. As a more recommended

10 prior art, mammalian expression systems may result in glycosylation of antibodies, particularly at the highly conserved N-terminal site of the Fc region. Stable clones are obtained by expression of antibodies specifically binding to the antigen. Positive clones are expanded in a serum-free medium of a bioreactor to produce antibodies. The antibody-secreting culture solution can be purified using conventional techniques. For example,

15 purification is carried out on an A or G Sepharose FF column. Non-specifically bound fractions are washed away. The bound antibody is eluted using a pH-gradient method, the antibody fragment is detected using SDS-PAGE and collected. The antibody can be filtered and concentrated using a conventional method. Soluble mixtures and polymers can also be removed using conventional methods, such as molecular sieves and ion

20 exchange. The resulting product is immediately frozen, e.g., at -70 °C, or lyophilized.

"Administration", "administering" and "treatment", when applied to an animal, a human, an experimental subject, a cell, a tissue, an organ or a biological fluid, refer to contact of an exogenous drug, a therapeutic agent, a diagnostic agent or a composition with the animal, the human, the subject, the cell, the tissue, the organ or the biological fluid.

25 "Administration", "administering" and "treatment" can refer to, for example, therapeutic, pharmacokinetic, diagnostic, research and experimental methods. The treatment of cells includes contacting a reagent with cells and contacting the reagent with a fluid, wherein the fluid contacts the cells. "Administration", "administering" and "treatment" also refer to the treatment of, e.g., cells in vitro and ex vivo, by using an agent, a diagnostic agent,

30 a binding composition, or by another cell. "Treatment", when applied to a human, veterinary or a research subject, refers to therapeutic treatment, prophylactic or preventative measures, research and diagnostic applications.

"Treatment" refers to administration of a therapeutic agent, e.g., a composition comprising any one of the binding compositions disclosed herein, either internally or

35 externally to a subject having one or more disease symptoms for which the therapeutic agent is known to have a therapeutic effect. Typically, the therapeutic agent is administered in an amount effective to alleviate one or more symptoms of the disease in the treated subject or population to induce regression of such symptoms or to inhibit the development of such symptoms to any clinically measurable degree. The amount of

40 therapeutic agent effective to alleviate any particular disease symptom (also referred to as the "therapeutically effective amount") may vary depending on factors such as the

disease state, age and weight of the subject, and the ability of the drug to produce a desired therapeutic effect in the subject. Whether a symptom of a disease has been alleviated or not can be assessed by using any clinical test method commonly used by physicians or other health care professionals to assess the severity or progression of the symptom.

5 Although embodiments of the present disclosure (e.g., treatment methods or articles of manufacture) may be ineffective in alleviating the symptoms of each disease of interest, they shall alleviate the symptoms of the disease of interest in a statistically significant number of subjects as determined by any statistical test method known in the art, such as the Student's t-test, chi-square test, U-test by Mann and Whitney, Kruskal-Wallis test (H-

10 test), Jonckheere-Terpstra test and Wilcoxon test.

"Conservative modifications" or "conservative replacements or substitutions" refer to the replacement of amino acids in a protein with other amino acids having similar characteristics (e.g., charge, side chain size, hydrophobicity/hydrophilicity, backbone chain conformation and rigidity) such that changes may be made frequently without

15 altering the biological activity of the protein. It is known to those skilled in the art that, in general, the replacement of a single amino acid in a non-essential region of a polypeptide does not substantially alter the biological activity (see, for example, Watson et al., (1987) *Molecular Biology of The Gene*, The Benjamin/Cummings pub. Co., page 224, (4th edition)). In addition, replacement of structurally or functionally similar amino

20 acids is unlikely to destroy biological activity. Exemplary conservative substitutions are set forth in the following table "Exemplary amino acid conservative substitutions".

Exemplary amino acid conservative substitutions:

	Original residue	Conservative substitution
	Ala (A)	Gly; Ser
25	Arg (R)	Lys; His
	Asn (N)	Gln; His; Asp
	Asp (D)	Glu; Asn
	Cys (C)	Ser; Ala; Val
	Gln (Q)	Asn; Glu
30	Glu (E)	Asp; Gln
	Gly (G)	Ala
	His (H)	Asn; Gln; Lys; Arg
	Ile (I)	Leu; Val
	Leu (L)	Ile; Val
35	Lys (K)	Arg; His
	Met (M)	Leu; Ile; Tyr
	Phe (F)	Tyr; Met; Leu
	Pro (P)	Ala
	Ser (S)	Thr
40	Thr (T)	Ser
	Trp (W)	Tyr; Phe

Tyr (Y) Trp; Phe
Val (V) Ile; Leu.

The "effective amount" or "effective dose" refers to the amount of a drug, compound or pharmaceutical composition necessary to achieve any one or more beneficial or desired therapeutic results. For prophylactic use, beneficial or desired results include elimination or reduction of risk, lessening the severity, or delaying the onset of the condition, including biochemical, histological and/or behavioral symptoms of conditions, complications thereof and intermediate pathological phenotypes exhibited during the development of the condition. For therapeutic use, beneficial or desired results include clinical results, such as reducing the incidence of or ameliorating one or more symptoms of various target antigen-associated conditions of the present disclosure, reducing the dosage of other agents required to treat the conditions, enhancing the therapeutic effect of another agent, and/or delaying the progression of a target antigen-associated condition of the present disclosure in a subject.

"Exogenous" refers to a substance produced outside an organism, a cell or a human accordingly.

"Endogenous" refers to a substance produced in an organism, a cell or a human accordingly.

"Homology" or "identity" refers to sequence similarity between two polynucleotide sequences or between two polypeptides. When positions in both compared sequences are occupied by the same base or amino acid monomer subunit, e.g., if each position of two DNA molecules is occupied by adenine, then the molecules are homologous at that position. The percent homology between two sequences is a function of the number of pairing or homologous positions shared by the two sequences divided by the number of positions compared $\times 100\%$. For example, if there are 6 matches or homologies at 10 positions in two sequences when the sequences are optimally aligned, then the two sequences are 60% homologous; two sequences are 95% homologous if there are 95 matches or homologies at 100 positions in the two sequences. Typically, two sequences, when aligned, are compared to give the maximum percent homology. For example, the comparison may be made by the BLAST algorithm, wherein the parameters of the algorithm are selected to give the maximum match between the reference sequences over the entire length of each sequence. The following references relate to the BLAST algorithm often used for sequence analysis: the BLAST algorithms: Altschul, S.F. et al., (1990) *J. Mol. Biol.*, 215: 403–410; Gish, W, et al., (1993) *Nature Genet.*, 3: 266–272; Madden, T.L. et al., (1996) *Meth. Enzymol.*, 266: 131–141; Altschul, S.F. et al., (1997) *Nucleic Acids Res.*, 25: 3389–3402; Zhang, J. et al., (1997) *Genome Res.*, 7: 649–656. Other conventional BLAST algorithms, such as one provided by NCBI BLAST, are also well known to those skilled in the art. In the present disclosure, for example, the "natural sequence numbering position relative to the XX sequence" includes both a position corresponding to the natural sequence number on the XX sequence and a position in the mutated sequence of the XX sequence at a position equivalent to the XX sequence,

wherein the equivalent position can be obtained by aligning the mutated sequence of the XX sequence with the XX sequence to obtain the highest percent identity, and the position on the mutated sequence of the XX sequence corresponding to the XX sequence is the equivalent position.

5 As used herein, the expressions of "cells", "cell lines" and "cell cultures" can be used interchangeably, and all such designations include progeny. Thus, the words "transformant" and "transformed cell" include the primary subject cells and cultures derived therefrom, regardless of the number of metastases. It shall be further understood that all progeny may not be precisely identical in DNA content due to deliberate or
10 inadvertent mutations. Mutated progeny having the same function or biological activity as screened for in the originally transformed cells are included. Where different names are intended, they are clear from the context.

"Polymerase chain reaction" or "PCR" as used herein refers to a procedure or technique in which minute amounts of a particular portion of nucleic acid, RNA and/or DNA are
15 amplified as described, for example, in US4683195. In general, it is desirable to obtain sequence information from the terminus of or beyond the target region so that oligonucleotide primers can be designed; these primers are identical or similar in sequence to the corresponding chains of the template to be amplified. The 5'-terminal nucleotide of 2 primers may coincide with the terminus of the material to be amplified.
20 PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and cDNA, phage or plasmid sequences transcribed from total cellular RNA, and the like. See generally Mullis et al., (1987) *Cold Spring Harbor Symp. Quant. Biol.*, 51: 263; Erlich ed., (1989) *PCR TECHNOLOGY* (Stockton Press, N.Y.). PCR, as used herein, is considered to be one example, but not the only example, of a nucleic acid
25 polymerase reaction method for amplifying a nucleic acid test sample that comprises using a known nucleic acid as a primer and a nucleic acid polymerase to amplify or generate a specific portion of the nucleic acid.

The terms "conjugate" and "drug conjugate" refer to a novel drug formed by linking a ligand to a biologically active drug via a stable linking unit. For example, an "antibody
30 drug conjugate" (ADC) is a drug formed by linking an antibody or antibody fragment to a biologically active drug via a linking unit. The antibody may be coupled to the drug directly or via a linker. The average number of drug moieties per antibody may range, for example, from about 0 to about 20 drug moieties per antibody, in some embodiments, from 1 to about 10 drug moieties per antibody, and in some embodiments, from 1 to about
35 8 drug moieties per antibody. For the conjugate disclosed herein, the average drug load per antibody is about 2 to about 5 or about 3 to about 4.

"Isolated" refers to a state of purification, and in this case means that the specified molecule is substantially free of other biomolecules, such as nucleic acids, proteins, lipids, carbohydrates or other materials, such as cell debris and growth media. Generally,
40 the term "isolated" is not intended to refer to the complete absence of such materials or the absence of water, buffers or salts, unless they are present in amounts that significantly

interfere with the experimental or therapeutic use of the compounds as described herein. The term "optional" or "optionally" means that the event or circumstance subsequently described may, but not necessarily, occur, and that the description includes instances where the event or circumstance occurs or does not occur.

5 The term "pharmaceutical composition" refers to a mixture containing one or more of the compounds described herein or a physiologically/pharmaceutically acceptable salt or pro-drug thereof, and other chemical components, for example physiologically/pharmaceutically acceptable carriers and excipients. The purpose of the pharmaceutical composition is to promote the administration to an organism, which
10 facilitates the absorption of the active ingredient, thereby exerting biological activities.

The term "pharmaceutically acceptable carrier" refers to any inactive substance suitable for use in formulations for delivery of the antibody or antigen-binding fragment. The carrier may be an anti-adherent, a binder, a coating, a disintegrating agent, a filler or a diluent, a preservative (e.g., an antioxidant, an antibacterial agent or an antifungal agent),
15 a sweetening agent, an absorption delaying agent, a wetting agent, an emulsifying agent, a buffer, or the like. Examples of suitable pharmaceutically acceptable carriers include water, ethanol, polyols (e.g., glycerol, propylene glycol and polyethylene glycol), dextrose, vegetable oils (e.g., olive oil), saline, buffers, buffered saline, and isotonic agents, such as sugars, polyols, sorbitol and sodium chloride.

20 In addition, the present disclosure comprises a pharmaceutical formulation for use in treating a disease or condition, e.g., an agent for treating a disease related to an antigen-positive cell of interest, wherein the formulation comprises the polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the pharmaceutical composition,
25 the nucleic acid molecule or the multispecific antibody disclosed herein as an active ingredient.

The disease disclosed herein is not limited, for example, a therapeutic response induced using the molecules disclosed herein can be achieved by binding to a human antigen, then blocking the binding of the antigen to a receptor/ligand thereof, or killing tumor cells that
30 overexpress the antigen.

In addition, the present disclosure relates to a method for immunodetection or assay of a target antigen, a reagent for use in immunodetection or assay of a target antigen, a method for immunodetection or assay of a cell expressing a target antigen, and a diagnostic agent for diagnosis of a disease related to a target antigen-positive cell, which comprises the
35 polypeptide complex, the multispecific polypeptide complex, the domain engineered antibody, the Fab fragment of a domain engineered antibody, the bispecific antibody, the pharmaceutical composition, the nucleic acid molecule or the multispecific antibody disclosed herein as an active ingredient.

In the present disclosure, the method for detection or assay of an amount of a target
40 antigen may be any known method. For example, it includes immunodetection or assay methods.

The immunodetection or assay method is a method for detection or assay of an amount of an antibody or an amount of an antigen using a labeled antigen or antibody. Examples of the immunodetection or assay methods include a radioactive substance-labeled immune antibody method (RIA), an enzyme immunoassay (EIA or ELISA), a fluorescence immunoassay (FIA), a luminescence immunoassay, a Western blotting method, physicochemical methods, and the like.

The above-mentioned diseases related to antigen-positive cells can be diagnosed by detection or assay of cells expressing an antigen with the antibody disclosed herein.

For detection of cells expressing the polypeptide, known immunodetection methods can be used, and immunoprecipitation, fluorescent cell staining, immunohistological staining and other methods are preferably used. In addition, a fluorescent antibody staining method using FMAT8100HTS system (Applied Biosystem) and the like can be used.

In the present disclosure, the living sample for use in detection or assay of a target antigen is not particularly limited as long as it has a possibility of comprising cells expressing the target antigen, such as tissue cells, blood, plasma, serum, pancreatic juice, urine, feces, interstitial fluid or culture fluid.

The diagnostic agent comprising the antibody or the antibody fragment thereof disclosed herein may further comprise a reagent for use in performing an antigen-antibody reaction or a reagent for use in detection of a reaction, depending on the desired diagnostic method.

The reagent for use in performing an antigen-antibody reaction include buffers, salts and the like. The reagent for use in detection includes reagents generally used in immunodetection or assay methods, such as a labeled second antibody recognizing the monoclonal antibody, an antibody fragment thereof or a binding substance thereof and a substrate corresponding to the label, and the like.

The details of one or more embodiments of the present disclosure are set forth in the specification above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are described below. Other features, objects and advantages of the present disclosure will be apparent from the specification and the claims. In the specification and claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same general meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs. All patents and publications cited in the specification are incorporated by reference. The following examples are set forth in order to more fully illustrate the preferred embodiments of the present disclosure. These examples should not be construed in any way as limiting the scope of the present disclosure.

The present invention is further described below with reference to examples, but these examples are not intended to limit the scope of the present invention. The experimental methods in the examples of the present invention, in which specific conditions are not specified, are generally performed under conventional conditions such as Cold Spring

Harbor Antibody Technical Guide and Molecular Cloning Manual, or under conditions recommended by the manufacturer of the raw material or the goods. Reagents without specific sources indicated are conventional reagents purchased from the market.

Although the antibodies used in the examples target specific antigens, those skilled in the art, in light of the teachings of the present disclosure, will appreciate that the technical effect is achieved independently of the specific CDR sequences and independently of the specific antigen sequences, but with the benefit of substitution of the Titin T chain/Obscurin-O chain, or the Titin T chain/Obscurin-like-O chain for CH1/CL to improve the mispairing between the heavy/light chains.

Example 1: Preparation Method for Antibody or Polypeptide Protein

The method comprises: designing a primer PCR to build a gene fragment (such as an antibody VH/VK gene fragment), carrying out homologous recombination on the gene fragment and an expression vector (such as pHr (with a signal peptide and a constant region gene (such as CH1-Fc/CL) fragment)) to construct an expression vector (such as VH-CH1-Fc-pHr/VK-CL-pHr), introducing the constructed expression vector into a prokaryote or a eukaryote for expression, and finally purifying a product to obtain the required antibody or polypeptide protein. Without limitation, the antibody constant region may be selected from the group consisting of a light chain constant region of a human κ and λ chain and a heavy chain constant region selected from the group consisting of IgG1, IgG2, IgG3 and IgG4. Non-limiting examples further include the optimization design of human antibody constant regions, such as mutations on positions L234A/L235A or L234F/L235E of the heavy chain constant region. Illustratively, antibody light/heavy chain constant region sequences are as follows:

> IgG1 heavy chain constant region (abbreviated as hIgG1):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHT
CPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 1);

Note: in the sequence, the single underlined part is CH1, the dotted underlined part is CH2, and the italicized part is CH3.

> knob-IgG1 heavy chain constant region (abbreviated as knob-IgG1):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHT
CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNHYT

QKSLSLSPGK (SEQ ID NO: 2);

Note: in the sequence, the single underlined part is CH1, the dotted underlined part is CH2, and the italicized part is CH3.

> hole-IgG1 heavy chain constant region (abbreviated as hole-IgG1):

5 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWE
10 SNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 3);

Note: in the sequence, the single underlined part is CH1, the dotted underlined part is CH2, and the italicized part is CH3.

> kappa light chain constant region (abbreviated as kappa or κ):

15 RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 4).

> lambda light chain constant region (abbreviated as lambda or λ):

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE
20 TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
(SEQ ID NO: 5).

The amino acid sequences of the light and heavy chain variable regions of antibodies against various antigens such as B7H3 and CD3 mentioned in the examples or test examples of the present disclosure are as follows:

25 > VH amino acid sequence of F0 antibody:

QVQLVQSGGGVVPQTSLRLSCAASGFISSSAMHWVRQAPGKGLEWVAVISY
DGSNKYYVDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARSARLYASF
DYWGQGALVTVSS (SEQ ID NO: 6);

> VL amino acid sequence of F0 antibody:

30 DTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTSHYPSWYQQTPGQAPRMLIYNTN
TRSSGV PDRFSGSILGNKAALTITGAQADDES DY YCAIHVDRDIWVFGGGTKLT
VL (SEQ ID NO: 7);

> VH amino acid sequence of N0 antibody:

DVQLVQSGGGLVQPGGSLRLSCAGSGFTSSLSWMSWLRQAPGKGLEWVANIN
35 QDGSEKNYVDSVKGRFTISRDN AQNSLYLQMSSLRAEDTAVYYCARGLWTFD
SWGQGTLLTVSP (SEQ ID NO: 8);

> VL amino acid sequence of N0 antibody:

EIVLTQSPGTLSPGERATLSCRASQNINRFLAWYQQRPGQAPRLLIYAASSR
40 ATGVPDRFSGSGSGTDFTLTISRLEAEDFAM YHCQQYGSFPRTFGQGT MVDIK
(SEQ ID NO: 9);

> VH amino acid sequence of S0 antibody:

EVQLQESGPGGLVKPGGSLRLSCAASGTFVSSYDMSWVRQTPERGLEWVAYISS
 GGGITYAPSTVKGRFTVSRDNAKNTLYLQMNSLTSEDNAVYYCAAHYFGSSGP
 FAYWGQGTLLTVSS (SEQ ID NO: 10);

> VL amino acid sequence of S0 antibody:

5 DIQMTQSPASLSASVGDRVTITCRASENIFSYLAWYQQKPGKSPKLLVYNTRL
 AEGVPSRFSGSGSGTDFSLTISSLQPEDFATYYCQHHYGPFTFGSGTKLEIK
 (SEQ ID NO: 11);

> VH amino acid sequence of V0 antibody:

QVQLQQSAAELARPGASVKMSCKASGYSFTSYTIHWVKQRPGQGLEWIGYINP
 10 NSRNTDYNQKFKDETTLTADRSSSTAYMQLISLTSEDSAVYYCARYSGSTPYW
 YFDVWGAGTTVTVSS (SEQ ID NO: 12);

> VL amino acid sequence of V0 antibody:

QIVLTQSPAILSASPGEKVTMTCRASSSVSYMNWYQQKPGSSPKPWIYATSNLA
 SGVPARFSVSVSGTSHSLTISRVEAEDAATYYCQQWSSNPLTFGAGTKLELK
 15 (SEQ ID NO: 13);

> VH amino acid sequence of J0 antibody:

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVGHIK
 SKTDAGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDNAVYYCAREIYY
 AFDSWGQGTLLTVSS (SEQ ID NO: 14);

20 > VL amino acid sequence of J0 antibody:

SYELTQPLSVSVALGQTARITCSGDNIGSKYVHWYQQKPGQAPVLVIYGDNERP
 SGIPERFSGSNSGNTATLTISRAGQAGDEADYYCQAADWVDFYVFGGGTKLTVL
 (SEQ ID NO: 15);

> VH amino acid sequence of H0 antibody:

25 EVQLVESGGGLVQPGGSLRLSCAASGFTFSHYMAWVRQAPGKGLEWVTSISY
 EGDITYYGDSVKGRFTISRDNKNTLYLQMNSLRAEDTATYYCASQTLRESFDY
 WGQGTLLTVSS (SEQ ID NO: 16);

> VL amino acid sequence of H0 antibody:

DIQMTQSPSSVSASVGDRVTITCRASQDIANYLSWYQQKPGKSPKLLIYGTSNLE
 30 VGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCLQDKEFPRTFGGGTKVEIK (SEQ
 ID NO: 17);

> VH amino acid sequence of R0 antibody:

EVQLVESGGGLVQPGGSLRLSCAVSGLSLTNSNVNWIRQAPGKGLEWVGLIWS
 NGDTDYNSAIKSRFTISRDTSKSTVYLQMNSLRAEDNAVYYCAREYYGYFDYW
 35 GQGTLLTVSS (SEQ ID NO: 18);

> VL amino acid sequence of R0 antibody:

DIQMTQSPSSLSASVGDRVTITCLASEGISSYLAWYQQKPGKAPKLLIYGANSLO
 TGVPSRFSGSGSATDYTLTISSLQPEDFATYYCQQSYKFPNTFGQGTKVEVK
 (SEQ ID NO: 19);

40 > VH amino acid sequence of Bmab (abbreviated as B0) antibody:

QVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMGGII

PMFGTAKYSQNFQGRVAITADESTGTASMESSLRSED TAVYYCARSRDLLFP
HHALSPWGRGTMVTVSS (SEQ ID NO: 20);

> VL amino acid sequence of Bmab (abbreviated as B0) antibody:
SSELTQDPAVSVALGQTVRVTCQGD SLRSYYASWYQQKPGQAPVLVIYGKNN
5 RPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELT
VL (SEQ ID NO: 21);

> VH amino acid sequence of Umab (abbreviated as U0) antibody:
EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSP
VDS DIRYSPSFQGGVTMSVDKSITTAYLQWNSLKASDTAMYYCARRRPGQGYF
10 DFWGQGTLVTVSS (SEQ ID NO: 22);

> VL amino acid sequence of Umab (abbreviated as U0) antibody:
DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNIYPYTFGQGGTKLEIK (SEQ
ID NO: 23);

15 > VH amino acid sequence of Dmab (abbreviated as D0) antibody:
EVQLLES GGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGITG
SGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDPGTTVIM
SWFDPWGQGTLVTVSS (SEQ ID NO: 24);

> VL amino acid sequence of Dmab (abbreviated as D0) antibody:
20 EIVLTQSPGTL SLSPGERATLSCRASQSVRGRYLA WYQQKPGQAPRLLIYGASS
RATGIPDRFSGSGSGTDFTLTISRLEPEDFA VFY CQQY GSSPRTFGQGGTKVEIK
(SEQ ID NO: 25);

> VH amino acid sequence of Tmab (abbreviated as I0) antibody:
QVQLQESG PGLVKPSETLSLTCTVSGFSLIGYDLNWIRQPPGKGLEWIGIHWGDG
25 TTDYNSAVKSRVTISKDT SKNQFSLKLSSVTAADTAVYYCARGGYWYATSYYF
DYWGQGTLVTVSS (SEQ ID NO: 26);

> VL amino acid sequence of Tmab (abbreviated as I0) antibody:
DIQMTQSPSSLSASVGDRVTITCRASQSISNNLNWYQQKPGKAPKLLIYYTSRFH
SGVPSRFSGSGSGTDFTFTISSLQPED IATYYCQQEHTLPYTFGQGGTKLEIK (SEQ
30 ID NO: 27);

> VH amino acid sequence of C0 antibody:
EVQLVQSGAEVKKPGASVKV SCKASGYTFTDYH MNWVRQAPGQRLEWMGDI
NPDIGGTSYNQNFKGRVTITRDT SASTAYMELSSLRSED TAVYYCARWDFDSFA
NWGQGTLVTVSS (SEQ ID NO: 28);

35 > VL amino acid sequence of C0 antibody:
DIVMTQSPDSLAVSLGERATINCRASESVSIIGTNLIHWYQQKPGQPPKLLIYHAS
NLETGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCLQSRKIPYTFGGGKVEIK
(SEQ ID NO: 29);

> VH amino acid sequence of A0 antibody:
40 EVQLVESGGGLVQPGGSLKLS CAASGFTFNKYAMNWVRQAPGKGLEWVARIR
SKYNNYATYYADSVKDRFTISRDD SKNTAYLQMNNLKTEDTAVYYCVRHGNF

GNEYISYWAYWGQGLTVTVSS (SEQ ID NO: 105);

> VL amino acid sequence of A0 antibody:

QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGT
KFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTK
LTVL (SEQ ID NO: 106);

The heavy chain constant region sequences of the antibodies F0, N0, S0, V0, J0, H0, R0, B0, U0, D0, I0, C0 and A0 are IgG1 heavy chain constant regions (SEQ ID NO: 1), and the light chain constant region sequences of the antibodies N0, S0, H0, R0, U0, I0 and C0 are kappa light chain constant regions (SEQ ID NO: 4); the light chain constant region sequences of the antibodies F0, V0, J0, B0, D0 and A0 are lambda light chain constant regions (SEQ ID NO: 5).

In addition, the sequence of hB7H3 antigen protein is as follows:

LEVQVPEDPVVALVGTDATLCCSFSPGFSLAQLNLIWQLTDTKQLVHSFAEG
QDQGSAYANRTALFPDLLAQGNASLRLQVRVADEGSFTCFVSIRDFGSAAVS
LQVAAPYSKPSMTLEPNKDLRPGDTVITCSSYQGYPEAEVFWQDGQGVPLTG
NVTTSQMANEQGLFDVHSILRVVLGANGTYSCLVRNPVLQQDAHSSVTITPQR
SPTGAVEVQVPEDPVVALVGTDATLRCSFSPEPGFSLAQLNLIWQLTDTKQLVH
SFTEGRDQGSAYANRTALFPDLLAQGNASLRLQVRVADEGSFTCFVSIRDFGS
AAVSLQVAAPYSKPSMTLEPNKDLRPGDTVITCSSYRGYPEAEVFWQDGQGV
PLTGNVTTSQMANEQGLFDVHSVLRVVLGANGTYSCLVRNPVLQQDAHGSVTI
TGQPM T DYKDDDDKHHHHHH (SEQ ID NO: 111);

the hCD3 antigen protein is a heterodimer consisting of a δ subunit and an ϵ subunit of hCD3 antigen, wherein the sequence of the δ subunit of hCD3 antigen is as follows:

FKIPIEELED RVFVNCNTSITWVEGT VGTLLSDITRLDLGKRILDP RGIYRCNGTD
IYKDKESTVQVHYRMCQSCVELDPATVASAENAQCEKELQALEKENAQLWE
LQALEKELAQDYKDDDDK (SEQ ID NO: 112);

the sequence of the ϵ subunit of hCD3 antigen is as follows:

DGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGS
DEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMDAKN
AQCKKKLQALKKKNAQLKWKLQALKKKLAQH HHHHHH (SEQ ID NO: 113).

Example 2: Substitution of Antibody CH1/CL Domain

CH1/CL domain engineered antibodies were obtained by substituting the CH1/CL domain of the antibody with the Ig-like domains of the natural Titin/Obscurin complex, Titin/Obscurin-like O complex and IL6Ra/IL6Rb complex, which possess natural intermolecular interactions, respectively.

In the IL6Ra/IL6Rb complex, the Ig-like domain in IL6Ra protein for substituting the antibody CH1 or CL is IL6Ra.0 chain, and the Ig-like domain in IL6Rb protein for substituting antibody CL or CH1 is IL6Rb.0 chain; in the Titin/Obscurin complex, the Ig-like domain (Titin Ig-like 152 domain) in the Titin protein used for substituting antibody CH1 or CL is T.0 chain, and the Ig-like domain (Obscurin Ig-like-1 domain) in the

- Obscurin protein used for substituting antibody CL or CH1 is O.0 chain; in the Titin/Obscurin-like O complex, the Ig-like domain (Obscurin-like-Ig-like-1 domain) in the Obscurin-like protein used for substituting antibody CH1 or CL is OL.0 chain, and the Ig-like domain (Titin Ig-like 152 domain) in the Titin protein used for substituting antibody CL or CH1 is T.0 chain, wherein:
- the > IL6Ra.0 chain sequence is:
 GILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSFYRLRFELRYRAERSKTF
 TTWMVKDLQHHCVIHDAWSGLRHVVQLRAQEEFGQGEWSEWSPEAMGTPW
 (SEQ ID NO: 30);
- the > IL6Rb.0 chain sequence is:
 FDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTW
 SQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGIT
 (SEQ ID NO: 31);
- the > T.0 chain sequence is:
 GIPPKIEALPSDISIDEGKVLTVACAFTGEPTPEVTWSCGGRKIHSQEQGRFHIE
 TDDLTTLIHMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 32);
- the > O.0 chain sequence is:
 SGAPRFLTRPKAFVVSVGKDATLSCQIVGNPTPQVSWEKDQQPVAAGARFRLA
 QDGDLYRLTILDALGDSGQYVCRARNAIGEAFAAVGLQVDAEA (SEQ ID NO:
 33);
- the > OL.0 chain sequence is:
 QGSPPCFLRFPRVRVSGAEAEKLCVVLGEPPPVVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGVYVCRARNAAGEAYAAAAVTVLEPP (SEQ ID
 NO: 34);
- A plurality of antibodies with substituted CH1/CL were constructed, and the purity and the binding activity to the corresponding antigen of the antibodies to be tested were detected according to the methods of Test Examples 2 and 4. The experimental results are shown in Table 1 below, and the experimental results showed that, after CH1/CL of antibodies such as F0, V0, S0, N0, J0, H0, R0 and C0 which bound to different antigens were simultaneously substituted with T.0 chain/O.0 chain or T.0 chain/OL.0 chain, the antibodies still maintained good binding activity and had high antibody purity.

Table 1. Purity and affinity of antibodies with substituted CH1/CL domain

Name of antibody		Antibody Domain substitution		Purity of antibody SEC (%)	Binding assay to the corresponding antigen EC50 (nM)
		Substitution of heavy chain CH1	Substitution of light chain CL		
Substitution of CH1/CL of F0	F0	CH1	CL	98	1.29
	F1	IL6Rb.0	IL6Ra.0	47	71.6
	F2	IL6Ra.0	IL6Rb.0	67	59.28
	F3	T.0	O.0	100	2.83
	F4	T.0	OL.0	100	2.17
	V0	CH1	CL	86	1.8
	V1	IL6Rb.0	IL6Ra.0	38	38.4

Substitution of CH1/CL of V0	V2	IL6Ra.0	IL6Rb.0	NA	-
	V3	T.0	O.0	99	3.6
	V4	T.0	OL.0	97	2.9
	V5	O.0	T.0	98	3.2
	V6	OL.0	T.0	97	4.7
Substitution of CH1/CL of S0	S0	CH1	CL	97	1.01
	S1	IL6Rb.0	IL6Ra.0	NA	-
	S2	IL6Ra.0	IL6Rb.0	NA	-
	S3	T.0	OL.0	83	3.5
	S4	OL.0	T.0	90	1.96
Substitution of CH1/CL of N0	N0	CH1	CL	99	0.82
	N1	IL6Rb.0	IL6Ra.0	100	1229
	N2	IL6Ra.0	IL6Rb.0	67	766.5
	N3	T.0	O.0	90	6.45
	N4	T.0	OL.0	83	5.93
	N5	O.0	T.0	90	5.24
Substitution of CH1/CL of J0	J0	CH1	CL	95	0.08
	J1	IL6Rb.0	IL6Ra.0	NA	-
	J2	IL6Ra.0	IL6Rb.0	NA	179
	J3	OL.0	T.0	93	0.25
Substitution of CH1/CL of H0	H0	CH1	CL	NA	1.74
	H1	IL6Rb.0	IL6Ra.0	75	19.35
	H2	IL6Ra.0	IL6Rb.0	80	24.38
	H3	T.0	O.0	95	2.753
	H4	T.0	OL.0	95	2.702
Substitution of CH1/CL of R0	R0	CH1	CL	NA	1.75
	R1	IL6Rb.0	IL6Ra.0	75	24.45
	R2	IL6Ra.0	IL6Rb.0	60	18.4
	R3	O.0	T.0	98	1.576
	R4	OL.0	T.0	98	1.667
	R5	T.0	O.0	98	1.589
	R6	T.0	OL.0	97	2.016
Substitution of CH1/CL of C0	C0	CH1	CL	96	5.81
	C1	O.0	T.0	95	17.7
	C2	OL.0	T.0	99	16.48

Note: For example, F1 indicates that the heavy chain CH1 of the F0 antibody was substituted with the IL6Rb.0 chain (SEQ ID NO: 31) and the light chain CL was substituted with the IL6Ra.0 chain (SEQ ID NO: 30), and the other portions remained the same as those of F0, and so on. In the table, "-" indicates no detection, and SEC indicates the purity of the antibody detected by size exclusion chromatography (NA indicates no detection due to underexpression).

Example 3: Optimization Design of CH1/CL Domain Engineered Antibody

Individual amino acids of the Titin Ig-like 152 domain (T.0 chain), the Obscurin Ig-like 1 domain (O.0 chain) and the Obscurin-like Ig-like 1 domain (OL.0 chain) were mutated,

including insertion, deletion or substitution of amino acids, to verify the activity of the domain engineered antibody.

Illustratively, firstly, inter-chain disulfide bonds were increased by mutation on a small number of amino acids on the T.0 chain, the O.0 chain and the OL.0 chains; secondly, other individual amino acids in the domain were also mutated, for example, amino acid mutations on positions 7, 62 and 11 of the Obscurin Ig-like 1 domain; amino acids were increased or decreased at the N-terminus of the Titin Ig-like 152 domain (e.g., 5 "KAGIR" amino acids of the wild-type Titin protein immediately adjacent to the N-terminus of the Titin Ig-like 152 domain were added); amino acids were increased or decreased at the N-terminus of the Obscurin Ig-like 1 domain (e.g., 5 "DQPQF" amino acids of the wild-type Obscurin protein immediately adjacent to the N-terminus of the Obscurin Ig-like 1 domain were added); in addition, a linker sequence was added at the N-terminus or the C-terminus of the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain (e.g., a "G₄S" or "(G₄S)₂" linker sequence was added at the N-terminus), and the C-terminus of the antibody VH or VL was linked to the Titin Ig-like 152 domain, the Obscurin Ig-like 1 domain or the Obscurin-like Ig-like 1 domain via the linker sequence. The optimization design of the specific domain is shown in Table 2.

Table 2. Amino acid mutations of T.0 chain, O.0 chain and OL.0 chain

Titin-T chain		Obscurin-O chain		Obscurin-like-O chain	
Name	Mode of mutation	Name	Mode of mutation	Name	Mode of mutation
T.0	Wild type (SEQ ID NO: 32)	O.0	Wild type (SEQ ID NO: 33)	OL.0	Wild type (SEQ ID NO: 34)
T.1	C25S, C39T, A8C	O.1	A88C	OL.1	C6E, V74C
T.2	C25S, C39T, V20C	O.2	A3C	OL.2	C6E, G84C
T.3	C25S, C39T, A26C	O.3	R9C	OL.3	C6E, A86C
T.4	C25S, C39T, T22C	O.4	C25S, C76S, A88C	OL.4	C6E, C26S, C77S, V74C
T.5	C25S, C39T, A8C + Titin_KAGIR	O.5	C25S, C76S, A3C	OL.5	C6E, C26S, C77S, G84C
T.6	C25S, C39T, A8C + (G ₄ S) ₁ linker sequence	O.6	C25S, C76S, R9C	OL.6	C6E, C26S, C77S, A86C
T.7	C25S, C39T, A8C + (G ₄ S) ₂ linker sequence	O.7	C25S, C76S, A88C, L7K, T62K		
		O.8	C25S, C76S, A88C, L7K, T62H		
		O.9	C25S, C76S, A88C, K11L, T62K		
		O.10	C25S, C76S, A88C, K11L, T62H		
		O.11	C25S, C76S, A88C+Obscurin_DQPQF		
		O.12	C25S, C76S, A88C, L7K,		

			T62K+Obscurin_DQP QF		
		O.13	C25S, C76S, A88C, L7K, T62H+Obscurin_DQP QF		
		O.14	C25S, C76S, A88C, L7R, T62K+Obscurin_DQP QF		
		O.15	C25S, C76S, A88C, L7R, T62H+Obscurin_DQP QF		
		O.16	C25S, C76S, A88C + (G4S) ₁ linker sequence		
		O.17	C25S, C76S, A88C + (G4S) ₂ linker sequence		

Note: The O.1 mode of mutation "A88C" in the Obscurin-O chain in the table indicates that the 88th amino acid residue of O.0 (SEQ ID NO: 33) sequence was mutated from A to C; the O.11 mode of mutation "C25S, C76S, A88C + Obscurin_DQPQF" indicates that O.0 (SEQ ID NO: 33) sequence was subjected to C25S, C76S and A88C amino acid mutations, and 5 "DQPQF" amino acids were added at the N-terminus, and so on.

The sequences of the Titin-T chain, the Obscurin-O chain and the Obscurin-like-O chain after mutations on partial amino acids are as follows:

> T.1 (T.0 has C25S, C39T and A8C mutations)

GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSSEQGRFHIENT

10 DDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 35);

> T.2 (T.0 has C25S, C39T and V20C mutations)

GIPPKIEALPSDISIDEGKCLTVASAFTGEPTPEVTWSTGGRKIHSSEQGRFHIENT

DDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 36);

> T.3 (T.0 has C25S, C39T and A26C mutations)

15 GIPPKIEALPSDISIDEGKVLTVASCFTGEPTPEVTWSTGGRKIHSSEQGRFHIENT

DDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 37);

> T.4 (T.0 has C25S, C39T and T22C mutations)

GIPPKIEALPSDISIDEGKVLCAVASAFTGEPTPEVTWSTGGRKIHSSEQGRFHIENT

TDDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 38);

20 > T.5 (T.0 has C25S, C39T and A8C mutations; KAGIR is added at the N-terminus)

KAGIRGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSSEQGR

FHIENTDDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 39);

> T.6 (T.0 has C25S, C39T and A8C mutations; (G4S)₁ linker is added at the N-terminus)

25 GGGGSGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSSEQGR

FHIENTDDLTTLIIMDVQKQDGGGLYTLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 40);

- > T.7 (T.0 has C25S, C39T and A8C mutations; (G₄S)₂ linker is added at the N-terminus)
GGGGSGGGSGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHS
QEQRFHIENTDDLTTLIIMDVQKQDGGGLYTLISLGNEFGSDSATVNIHIRSI (SEQ
ID NO: 41);
- 5 > O.1 (O.0 has A88C mutation)
SGAPRFLTRPKAFVVSVGKDATLSCQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLTILDLALGDSGQYVCRARNAIGEAFACVGLQVDAAE (SEQ ID NO:
42);
- > O.2 (O.0 has A3C mutation)
- 10 SGCPRFLTRPKAFVVSVGKDATLSCQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLTILDLALGDSGQYVCRARNAIGEAFAAVGLQVDAAE (SEQ ID NO:
43);
- > O.3 (O.0 has R9C mutation)
SGAPRFLTCPKAFVVSVGKDATLSCQIVGNPTPQVSWEKDQQPVAAGARFRLA
15 QDGDLYRLTILDLALGDSGQYVCRARNAIGEAFAAVGLQVDAAE (SEQ ID NO:
44);
- > O.4 (O.0 has C25S, C76S and A88C mutations)
SGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLTILDLALGDSGQYVSRARNAIGEAFACVGLQVDAAE (SEQ ID NO:
20 45);
- > O.5 (O.0 has C25S, C76S and A3C mutations)
SGCPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLTILDLALGDSGQYVSRARNAIGEAFAAVGLQVDAAE (SEQ ID NO:
46);
- 25 > O.6 (O.0 has C25S, C76S and R9C mutations)
SGAPRFLTCPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLTILDLALGDSGQYVSRARNAIGEAFAAVGLQVDAAE (SEQ ID NO:
47);
- > O.7 (O.0 has C25S, C76S, A88C, L7K and T62K mutations)
- 30 SGAPRFKTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAAE (SEQ ID NO:
48);
- > O.8 (O.0 has C25S, C76S, A88C, L7K and T62H mutations)
SGAPRFKTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
35 QDGDLYRLHILDLALGDSGQYVSRARNAIGEAFACVGLQVDAAE (SEQ ID NO:
49);
- > O.9 (O.0 has C25S, C76S, A88C, K11L and T62K mutations)
SGAPRFLTRPLAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAAE (SEQ ID NO:
40 50);
- > O.10 (O.0 has C25S, C76S, A88C, K11L and T62H mutations)

SGAPRFLTRPLAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
 QDGDLYRLHILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ ID NO:
 51);

> O.11 (O.0 has C25S, C76S and A88C mutations; DQPQF is added at the N-terminus)

5 DQPQFSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLTILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 52);

> O.12 (O.0 has C25S, C76S, A88C, L7K and T62K mutations; DQPQF is added at the
 N-terminus)

10 DQPQFSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 53);

> O.13 (O.0 has C25S, C76S, A88C, L7K and T62H mutations; DQPQF is added at the
 N-terminus)

15 DQPQFSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLHILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 54);

> O.14 (O.0 has C25S, C76S, A88C, L7R and T62K mutations; DQPQF is added at the
 N-terminus)

20 DQPQFSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 55);

> O.15 (O.0 has C25S, C76S, A88C, L7R and T62H mutations; DQPQF is added at the
 N-terminus)

25 DQPQFSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLHILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 56);

> O.16 (O.0 has C25S, C76S and A88C mutations; (G₄S)₁ linker is added at the N-
 terminus)

30 GGGGSSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQPVAAGA
 RFRLAQDGDLYRLTILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ
 ID NO: 57);

> O.17 (O.0 has C25S, C76S and A88C mutations; (G₄S)₂ linker is added at the N-
 terminus)

35 GGGGSGGGGSSGAPRFLTRPKAFVVSVGKDATLSSQIVGNPTPQVSWEKDQQP
 VAAGARFRLAQDGDLYRLTILDLALGDSGQYVSRARNAIGEAFACVGLQVDAE
 A (SEQ ID NO: 58);

> OL.1 (OL.0 has C6E and V74C mutations)

40 QGSPPEFLRFPRPVRVVSAGAEAEKLCVVLGEPPPVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGCYVCRARNAAGEAYAAA VTVLEPP (SEQ ID NO:
 59);

- > OL.2 (OL.0 has C6E and G84C mutations)
 QGSPPEFLRFPRPVRVVSAGAEAEELKCVVLGEPPPVVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGVYVCRARNAACEAYAAAATVLEPP (SEQ ID NO:
 60);
- 5 > OL.3 (OL.0 has C6E and A86C mutations)
 QGSPPEFLRFPRPVRVVSAGAEAEELKCVVLGEPPPVVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGVYVCRARNAAGECYAAAATVLEPP (SEQ ID NO:
 61);
- > OL.4 (OL.0 has C6E, C26S, C77S and V74C mutations)
 10 QGSPPEFLRFPRPVRVVSAGAEAEELKSVVLGEPPPVVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGCYVSRARNAAGEAYAAAATVLEPP (SEQ ID NO:
 62);
- > OL.5 (OL.0 has C6E, C26S, C77S and G84C mutations)
 QGSPPEFLRFPRPVRVVSAGAEAEELKSVVLGEPPPVVVWEKGGQQLAASERLSFP
 15 ADGAEHGLLLTAALPTDAGVYVSRARNAACEAYAAAATVLEPP (SEQ ID NO:
 63);
- > OL.6 (OL.0 has C6E, C26S, C77S and A86C mutations)
 QGSPPEFLRFPRPVRVVSAGAEAEELKSVVLGEPPPVVVWEKGGQQLAASERLSFP
 ADGAEHGLLLTAALPTDAGVYVSRARNAAGECYAAAATVLEPP (SEQ ID NO:
 20 64).

A plurality of antibodies with substituted CH1/CL were constructed by utilizing the mutated or domain-engineered Titin-T chain, Obscurin-O chain and Obscurin-like-O chain, the binding activity of each optimized mutated antibody and the corresponding antigen was detected by using the method of Test Example 4 disclosed herein, and the experimental results are shown in Table 3. The results showed that the disulfide-bond-modified antibody maintained good antigen binding activity.

Table 3. Affinity of antibodies engineered with CH1/CL domain

Name of antibody		Antibody Domain substitution		Binding assay to the corresponding antigen EC50 (nM)
		Substitution of heavy chain CH1	Substitution of light chain CL	
Substitution of CH1/CL of F0	F3	T.0	O.0	2.64
	F5	T.1	O.1	1.21
	F6	T.2	O.2	2.71
	F7	T.3	O.3	3.38
	F8	T.1	O.4	3.14
	F9	T.2	O.5	3.52
	F10	T.3	O.6	3.94
	F4	T.0	OL.0	3.01
	F11	T.1	OL.1	6.15
	F12	T.2	OL.2	8.19
	F13	T.4	OL.3	6.08
	F14	T.1	OL.4	5.15

	F15	T.2	OL.5	4.44
Substitution of CH1/CL of H0	H3	T.0	O.0	3.24
	H5	T.1	O.1	3.40
	H6	T.2	O.2	2.10
	H7	T.3	O.3	2.70
	H8	T.1	O.4	2.11
	H9	T.2	O.5	2.92
	H10	T.3	O.6	2.86
	H4	T.0	OL.0	3.28
	H11	T.1	OL.1	3.38
	H12	T.2	OL.2	4.34
	H13	T.4	OL.3	3.56
	H14	T.1	OL.4	2.61
	H15	T.4	OL.6	4.26
Substitution of CH1/CL of R0	R5	T.0	O.0	4.13
	R7	T.1	O.1	4.89
	R8	T.2	O.2	3.84
	R9	T.3	O.3	3.95
	R10	T.1	O.4	3.20
	R11	T.2	O.5	3.30
	R12	T.3	O.6	4.36
Substitution of CH1/CL of N0	N3	T.0	O.0	4.5
	N6	T.2	O.5	8.4
	N4	T.0	OL.0	4.6
	N7	T.5	OL.1	2.8
	N8	T.5	OL.4	2.6

Note: For example, antibody "F5" in the table indicates that the heavy chain CH1 of the F0 antibody was substituted with the T.1 chain (SEQ ID NO: 35) and the light chain CL was substituted with the O.1 chain (SEQ ID NO: 42), and the other portions remained the same as those of F0, and so on.

- 5 In addition, the antibodies with substituted CH1/CL were constructed by utilizing the mutated or domain-engineered Titin-T chain and Obscurin-O chain, and the functional activity of the antibodies with other substituted CH1/CL was detected by using the methods of Test Example 2 and Test Example 4 disclosed herein. The experimental results are shown in Table 4, and the experimental results showed that the antibodies with
- 10 substituted CH1/CL still maintained good antigen binding activity, and the SEC (%) of the antibody purity was relatively high.

Table 4. Detection results of purity and binding activity of antibodies with domain engineered CH1/CL

Name of antibody		Antibody Domain substitution		Purity of antibody SEC (%)	Binding assay to the corresponding antigen EC50 (nM)
		Substitution of heavy chain CH1	Substitution of light chain CL		
Substitution of CH1/CL	F16	T.5	O.4	65	2.0
	F17	T.5	O.7	72	4.8

of F0	F18	T.1	O.8	70	3.9
	F19	T.5	O.8	68	2.2
	F20	T.1	O.9	71	1.9
	F21	T.5	O.9	68	3.4
	F22	T.1	O.10	74	2.4
	F23	T.5	O.10	73	4.1
	F24	T.1	O.12	71	2.4
	F25	T.5	O.12	66	2.6
	F26	T.1	O.13	73	2.6
	F27	T.5	O.13	71	1.2
	F28	T.1	O.14	75	2.4
	F29	T.5	O.14	68	3.6
	F30	T.1	O.15	75	3.4
	F31	T.5	O.15	69	2.4
	F32	T.6	O.17	72	3.69
	F33	T.7	O.16	69	1.92
	F34	T.7	O.17	73	2.38
Substitution of CH1/CL of N0	N10	T.5	O.4	89	3.0
	N11	T.1	O.7	86	5.0
	N12	T.1	O.8	84	5.3
	N13	T.5	O.8	82	2.9
	N14	T.1	O.9	92	1.9
	N15	T.5	O.9	92	2.6
	N16	T.5	O.10	91	3.4
	N17	T.1	O.11	90	2.2
	N18	T.5	O.11	89	3.2
	N19	T.1	O.12	84	4.3
	N20	T.5	O.12	84	2.8
	N21	T.5	O.13	84	5.2
	N22	T.5	O.14	87	4.5
	N23	T.1	O.15	86	9.4
	N24	T.5	O.15	84	6.7
	N25	T.6	O.17	92	0.62
	N26	T.7	O.16	93	0.84
	N27	T.7	O.17	94	0.67
Substitution of CH1/CL of R0	R10	T.1	O.4	84	0.37
	R13	T.5	O.4	76	0.4
	R14	T.5	O.7	78	0.2
	R15	T.5	O.8	82	0.3
	R16	T.5	O.9	80	0.33
	R17	T.5	O.10	77	0.4
	R18	T.5	O.11	71	0.44
	R19	T.5	O.12	78	0.36
	R20	T.5	O.13	75	0.39
	R21	T.5	O.14	77	0.37
	R22	T.5	O.15	74	0.39

Note: For example, antibody "F16" in the table indicates that the heavy chain CH1 of the

F0 antibody was substituted with the T.5 chain (SEQ ID NO: 39) and the light chain CL was substituted with the O.4 chain (SEQ ID NO: 45), and the other portions remained the same as those of F0, and so on.

In addition, mutations were made on other amino acids in the Titin Ig-like 152 domain and the Obscurin Ig-like 1 domain, and the specific amino acid mutations were designed as shown in Table 5.

Table 5. Amino acid mutation design of T.1 chain/O.9 chain

Titin-T chain		Obscurin-O chain	
Name	Mode of mutation	Name	Mode of mutation
T.1	T.1 (SEQ ID NO: 35)	O.9	O.9 (SEQ ID NO: 50)
T.8	T.1 + (M66S, T77S)	O.18	O.9 + (L11K, A12S, F13Y, V14T, T22S)
T.9	T.1 + (M66K, K70R, S79T, G81R)	O.19	O.9 + (G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S, A97G)
T.10	T.1 + (P3W, S11I, I13L, T22M, N82M)	O.20	O.9 + (D20L, T22M, A53L)
T.11	T.1 + (S11I, M66K, S79T, G81R)	O.21	O.9 + (Q41K, A45T, A67Q, G69S, V89L)
T.12	T.1 + (G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D, F84L)	O.22	O.9 + (Q42L, A45T, A67T, G69S, Q92E, D94G)
T.13	T.1 + (Q47E, Q49G, N56S, D58E, L75V)	O.23	O.9 + (A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E, D94G)
T.14	T.1 + (N56S, D58E, L75V)	O.24	O.9 + (Q41K, A45T, A67Q, G69S and V89L) + (G ₄ S) ₁ linker sequence
T.15	T.1 + (N56S, D58E, M66S, T77S)	O.25	O.9 + (A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G), + (G ₄ S) ₁ linker sequence
T.16	T.1 + (S11I, M66K, S79T and G81R), + (G ₄ S) ₁ linker sequence	O.26	O.9 + (A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E, D94G), + DQPQF
T.17	T.1 + (N56S, D58E, M66S, T77S), + KAGIR	O.27	O.9 + (A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G), + DQPQF, + (G ₄ S) ₁ linker sequence
T.18	T.1 + (N56S, D58E, M66S and T77S), + KAGIR, + (G ₄ S) ₁ linker sequence		
T.19	T.1 + (N56S, D58E, M66S and T77S), + (G ₄ S) ₁ linker sequence		

Note: In the table, for example, T.8 indicates a Titin-T chain obtained by amino acid mutation on the T.1 (SEQ ID NO: 35) sequence at M66S and T77S; O.24 indicates an Obscurin-O chain obtained by amino acid mutations on O.9 (SEQ ID NO: 50) at A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G, then addition of a "DQPQF" sequence at the N-terminus, and finally addition of a "GGGGS" linker sequence at the N-terminus, and so on.

The mutant sequences of the T.1 chain and the O.9 chain are as follows:

> T.8 (T.1 has M66S and T77S mutations)

GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIENT
DDLTTLIISDVQKQDGGGLYSLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 65);

5 > T.9 (T.1 has M66K, K70R, S79T and G81R mutations)

GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIENT
DDLTTLIKDVQRQDGGGLYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 66);

> T.10 (T.1 has P3W, S11I, I13L, T22M and N82M mutations)

10 GIWPKIECLPIDLSIDEGKVLMTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIE
NTDDLTTLIIMDVQKQDGGGLYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 67);

> T.11 (T.1 has S11I, M66K, S79T and G81R mutations)

GIPPKIECLPIDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIENT
DDLTTLIKDVQKQDGGGLYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 68);

15 > T.12 (T.1 has G40S, R42K, H45S, Q47E, Q49G, N56S, D58E, L75V, E83D and F84L
mutations)

GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTSGKKISSEEGGRFHIESTE
DLTTLIIMDVQKQDGGVYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 69);

> T.13 (T.1 has Q47E, Q49G, N56S, D58E and L75V mutations)

20 GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEGGRFHIE
EDLTTLIIMDVQKQDGGVYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 70);

> T.14 (T.1 has N56S, D58E and L75V mutations)

GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIE
EDLTTLIIMDVQKQDGGVYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO: 71);

> T.15 (T.1 has N56S, D58E, M66S and T77S mutations)

25 GIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGRFHIE
EDLTTLIISDVQKQDGGGLYSLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 72);

> T.16 (T.1 has S11I, M66K, S79T and G81R mutations + (G₄S)₁ linker sequence)

30 GGGGSGIPPKIECLPIDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGR
FHIENTDDLTTLIKDVQKQDGGGLYTLTLRNEFGSDSATVNIHIRSI (SEQ ID NO:
73);

> T.17 (T.1 has N56S, D58E, M66S and T77S mutations, + KAGIR)

KAGIRGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGR
FHIESTEDLTTLIISDVQKQDGGGLYSLSLGNEFGSDSATVNIHIRSI (SEQ ID NO:
74);

35 > T.18 (T.1 has N56S, D58E, M66S and T77S mutations, + KAGIR, + (G₄S)₁ linker
sequence)

GGGGSKAGIRGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIH
SEEQGRFHIESTEDLTTLIISDVQKQDGGGLYSLSLGNEFGSDSATVNIHIRSI (SEQ
ID NO: 75);

40 > T.19 (T.1 has N56S, D58E, M66S and T77S mutations, + (G₄S)₁ linker sequence)

GGGGSGIPPKIECLPSDISIDEGKVLTVASAFTGEPTPEVTWSTGGRKIHSEEQGR

FHIESTEDLTTLISDVQKQDGGLYSLSLGNEFGSDSATVNIHIRSI (SEQ ID NO: 76);

> O.18 (O.9 has L11K, A12S, F13Y, V14T and T22S mutations)

5 SGAPRFLTRPKSYTVSVGKDASLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ ID NO: 77);

> O.19 (O.9 has G2E, V17E, N30D, T32P, Q34E, S36T, V44I, A45T, L58V, K62E, A67Q, G69S and A97G mutations)

10 SEAPRFLTRPLAFVVSEGKDATLSSQIVGDPPEVTWEKDQQPITAGARFRLAQ
DGDVYRLEILDLQLSDSGQYVSRARNAIGEAFACVGLQVDAEG (SEQ ID NO: 78);

> O.20 (O.9 has D20L, T22M and A53L mutations)

15 SGAPRFLTRPLAFVVSVGKLAMLSSQIVGNPTPQVSWEKDQQPVAAGARFRLA
QDGDLYRLKILDLALGDSGQYVSRARNAIGEAFACVGLQVDAEA (SEQ ID NO: 79);

> O.21 (O.9 has Q41K, A45T, A67Q, G69S and V89L mutations)

SGAPRFLTRPLAFVVSVGKDATLSSQIVGNPTPQVSWEKDKQPVTAGARFRLA
QDGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACLGLQVDAEA (SEQ ID NO: 80);

20 > O.22 (O.9 has Q42L, A45T, A67T, G69S, Q92E and D94G mutations)

SGAPRFLTRPLAFVVSVGKDATLSSQIVGNPTPQVSWEKDQLPVTAGARFRLAQ
DGDLYRLKILDLTLSDSGQYVSRARNAIGEAFACVGLEVGAEA (SEQ ID NO: 81);

> O.23 (O.9 has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G mutations)

25 SGAPRFLTRPLSYVVSVGKDASLSSQIVGNPTPQVSWEKDQLPVTAGARFRLAQ
DGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACVGLEVGAEA (SEQ ID NO: 82);

> O.24 (O.9 has Q41K, A45T, A67Q, G69S and V89L mutations; + (G₄S)₁ linker sequence)

30 GGGGSSGAPRFLTRPLAFVVSVGKDATLSSQIVGNPTPQVSWEKDKQPVTAGARFRLAQDGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACLGLQVDAEA (SEQ ID NO: 83);

> O.25 (O.9 has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G mutations, + (G₄S)₁ linker sequence)

35 GGGGSSGAPRFLTRPLSYVVSVGKDASLSSQIVGNPTPQVSWEKDQLPVTAGARFRLAQDGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACVGLEVGAEA (SEQ ID NO: 84);

> O.26 (O.9 has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G mutations; + DQPQF)

40 DQPQFSGAPRFLTRPLSYVVSVGKDASLSSQIVGNPTPQVSWEKDQLPVTAGAR

FRLAQDGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACVGLGVGAEA (SEQ ID NO: 85);

> O.27 (O.9 has A12S, F13Y, T22S, Q42L, A45T, A67Q, G69S, Q92E and D94G mutations; + DQPQF; and + (G₄S)₁ linker sequence)

5 GGGGSDQPQFSGAPRFLTRPLSYVSVVGKDASLSSQIVGNPTPQVSWEKDQLPV
TAGARFRLAQDGDLYRLKILDLQLSDSGQYVSRARNAIGEAFACVGLGVGAEA
(SEQ ID NO: 86).

10 The antibodies with substituted CH1/CL were constructed by utilizing the mutated or domain-engineered Titin-T chain and Obscurin-O chain, the antibodies with substituted CH1/CL were detected by using the method of Test Example 4 disclosed herein, and the experimental results are shown in Table 6. The results showed that the antibodies still maintained good antigen binding activity after the CH1/CL was substituted with the optimized Titin-T chain and the Obscurin-O chain.

15 Table 6. Experimental results of binding of antibodies with substituted CH1/CL to corresponding antigens

Antibody		Antibody Domain substitution		Binding assay to the corresponding antigen EC50 (nM)
		Substitution of heavy chain CH1	Substitution of light chain CL	
Substitution of CH1/CL of B0	B0	CH1	CL	0.2
	B1	T.1	O.9	0.28
	B2	T.8	O.18	0.19
	B3	T.9	O.19	0.5
	B4	T.11	O.21	0.25
	B5	T.12	O.22	0.29
	B6	T.13	O.22	0.19
	B7	T.14	O.22	0.35
	B8	T.15	O.23	0.16
Substitution of CH1/CL of U0	U0	CH1	CL	0.06
	U1	T.1	O.9	0.03
	U2	T.8	O.18	0.07
	U3	T.9	O.19	0.02
	U4	T.11	O.21	0.06
	U5	T.12	O.22	0.11
	U6	T.13	O.22	0.11
	U7	T.14	O.22	0.07
	U8	T.15	O.23	0.16
Substitution of CH1/CL of D0	D0	CH1	CL	0.089
	D1	T.1	O.9	0.026
	D2	T.9	O.19	0.056
	D3	T.11	O.21	0.083
	D4	T.12	O.22	0.103
	D5	T.13	O.22	0.134
	D6	T.14	O.22	0.132
	D7	T.15	O.23	0.102
	I0	CH1	CL	1.424

Substitution of CH1/CL of I0	I2	T.8	O.18	3.195
	I3	T.11	O.21	2.989
	I4	T.12	O.22	4.132
	I5	T.13	O.22	3.592
	I6	T.14	O.22	4.121
	I7	T.15	O.23	3.153

Note: In the table, for example, antibody "B1" indicates an antibody obtained by substitution of the heavy chain CH1 of B0 antibody with T.1 chain (SEQ ID NO: 35) and substitution of the light chain CL with O.9 chain (SEQ ID NO: 50), and the other portions were the same as those of B0, and so on.

- 5 In addition, the protein expression level of the antibody with substituted CH1/CL was measured by using the method of Test Example 1 disclosed herein, and the experimental results are shown in Table 7. The results showed that the expression level of antibodies was greatly improved after partial amino acid mutations of the Titin Ig-like 152 domain and the Obscurin Ig-like 1 domain.

10 Table 7. Expression level of CH1/CL domain engineered antibodies

Antibody		Antibody Domain substitution		Expression level of antibody (mg/L)
		Substitution of heavy chain CH1	Substitution of light chain CL	
Substitution of CH1/CL of B0	B1	T.1	O.9	9.4
	B2	T.8	O.18	25.6
	B3	T.9	O.19	13.9
	B4	T.11	O.21	21.4
Substitution of CH1/CL of D0	D1	T.1	O.9	5.9
	D2	T.9	O.19	44.4
	D3	T.11	O.21	40.5
	D4	T.12	O.22	17.8
	D5	T.13	O.22	21.4
	D6	T.14	O.22	23.3
	D7	T.15	O.23	34.3
Substitution of CH1/CL of I0	I1	T.1	O.9	2.1
	I2	T.8	O.18	11.0
	I3	T.11	O.21	10.4
	I4	T.12	O.22	4.0
	I5	T.13	O.22	4.6
	I6	T.14	O.22	8.2
	I7	T.15	O.23	6.9

Example 4: Half-Life of CH1/CL Domain Engineered Antibody

- To evaluate whether the stability of the antibody in the animal body was affected after CH1/CL of the antibody was substituted with a Titin-T chain/Obscurin-O chain or a Titin-T chain/Obscurin-like-O chain, we examined the half-life of the antibody in the rat body before and after the substitution. Illustratively, we examined the half-lives in rats of antibody F20, in which CH1/CL of F0 antibody was substituted with T.1/O.9, and of antibody C3, in which CH1/CL of C0 antibody was substituted with T.1/O.9,
- 15

respectively. The specific method comprises the following steps:

The 3mpk antibody was administered intravenously to rats, and 0.3 mL of whole blood was collected 5 min, 8 h, 1 d, 2 d, 4 d, 7 d, 10 d, 14 d, 21 d and 28 d after administration, respectively, without anticoagulation, and after blood collection, the blood was left at 4 °C for 30 min and centrifuged at 1000 g for 15 min, and the supernatant (serum) was placed in an EP tube and stored at -80 °C. The detection method for antibody drug concentrations at each time point adopted sandwich ELISA, namely, corresponding antigens were coated on an ELISA plate, and the plate was incubated overnight at 4 °C, washed with a washing liquid, then added with a blocking buffer and incubated at room temperature for 1–3 h, then washed with a washing liquid, added with 100 µL of standard substance or serum sample to be detected and incubated at 37 °C for 3 h, then washed with a washing liquid, added with a secondary antibody anti-Human IgG FC (HRP) mouse preadsorbed (Abcam, product No. ab98624, 1:10000 dilution) and incubated at 37 °C for 1–1.5 h, then washed with a washing buffer, added with TMB and incubated in dark at room temperature for 10 min, and then added with a stop buffer; OD450 values were read.

The experimental results are shown in Table 8, and the results showed that, after CH1/CL of the antibody was substituted with a Titin-T chain/Obscurin-O chain, the half-life of the original antibody in the rat body was still maintained, which indicates that the antibody with substituted CH1/CL had good stability in the body like the original antibody.

Table 8. Half-life of antibodies with substituted CH1/CL domain

Name of antibody	<i>In-vivo</i> half-life of rat (3mpk) T1/2 (day)
F0	13.3 ± 1.0
F20	12.8 ± 0.3
C0	17.3 ± 2.2
C3	15.4 ± 4.1

Example 5: Construction and Detection of Bispecific Antibodies

A bispecific antibody was constructed through bridge PCR of an antibody binding to a first antigen and an antibody binding to a second antigen. Illustratively, we constructed a variety of bispecific antibodies.

I. Construction of bispecific antibodies

Firstly, we constructed a DI-1 bispecific antibody which is an IgG-like bispecific antibody composed of a heavy chain (with knob modification in Fc region) and a light chain of a D0 antibody, and a heavy chain (with hole modification in Fc region) and a light chain of a modified antibody obtained by substituting CH1/CL of an I0 antibody with a Titin-T chain/Obscurin-O chain; its structural schematic diagram is shown in FIG. 5, and its sequence is shown as follows:

Amino acid sequence of DI-1 chain 1 (DI-1-H1):

EVQLLES GGGGLVQPGGSLRLS CAASGFT FSSYAMSWVRQAPGKGLEWVSG

ITGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDPG
 TTVIMSWFDPWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD
 YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVN
 HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
 5 VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
 QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS
 LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 87);

Note: In the sequence, the bold part is VH of D0, the single underlined part is CH1, the
 10 dotted underlined part is CH2, and the italicized part is CH3.

Amino acid sequence of DI-1 chain 2 (DI-1-L1):

EIVLTQSPGTL S LSPGERATLSCRASQSVRGRYLAWYQQKPGQAPRLLIYG
 ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVFY CQQYGSSPRTFGQGT
 KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQ
 15 SGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSF
 NRGEC (SEQ ID NO: 88);

Note: In the sequence, the bold part is VL of D0, and the single underlined part is light
 chain constant region CL of D0.

20 Amino acid sequence of DI-1 chain 3 (DI-1-H2):

QVQLQESGPGLVKPSETLSLTCTVSGFSLIGYDLNWIRQPPGKGLEWIGIIW
 GDGTTDYN SAVKSRVTISKDT SKNQFSLKLSSVTAADTAVYYCARGGYWY
 ATSY YFDYWGQGT LVTVSSGGGGSGIPPKIECLPIDISIDEGKVLTVASAFTGEP
 TPEVTWSTGGRKIHSQE QGRFHIENTDDLTT LIKDVQKQDGGGLYTLTLRNEFGS
 25 DSATVNIHIRSIDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
 GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVK
 GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSV
 MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 89);

30 Note: In the sequence, the bold part is VH of I0, the single underlined part is T.16, the
 dotted underlined part is CH2, and the italicized part is CH3.

Amino acid sequence of DI-1 chain 4 (DI-1-L2):

DIQMTQSPSSLSASVGDRVTITCRASQSSNNLNWYQQKPGKAPKLLIYYTS
 35 RFHSGVPSRFSGSGSGTDFTFTISS LQPED IATYYCQQEHTLPYTFGQGTKL
 EIKGGGGSSGAPRFLTRPLAFVVS VGKDATLSSQIVGNPTPQVSWEKDKQPVT A
 GARFRLAQDGDLYRLKILDQLSDSGQYVSRARNAIGEAFACLG LQVDAEA
 (SEQ ID NO: 90);

Note: In the sequence, the bold part is VL of I0, and the single underlined part is O.24.

40 In addition, an IgG-like bispecific antibody was constructed from B0 or the CH1/CL
 domain engineered antibody of B0 and U0 or the CH1/CL domain engineered antibody

of U0 (illustratively, the schematic structural diagram of BU5 is shown in FIG. 8), and four chain sequences of the obtained bispecific antibody are shown in Table 9 below:

Table 9. IgG-like bispecific antibody sequence listing

Name of diabody	Four-chain sequence of IgG-like bispecific antibody			
	Chain 1	Chain 2	Chain 3	Chain 4
BU1	Heavy chain of B0 (knob)	Light chain of B0	Heavy chain of U0 (hole), and CH1 is substituted with T.19	Light chain of U0, and CL is substituted with O.25
	QVQLQQSGAEVKKPG SSVRVSCASGGTFNN NAINWVRQAPGQGLE WMGGIIPMFGTAKYS QNFQGRVAITADESTG TASMELSSLRSED TAV YYCARSRDLLLP PHHA LSPWGRGTMVTVSSAS TKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEP VTVSWNSGALTSGVHT FPAVLQSSGLYSLSSV TVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKS CDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHN AKTKPREEQYNSTYRV VSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPP CREEMTKNQVSLWCLVK GFYPSDIAVEWESNGQPE NNYKTPPVLDSDGSFFL YSKLTVDKSRWQQGNVF SCSVMHREALHNHYTQKS LSLSPGK (SEQ ID NO: 91)	SSELTQDPA VSVALGQTV RVTCQGDSL RSYYASWY QQKPGQAP VLVIYGKNN RPSGIPDRFS GSSSGNTAS LTITGAQAE DEADYYCSS RDSSGNHW VFGGGTELT VLGQPKAAP SVTLFPPSSE ELQANKATL VCLISDFYPG AVTVAWKA DSSPVKAGV ETTPSKQSN NKYAASSYL SLTPEQWKS HRSYSCQVT HEGSTVEKT VAPTECS (SEQ ID NO: 92)	EVQLVQSGAEVKKPGESL KISCKGSGYSFTTYWLG WVRQMPGKGLDWIGIMS PVDSDIRYSPSFQGV TM SVDKSITTAYLQWNSLKA SDTAMYYCARRRPGQGY FDWVGQGT LTVTVSSGGG GSGIPPKIECLPSDISIDEGK VLTVASAFTGEPTPEVTWS TGGRKIHSQEQGRFHIESTE DLTTLISDVQKQDGGGLYS LSLGNEFGSDSATVNIHRS IDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDW LNGKEYCKCKVSNKALPAPI EKTISKAKGQPREPQVCTLP PSREEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYK TPPVLDSDGSFFLVSKLTV DKSRWQQGNVFS CSVMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 93)	DIQMTQSPS SLSASVGDR VTITCRASQ GISSWLAW YQQKPEKA PKSLIYAAS SLQSGVPSR FSGSGSGTD FTLTISSLQP EDFATYYC QQYNIYPYT FGQGTKLEI KGGGGSSG APRFLTRPLS YVVS VGKD ASLSSQIVG NPTPQVSWE KDQLPVTAG ARFRLAQDG DLYRLKILD LQLSDSGQY VSRARNAIG EAFACVGLE VGAEA (SEQ ID NO: 94)
BU2	Heavy chain of U0 (knob)	Light chain of U0	Heavy chain of B0 (hole), and CH1 is substituted with T.19	Light chain of B0, and CL is substituted with O.27
	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTTY WLGWVRQMPGKGLD WIGIMSPVDSDIRYSPS FQGQVTMSVDKSITTA YLQWNSLKASDTAMY YCARRRPGQGYFDW GQGT LTVTVSSASTKGP SVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAV LQSSGLYSLSSVTVPS SLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTH TCPPCPAPEAAGGPSVF	DIQMTQSPS SLSASVGDR VTITCRASQ GISSWLAW YQQKPEKA PKSLIYAASS LQSGVPSRF SGSGSGTDF TLTISSLOPE DFATYYCQ QYNIYPYTF GQG TKLEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLL	QVQLVQSGAEVKKPGSS VRVSCASGGTFNNNAIN WVRQAPGQGLEWMGGII PMFGTAKYSQNFQGRVAI TADESTGTASMELSSLR EDTAVYYCARSRDLLLP HHALSPWGRGTMVTVSS GGGGSGIPPKIECLPSDISID EGKVLTVASAFTGEPTPEV TWSTGGRKIHSQEQGRFHI ESTEDLTTLISDVQKQDGG LYSLSLGNEFGSDSATVNI HIRSIDKTHTCPPCPAPEA GGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVK	SSELTQDPA VSVALGQT VRVTCQGD SLRSYYAS WYQQKPG QAPVLVIYG KNNRPSGIP DRFSGSSSG NTASLTITG AQA EDEAD YYCSSRDSS GNHWVFGG GTH ELTVLG GGGSDQPQF SGAPRFLTR

	<u>LFPPKPKDTLMISRTPEV</u> <u>TCVVVDVSHEDPEVKF</u> <u>NWYVDGVEVHNAKTK</u> <u>PREEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKCK</u> <u>VSNKALPAPIEKTISKAK</u> <u>GQPREPQVYTLPPCREE</u> <u>MTKNQVSLWCLVKGFYP</u> <u>SDIAVEWESNGQPENNYK</u> <u>TTPPVLDSDGSFFLYSKL</u> <u>TVDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSLSP</u> <u>GK (SEQ ID NO: 95)</u>	<u>NNFYBREAK</u> <u>VQWKVDNA</u> <u>LQSGNSQES</u> <u>VTEQDSKDS</u> <u>TYSLSTLT</u> <u>SKADYEKHK</u> <u>VYACEVTHQ</u> <u>GLSSPVTKSF</u> <u>NRGEC (SEQ</u> <u>ID NO: 96)</u>	<u>FNWYVDGVEVHNAKTKPR</u> <u>EEQYNSTYRVVSVLTVLH</u> <u>QDWLNGKEYKCKVSNKA</u> <u>LPAPIEKTISKAKGQPREPQ</u> <u>VCTLPPSREEMTKNQVSLSC</u> <u>AVKGFYP</u> <u>SDIAVEWESNGQP</u> <u>ENNYKTTPPVLDSDGSFFLV</u> <u>SKLTVDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSLSPGK</u> <u>(SEQ ID NO: 97)</u>	<u>PLSYVSVSG</u> <u>KDASLSSQI</u> <u>VGNPTQVS</u> <u>WEKDQLPV</u> <u>TAGARFRLA</u> <u>QDGDLYRL</u> <u>KILDLQLSDS</u> <u>GQYVSRAR</u> <u>NAIGEAFA</u> <u>VGLEVGAEA</u> <u>(SEQ ID NO: 98)</u>
BU3	Heavy chain of B0 (knob), and CH1 is substituted with T.19	Light chain of B0, and CL is substituted with O.27	Heavy chain of U0 (hole)	Light chain of U0
	<u>QVQLQQSGAEVKKPG</u> <u>SSVRVSCASGGTFNN</u> <u>NAINWVRQAPGQGLE</u> <u>WMGGIIPMFGTAKYS</u> <u>QNFQGRVAITADESTG</u> <u>TASMELSSLRSED</u> <u>YVCARSRDLLFP</u> <u>HHALSPWGRGTMVTVSS</u> <u>G</u> <u>GGSGIPPKIECLPSDISI</u> <u>DEGKVLTVASAFTGEPT</u> <u>PEVTWSTGGRKIHSQEQ</u> <u>GRFHIEDTLTTLISDV</u> <u>QKQDGGLYSLSLGNEF</u> <u>GSDSATVNIHRSIDKTH</u> <u>TCPPCAPEAAAGGPSVF</u> <u>LFPPKPKDTLMISRTPEV</u> <u>TCVVVDVSHEDPEVKF</u> <u>NWYVDGVEVHNAKTK</u> <u>PREEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKCK</u> <u>VSNKALPAPIEKTISKAK</u> <u>GQPREPQVYTLPPCREE</u> <u>MTKNQVSLWCLVKGFYP</u> <u>SDIAVEWESNGQPENNYK</u> <u>TTPPVLDSDGSFFLYSKL</u> <u>TVDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSLSP</u> <u>GK (SEQ ID NO: 99)</u>	<u>SSELTQDPA</u> <u>VSVALGQTV</u> <u>RVTCQGD</u> <u>SLRSYYASWY</u> <u>QKQPGQAP</u> <u>VLVIYGKNN</u> <u>RPSGIPDRFS</u> <u>GSSSGNTAS</u> <u>LTITGAQAE</u> <u>DEADYYCSS</u> <u>RDSSGNHW</u> <u>VFGGGTELT</u> <u>VLGGGSDQ</u> <u>POFSGAPRFL</u> <u>TRPLSYVVS</u> <u>VGKDASLSS</u> <u>QIVGNPTQ</u> <u>VSWEKDQLP</u> <u>VTAGARFRL</u> <u>AQDGDLYRL</u> <u>KILDLQLSDS</u> <u>GQYVSRARN</u> <u>AIGEAFA</u> <u>CVGLEVGAEA</u> <u>(SEQ ID NO: 100)</u>	<u>EVQLVQSGAEVKKPGESL</u> <u>KISCKGSGYSFTTYWLG</u> <u>WVRQMPGKGLDWIGIMS</u> <u>PVDSDIRYSPSFQGV</u> <u>TM</u> <u>SVDKSITTAYLQWNSLKA</u> <u>SDTAMYYCARRRPGQGY</u> <u>DFWGGQGLTVTVSSASTK</u> <u>GPSVFPLAPSSKSTSGGTA</u> <u>ALGCLVKDYFPEPVTVSWNS</u> <u>GALTSGVHTFPAVLQSSGL</u> <u>YSLSSVTVPSSSLGTQTYI</u> <u>CNVNHPKPSNTKVDKKVEP</u> <u>KSCDKTHTCPPCPAPEAAG</u> <u>GPSVFLFPPKPKDTLMISRT</u> <u>PEVTCVVVDVSHEDPEVKF</u> <u>NWYVDGVEVHNAKTKPR</u> <u>EEQYNSTYRVVSVLTVLH</u> <u>QDWLNGKEYKCKVSNKA</u> <u>LPAPIEKTISKAKGQPREPQ</u> <u>VCTLPPSREEMTKNQVSLSC</u> <u>AVKGFYP</u> <u>SDIAVEWESNGQP</u> <u>ENNYKTTPPVLDSDGSFFLV</u> <u>SKLTVDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSLSPGK</u> <u>(SEQ ID NO: 101)</u>	<u>DIQMTQSPS</u> <u>SLSASVGD</u> <u>RVTITCRASQ</u> <u>GISSWLAW</u> <u>YQQKPEKA</u> <u>PKSLIYAAS</u> <u>SLQSGVPSR</u> <u>FSGSGSGTD</u> <u>FTLTISLQPE</u> <u>EDFATYYC</u> <u>QQYNIYPYT</u> <u>FGQGTKLEI</u> <u>KRTVAAPSV</u> <u>FIFPPESL</u> <u>LSLQGS</u> <u>ASVVC</u> <u>KSGTASVVC</u> <u>LLNNFYPRE</u> <u>AKVQWKVD</u> <u>NALQSGNSQ</u> <u>ESVTEQDSK</u> <u>DSTYSLSTL</u> <u>TLSKADYEK</u> <u>HKVYACEV</u> <u>THQGLSSPV</u> <u>TKSFNRGEC</u> <u>(SEQ ID NO: 96)</u>
BU4	Heavy chain of U0 (knob)	Light chain of U0	Heavy chain of B0 (hole), and CH1 is substituted with T.18	Light chain of B0, and CL is substituted with O.27
	<u>EVQLVQSGAEVKKPG</u> <u>ESLKISCKGSGYSFTTY</u> <u>WLGWVRQMPGKGLD</u> <u>WIGIMSPVDSDIRYSPS</u> <u>FQGV</u> <u>TM</u> <u>SVDKSITTA</u> <u>YLQWNSLKASDTAMY</u> <u>YCARRRPGQGYDFW</u> <u>GQGLTVTVSSASTKGP</u> <u>SVFPLAPSSKSTSGGTA</u> <u>ALGCLVKDYFPEPVTVS</u> <u>WNSGALTSGVHTFPAV</u>	<u>DIQMTQSPS</u> <u>SLSASVGD</u> <u>RVTITCRASQ</u> <u>GISSWLAW</u> <u>YQQKPEKA</u> <u>PKSLIYAASS</u> <u>LQSGVPSRF</u> <u>SGSGSGTDF</u> <u>TLTISLQPE</u> <u>DFATYYCQ</u> <u>QYNIYPYTF</u>	<u>QVQLQQSGAEVKKPGSS</u> <u>VRVSCASGGTFNNNAIN</u> <u>WVRQAPGQGLEWMGGII</u> <u>PMFGTAKYSQNFQGRVAI</u> <u>TADESTGTASMELSLRS</u> <u>EDTAVYYCARSRDLLFP</u> <u>HHALSPWGRGTMVTVSS</u> <u>GGGGSKAGIRGIPPKIECLP</u> <u>SDISIDEGKVLTVASAFTGE</u> <u>PTPEVTWSTGGRKIHSQEQ</u> <u>GRFHIEDTLTTLISDVQ</u>	<u>SSELTQDPA</u> <u>VSVALGQT</u> <u>VRVTCQGD</u> <u>SLRSYYAS</u> <u>WYQQKPG</u> <u>QAPVLVIYG</u> <u>KNNRPSGIP</u> <u>DRFSGSSSG</u> <u>NTASLTITG</u> <u>AQAED</u> <u>AD</u> <u>YVCSSRDSS</u>

	<u>LQSSGLYSLSSVTVPS</u> <u>SLGTQTYICNVNHKPSN</u> <u>TKVDKKVEPKSCDKTH</u> <u>TCPPCPAPEAAGGPSVF</u> <u>LFPPKPKDTLMISRTPEV</u> <u>TCVVVDVSHEDPEVKF</u> <u>NWYVDGVEVHNAKTK</u> <u>PREEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKCK</u> <u>VSNAKALPAPIEKTISKAK</u> <u>GQPREPQVYTLPPCREE</u> <u>MTKNQVSLWCLVKGFYP</u> <u>SDIAVEWESNGQPENNYK</u> <u>TTPPVLDSDGSFFLYSKL</u> <u>TVDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSLSP</u> <u>GK (SEQ ID NO: 95)</u>	GQGTKLEIK <u>RTVAAPSVFI</u> <u>FPPSDEQLKS</u> <u>GTASVVCLL</u> <u>NNFYPREAK</u> <u>VQWKVDNA</u> <u>LQSGNSQES</u> <u>VTEQDSKDS</u> <u>TYSLSSTLT</u> <u>SKADYEKHK</u> <u>VYACEVTHQ</u> <u>GLSSPVTKSF</u> <u>NRGEC (SEQ</u> <u>ID NO: 96)</u>	<u>KQDGGLYSLSLGNEFGSDS</u> <u>ATVNIHIRSIDKTHTCPPCP</u> <u>APEAAGGPSVFLFPPKPKD</u> <u>TLMISRTPEVTCVVVDVSH</u> <u>EDPEVKFNWYVDGVEVHN</u> <u>AKTKPREEQYNSTYRVVS</u> <u>VLTVLHQDWLNGKEYKCK</u> <u>VSNAKALPAPIEKTISKAKG</u> <u>QPREPQVCTLPSSREEMTKN</u> <u>QVSLSCAVKGFYPSDIAVEW</u> <u>ESNGQPENNYKTTPPVLDSD</u> <u>GSFFLVSKLTVDKSRWQQG</u> <u>NVFSCSVMHEALHNHYTQKS</u> <u>LSLSPGK (SEQ ID NO: 102)</u>	GNHWVF GG GTELT VLG GGGSD QPPQF SGAPR FLTR PLSYV SVG KDASL SSQI VGNPT PQVS WEKD QLPV TAGAR FRLA QDGD LYRL KILD LQLSDS GQYV SRAR NAIGE AFAC VGLEV GAEA (SEQ ID NO: 100)
BU5	Heavy chain of B0 (hole), and CH1 is substituted with T16	Light chain of B0, and CL is substituted with O.24	Heavy chain of U0 (knob)	Light chain of U0
	QVQL QQSGAEVKKPG SSRV SCKASGGTFNN NAIN WVRQAPGQGLE WMGG IIPMFGTAKYS QNFQ GRVAITADESTG TASME SSLRSEDTAV YYCAR SRDLLLFPHHA LSPW GRGTMVTVSSG GGGSG IPPKIECLPIDISI DEGK VLTVASAFTGEPT PEVT WSTGGRKIHSQE QGRF HIENDDLTTLIKD VQKQ DGGLYTLTLRNE FGSD SATVNIHIRSIDKT HTCP PCPAPEAAGGPSV FLFP KPKDTLMISRTPE VTCV VVDVSHEDPEVK FNWY VDGVEVHNAKT KPRE EQYNSTYRVVSVL TVLH QDWLNGKEYKC KVSN KALPAPIEKTISKA KGQ PREPQVCTLPSSRE EMTK NQVSLSCAVKGFY PSDI AVEWESNGQPENNY KTTP PVLDSDGSFFLVSK LTVD KSRWQQGNVFSCS VMHE ALHNHYTQKSLSL PGK (SEQ ID NO: 103)	SSELT QDPA VSVA LGGQTV RVTC QGDSL RSYY ASWY QKPK GQAP VLVI YGKNN RPSG IPDRFS GSSSG NTAS LTIT GAQAE DEAD YYCSS RDSS GNHW VFGG GTELT VLGG GSSG APRFL TRPLA FVVSV GKDA TLSS QIVGNP TPQV SWEKD KQPV TAGAR FRLA QDGL YRLK LDLQL SDSG QYVSR ARNA IGAEF ACLG LQVDA EA (SEQ ID NO: 104)	EVQL VQSGAEVKKPGESL KISCK GSGYSFTTYWLG WVRQ MPGKGLDWIGIMS PVDS DIRYSPSFQGV TM SVDK SITTAYLQWNSLKA SDTA MYCARRRPGQGY FDFW GQGLTVTVSSASTK GPSV FPLAPSSKSTSGGTAA LGCL VKDYFPEPVTVSWNS GALT SGVHTFPAVLQSSGL YSLSS VTVPSSSLGTQTYI CNVN HKPSNTKVDDKKVEP KSCD KTHTCPPCPAPEAAG GPSV FLFPPKPKDTLMISRT PEVT CVVVDVSHEDPEVKF NWYV DGVEVHNAKTKPR EEQY NSTYRVVSVLTVLH QDWL NGKEYKCKVSNKA LPAP IEKTISKAKGQPREPQ VYTL PPCREEMTKNQVSLWC LVKG FYPSDIAVEWESNGQP ENNY KTTPPVLDSDGSFFLY SKLT VDKSRWQQGNVFSCSV MHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 95)	DIQMT QSPS SLSA SVGDR VTIT CRASQ GISS WLAW YQQK PEKA PKSL IYAAS SLQS GVPSR FSGS GSGTD FTLT ISSLOP EDFA TYIC QQYNI YPYT FGQG TKLEI KRTVA APSV FIFPS DEQL KSGT ASVVC LLNN FYPRE AKVQ WKVD NALQ SGNSQ ESVTE QDSK DSTY LSSTL TLSK ADYEK HKVY ACEV THQG LSSPV TKSF NRGEC (SEQ ID NO: 96)

Note: In the sequence, the bold part is the variable region sequence, the single underlined part is CH1 or Titin-T chain, the dotted underlined part is CH2, the italicized part is CH3, and the double underlined part is CL or Obscurin-O chain.

Furthermore, an FA-1 bispecific antibody was constructed, which is an IgG-like bispecific antibody composed of a heavy chain (knob modification of Fc region) and a light chain of A0 antibody, and a heavy chain (hole modification of Fc region, substitution of CH1 with T.16) and a light chain (substitution of CL with O.24) of F0 antibody. The four-chain sequences of FA-1 are shown in Table 10 below:

Table 10. FA-1 bispecific antibody sequence listing

Name of diabody	Four-chain sequence of IgG-like bispecific antibody			
	Chain 1	Chain 2	Chain 3	Chain 4
FA-1	Heavy chain of F0 (hole), and CH1 is substituted with T.16	Light chain of F0, and CL is substituted with O.24	Heavy chain of A0 (knob)	Light chain of A0
	QVQLVQSGGGVVP PGT SLRLSCAASGFISSAM HWVRQAPGKGLEWVA VISYDGSNKYYVDSVKG RFTISRDNKNTLYLQM NSLRAEDTAVYYCARSA RLYASF <u>FDYW</u> <u>WGQ</u> <u>GALVT</u> <u>VSSGGGGSGIPPKIECLPID</u> <u>ISIDEGKVLTVASAFTGEP</u> <u>TPEVTWSTGGRKIHSQE</u> <u>Q</u> <u>GRFHIENTDDLTTLIKDV</u> <u>QKQDGGGLYTLTLRNEFGS</u> <u>DSATVNIHRSIDKTHTCP</u> <u>PCPAPEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCVVV</u> <u>DVSHEDPEVKFNWYVDG</u> <u>VEVHNAKTKPREEQYNS</u> <u>TYRVSVSLTVLHQDWLN</u> <u>GKEYKCKVSNKALPAPIE</u> <u>KTISKAKGQPREPQVCTLP</u> <u>PSREEMTKNQVSLSCAVKG</u> <u>FYP</u> <u>SDIAVEWESNGQ</u> <u>PENN</u> <u>YKTPVLDS</u> <u>DGSFFLVSKL</u> <u>TVDKSRWQQGNVFSCSV</u> <u>HEALHNHYTQKSLSLSPGK</u> (SEQ ID NO: 107)	DTVVTQEPSF SVSPGGTVTL TCGLSSGSVS TSHYPSWYQ QTPGQAPRM LIYNTNTRSS GVPDRFSGSIL GNKAALTITG AQADDES <u>DYY</u> CAIHVDRDIW VFGGGTKLT VLGGGGSSGA PRFLTRPLAFV VSVGKD <u>ATLS</u> <u>SQIVGNPTPQV</u> <u>SWEKDKQPVT</u> <u>AGARFRLAOD</u> <u>GDLYRLKILDL</u> <u>QLSDSGQYVS</u> <u>RARNAIGEAF</u> <u>ACLGLQVDAE</u> <u>A</u> (SEQ ID NO: 108)	EVQLVESGGGLVQPG GSLKLSCAASGFTFNK YAMNWVRQAPGKGL EWVARIRSKYNNYAT YYADSVKDRFTISRDD SKNTAYLQMN <u>LKTE</u> DTAVYYCVRHGNFGN EYISYWAYWGQ <u>GLTV</u> <u>TVSSASTKGPSVFPLAP</u> <u>SSKSTSGGTAALGCLV</u> <u>KDYFPEPVTVSWNSGA</u> <u>LTSGVHTFPAVLQSSGL</u> <u>YSLSSVTVPSSSLGTQ</u> <u>TYICNVNHKPSNTKVD</u> <u>KKVEPKSCDKTHTCPP</u> <u>CPAPEAAGGPSVFLFPP</u> <u>KPKDTLMISRTPEVTCV</u> <u>VVDVSHEDPEVKFNWY</u> <u>VDGVEVHNAKTKPREE</u> <u>QYNSTYRVVSVLTVLH</u> <u>QDWLNGKEYKCKVSN</u> <u>KALPAPIEKTISKAKGQ</u> <u>PREPQVYTLPPCREEMT</u> <u>KNQVSLWCLVKGFYPSD</u> <u>IAVEWESNGQ</u> <u>PENNYKT</u> <u>TPPVLDSDGSFFLYSKLT</u> <u>VDKSRWQQGNVFSCSV</u> <u>MHEALHNHYTQKSLSL</u> <u>PGK</u> (SEQ ID NO: 109)	QTVVTQEPS LTVSPGGTV TLTCGSSTG AVTSGNYP NWVQKPG QAPRGLIG GTKFLAPG TPARFSGSL LGGKAALT LSGVQPEDE AEYYCVLW YSNRWVFG GGTKLTVL RTVAAPSVFI FPPSDEQLKS GTASV <u>VCLL</u> <u>NNFYPREAK</u> <u>VQWKVDNA</u> <u>LQSGNSQES</u> <u>VTEQDSKDS</u> <u>TYSLSTLT</u> <u>SKADYEKH</u> <u>KVYACEVT</u> <u>HQGLSSPVT</u> <u>KSENRGEC</u> (SEQ ID NO: 110)

Note: In the sequence, the bold part is the variable region sequence, the single underlined part is CH1 or Titin-T chain, the dotted underlined part is CH2, the italicized part is CH3, and the double underlined part is CL or Obscurin-O chain.

5 II. Detection of bispecific antibodies

DI-1 was detected by using the method of Test Example 3 disclosed herein, and four chains of DI-1 were co-transfected into cells for expression and then subjected to mass spectrometry. The experimental results are shown in Table 11 and FIGs. 6A–6C, homodimers and mispaired molecules were undetectable in mass spectrometry results, and DI-1 was correctly assembled.

Table 11. DI-1 mass spectrometry data

DI-1 chain	Chain 1 (DI-1-H1)	Chain 2 (DI-1-L1)	Chain 3 (DI-1-H2)	Chain 4 (DI-1-L2)	DI-1-L1+DI-1-L2+DI-1-H1+DI-1-H2	MS results
Molecular weight	49983.82	23487.38	50450.05	22567.45	146488.70	Correct, homodimers and mispaired molecules

						undetectable
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In addition, BU5 expression was detected by using the methods of Test Example 3 and Test Example 2 disclosed herein. Firstly, the four chains of BU5 were co-transfected into cells for expression of the bispecific antibody, with B0 and U0 as controls. Then, the expressed product was subjected to purity and mass spectrometry analysis. The experimental results are shown in Table 12 and FIGs. 9A–9C, and the results show that the bispecific antibody BU5 was successfully expressed, and four chains of BU5 were successfully assembled into the target molecules without mispairing. In addition, the purity of the bispecific molecule BU5 was high, and the SEC% reached 88%.

Table 12. BU5 mass spectrometry results

Antibody	Mass spectrometry
Control B0	✓
Control U0	✓
BU5	✓

Note: In the table, "✓" indicates correct pairing.

In addition, the constructed BU1-BU4 bispecific antibody was detected for antibody purity and antigen binding activity by using the methods of Test Example 2 and Test Example 4 disclosed herein. The experimental results are shown in Table 13, and the results showed that the bispecific antibody with substituted CH1/CL still maintained good antigen binding activity and had high antibody purity.

Table 13. Experimental results of antigen binding activity and purity of bispecific antibody

Name of antibody	Purity of antibody SEC (%)	Antigen binding EC50 (nM)	
		Antigen BAFF	Antigen P40
B0	99.05	0.2193	-
U0	99.63	-	0.08881
BU1	95.23	0.3561	0.08397
BU2	91.09	0.4693	0.05674
BU3	83.45	0.4131	0.2238
BU4	91.85	0.5057	0.04429

Test Examples

Test Example 1: Method for Measuring Expression Level of Antibody

HEK293E cells were transfected with expression plasmids of monoclonal antibodies or bispecific antibodies, and after 6 days expression supernatants were collected and centrifuged at high speed to remove impurities. The supernatant was purified using Protein A column (GE Healthcare). The column was washed with PBS until the A280 reading dropped to a baseline, and the column was washed with 100 mM acetate buffer (pH 3.5) and neutralized with 1 M Tris-HCl, pH 8.0. The expression level of the antibody was quantified from the amount of the antibody/expression volume obtained by the final

purification.

Test Example 2: Method for Detecting Purity of Antibody

The purity of an antibody was monitored using SEC-HPLC. Detection was performed according to the instrument operating instructions using a Waters e2695 chromatograph, wherein Waters Xbridge BEH 200A SEC column was applied, PBS was taken as a mobile phase (pH was adjusted to 6.8 with dilute hydrochloric acid), 100 µg of protein was injected, and gradient elution was performed, with a flow rate of 0.5 mL/min. The purity of antibody was indicated as the percentage of the peak area of the main peak to the total peak area (SEC (%)).

Test Example 3: Method for Detecting Antibody by Mass Spectrometry

(I) Sample preparation:

1. Determination of complete molecular weight after deglycosylation: taking 30 µg of expressed antibody, adding 10 µL of 8 M Gua-HCl after freeze-drying, and performing water bath denaturation at 70 °C for 10 min; adding 90 µL of distilled water, taking 30 µL and adding 0.8 µL of PNG enzyme F (peptide N-glycosidase F), placing the resulting solution in a water bath at 37 °C for incubation for 2 h, and taking 0.5 µg for determination of complete molecular weight after deglycosylation.
2. Determination of molecular weight after deglycosylation and reduction: taking 30 µg of expressed antibody, adding 10 µL of 8 M Gua-HCl after freeze-drying, and performing water bath denaturation at 70 °C for 10 min; adding 90 µL of distilled water, taking 30 µL and adding 0.8 µL of PNG enzyme F (peptide N-glycosidase F), and placing in a water bath at 37 °C for incubation for 2 h; and then adding 2 µL of 0.025 M DTT, reducing for 10 min in a water bath at 70 °C, and taking 0.5 µg for determination of the molecular weight after deglycosylation and reduction.

(II) Chromatography-mass spectrometry conditions:

Chromatographic conditions are as follows:

Chromatographic column: Poroshell 300SB-C8 5 µm 2.1 × 75 mm

Mobile phase: A: 0.1% HCOOH/H₂O B: 0.1% HCOOH/CAN

Column temperature: 75 °C

Gradient:

Time (min)	0	5	8	12	12.1	15
B%	5	5	95	95	5	5

Mass spectrometry conditions are as follows:

Mass spectrum: Agilent 6530 Q-TOF LC-MS

Ionization mode ESI

Acquisition mode: 1 GHz (mass range: 500–5000 m/z)

Temperature of drying gas: 325 °C

Flow rate of drying gas: 10 L/min

Atomizer: 40 psi

Temperature of sheath gas: 350 °C

Flow rate of sheath gas: 12 L/min

Spray voltage: 500 V

Capillary voltage: 3500 V

5 Cleavage voltage: 200 V

Skimmer voltage: 65 V

Rf voltage: 7500 V

Mass spectrometry was performed on the antibody to be detected, and the experimental results showed that the antibody remained being correctly assembled after CH1/CL was substituted with Titin-T/Obscurin-O.

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Test Example 4: Method for Detecting Antibody Binding Activity

The binding activity of an antibody against a membrane protein target to an antigen may be detected using FACS. For example, C0, N0, F0, V0 and S0 and CH1/CL domain engineered antibodies thereof may be detected using FACS method. FACS buffer (98% PBS, 2% FBS) resuspended cells (2×10^6 cells/mL, 90 μ L) were added to a 96-well U-shaped bottom plate (Corning, 3795), and 10 μ L of gradiently-diluted antibody was added; the reaction mixture was incubated at 4 °C for 1 h, washed 2 times with an FACS buffer, then added with Alexa Fluor 488 goat anti-human IgG (H + L) (Invitrogen, Cat # 2015982, 1:1000 dilution) per well, incubated at 4 °C for 1 h and then washed 2 times, cells were resuspended with an FACS buffer, and finally fluorescence signal values were read using FACS CantoII (BD). Finally, the data were processed and analyzed using FlowJo 7.6 and Graphpad Prism 5.

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For antibodies targeting soluble proteins, the binding activity of the antibodies to the soluble proteins was measured using ELISA, for example, D0, I0, B0, U0, H0, R0 and J0 and CH1/CL domain-engineered antibodies thereof may be measured using ELISA. The method comprises the following steps: diluting the protein to 1 μ g/mL with a PBS (Basalmedia, B320) buffer (pH 7.4), adding the resulting solution to a 96-well microplate (Corning, 9018) at a volume of 100 μ L/well, and incubating at 4 °C overnight; after the solution was discarded, adding 300 μ L of 5% skim milk (BD, 232100) diluted with PBS to each well for blocking, and incubating at 37 °C for 2 h; after blocking was completed, discarding the blocking solution, and after the plate was washed 3 times with a PBST buffer (pH 7.4, PBS containing 0.1% tween-20), adding 100 μ L of gradiently-diluted antibody solution to each well and incubating at 37 °C for 1 h; after the incubation was completed, washing the plate 3 times with PBST, adding 100 μ L of mouse anti-human IgG (H + L) (Jackson ImmunoResearch, 209-035-088, 1:8000 dilution) to each well, and incubating at 37 °C for 1 h; and after the plate was washed 3 times with PBST, adding 100 μ L of TMB chromogenic substrate (KPL, 5120-0077) to each well and incubating at room temperature for 10–15 min, adding 50 μ L of 1 M H₂SO₄ to stop the reaction, reading absorption values at 450 nm using a microplate reader, and fitting a binding curve of antibodies to antigens using software to calculate EC₅₀ values.

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The antigens corresponding to the antibodies in this test example are as follows: the antigen binding to D0 and a CH1/CL domain-engineered antibody thereof was hRANKL (available from Sino biological, 11682-HNCH); the antigen binding to I0 and a CH1/CL domain-engineered antibody thereof was hNGF (available from Sino biological, 11050-HNAC); the antigen binding to B0 and a CH1/CL domain-engineered antibody thereof was hBAFF (available from Sino biological, 10056-HNCH); the antigen binding to U0 and a CH1/CL domain-engineered antibody thereof was hP40 (available from Sino biological, 10052-H08H); the antigen binding to H0 and R0 and CH1/CL domain-engineered antibodies thereof was hIL-5 (available from R&D systems, 205-IL-025/CF); the antigen binding to J0 and a CH1/CL domain-engineered antibody thereof was hTSLP (available from Sino biological, 16135-H08H); the antigen binding to C0 and N0 and CH1/CL domain-engineered antibodies thereof was CEA (overexpression in CEA cells MKN45 (available from Nanjing Cobioer, CBP60488)); the antigen binding to F0, V0 and S0 and CH1/CL domain-engineered antibodies thereof was B7H3 (overexpression in B7H3 recombinant cell lines CT26-B7H3 (CT26 was derived from the Chinese Academy of Cell Bank, and the sequence of B7H3 is shown in ID: XP_005254757.1)).

Test Example 5: Experimental Method for Mispairing Reduction in CH1/CL Domain Engineered Antibody

I. Detection method for expression of light/heavy chain cross-mispaird molecules of different antibodies

The experiment verified that CH1/CL could effectively reduce the heavy/light chain mispairing after being substituted with a Titin-T chain/Obseurin-O chain or a Titin-T chain/Obseurin-like-O chain through analysis of the paired expression of different light/heavy chain antibodies. Specifically, when the transfected cells expressed the antibodies, heavy/light chains of D0 and I0 were respectively exchanged (i.e., I/D-1 (heavy chain of D0 + light chain of I0); I/D-2 (heavy chain of I0 + light chain of D0)) was to detect whether cross-mispaird molecules would be formed in wild-type CH1 and CL; meanwhile, heavy and light chains of antibody D3 (heavy chain CH1 of D0 was substituted with T.11, light chain CL was substituted with O.21) and antibody I3 (heavy chain CH1 of I0 was substituted with T.11, and light chain CL was substituted with O.21) were respectively exchanged after CH1/CL of D0 and I0 was substituted with the Titin-T chain/Obseurin-O chain, and the mispaird molecules I/D-3 (heavy chain of D0 + light chain of I3), I/D-4 (heavy chain of D3 + light chain of I0), I/D-5 (heavy chain of I0 + light chain of I3) and I/D-6 (heavy chain of I3 + light chain of D0) were constructed; the schematic structural diagrams of the constructed antibodies are shown in FIG. 7.

The expression level of the antibodies was measured by using the method of Test Example 1, and whether the mispaird molecules would be formed was determined by mass spectrometry of the expression product by using the method of Test Example 3. The experimental results are shown in Table 14, and the experimental results showed that when the heavy chain of D0 + the light chain of I0 or the heavy chain of I0 + the light

chain of D0 were co-expressed, complete IgG molecules (150 kDa) could be formed, with high expression levels of 74.4 mg/L and 73.8 mg/L respectively; and LC-MS results showed that the obtained proteins were mismatched IgG molecules, which indicated that if CH1-CL was not engineered or replaced, a large amount of light/heavy chain mispaired molecules could be formed when four different heavy and light chains of the bispecific antibody were co-expressed. After CH1/CL was substituted with a Titin-T chain/Obsecurin-O chain, no target molecules (150 kDa) were generated in four forms of I/D-3 (heavy chain of D0 + light chain of I3), I/D-4 (heavy chain of D3 + light chain of I0), I/D-5 (heavy chain of I0 + light chain of I3) and I/D-6 (heavy chain of I3 + light chain of D0) through cross-mispairing expression, and no mispaired molecules were generated in the other three forms except that a small amount of error molecules (the molecular weight was 100 kDa) of two heavy chains were formed by the combination of the heavy chain of D3 and the light chain of I0, which indicated that the non-homologous pairing after modification cannot form mispaired molecules in an IgG structural form. Thus, substitution of CH1-CL with a Titin-T chain/Obsecurin-O chain effectively avoids or reduces the formation of non-homologous cross-pairing molecules between the light/heavy chains of IgG-like bispecific antibodies.

Table 14. Expression level of antibodies with different cross-paired light/heavy chains and mass spectrometry analysis

Name of mispairing	Heavy chain	Light chain	Expression level of antibody (mg/L)	Mass spectrometry
I/D-1	Heavy chain of D0	Light chain of I0	74.4	√
I/D-2	Heavy chain of I0	Light chain of D0	73.8	√
I/D-3	Heavy chain of D0	Light chain of I3	0.04	×
I/D-4	Heavy chain of D3	Light chain of I0	12.75	Only heavy chain, without light chain
I/D-5	Heavy chain of I0	Light chain of D3	0.04	×
I/D-6	Heavy chain of I3	Light chain of D0	0.25	×

Note: In the table, "√" indicates that the mispaired molecule was detected, and "×" indicates that the mispaired molecule was undetectable.

II. Detection method for expression of mispaired light/heavy chains of bispecific antibodies

To verify that there was no mispairing or mispairing reduction in CH1/CL which had been substituted with the Titin-T chain/Obsecurin-O chain, the test example designed three forms of light/heavy chain cross-pairing expression, namely, two different heavy chains and one identical VL-CL light chain for bispecific antibody expression, or two different heavy chains and one identical light chain with CL substituted with the Obsecurin-O chain for expression, or two different heavy chains and two different light chains for normal expression as control (see Table 15 for specific pairings).

The expression product was then subjected to mass spectrometry (for the method, see Test Example 3 disclosed herein) and the antibody purity SEC was detected (for the method, see Test Example 2 disclosed herein). The experimental results are shown in Table 15, and the results showed that the correct molecules were formed when the light chain substituted with the Obscurin-O chain and the light chain not substituted with CL were added together, and the correct target molecules were not found in the cross-pairing when only one light chain not substituted with CL was added or only one light chain with CL substituted with the Obscurin-O chain was added. This indicates that the light chain with CL substituted with the Obscurin-O chain could be more easily bound to the heavy chain with CH1 substituted with the Titin-T chain to form a molecule, but would not cross-mispaired with the heavy chain with CH1 not substituted with the Titin-T chain; the light chain with CL not substituted with the Obscurin-O chain was more easily bound to the heavy chain with CH1 not substituted with the Titin-T chain, but would not bound to the heavy chain with CH1 substituted with the Titin-T chain.

Table 15. Detection results of light/heavy chain mispairing of bispecific antibodies

Name of mispairing	First heavy chain (B-H1)	Second heavy chain (B-H2)	First light chain (B-L1)	Second light chain (B-L2)	Mass spectrometry				Purity of antibody SEC (%)	Expression level of antibody (mg/L)
					B-H1 B-H2 B-L1 B-L2	B-H1 B-H2 B-L1 B-L2	B-H1 B-H2 B-L1 B-L2	B-H1 B-H2 B-L1 B-L2		
B/U-1	Chain formed by substitution of CH1 of heavy chain of B0 with T11 (with hole modification)	Heavy chain of U0 (with knob modification)	Chain formed by substitution of CL of light chain of B0 with O.21	Light chain of U0	✓	--	--	--	91	25.6
B/U-2	Heavy chain of B0 (with hole modification)	Heavy chain of U0 (with knob modification)	Chain formed by substitution of CL of light chain of B0 with O.21	Chain formed by substitution of CL of light chain of B0 with O.21	--	--	--	--	--	0.5
B/U-3	Chain formed by substitution of CH1 of heavy chain of B0 with T11 (with hole modification)	Heavy chain of U0 (with knob modification)	Light chain of U0	Light chain of U0	--	--	--	✓	33	15.6

Note: In the table, "✓" indicates that the four-chain-paired molecule was detected, and "--" indicates that the four-chain-paired molecule was undetectable.

Test Example 6: Detection of Affinity of Bispecific Antibody to Antigen

The affinity of the antibody to be detected to the antigen protein was determined by using Biacore T200 (GE) instrument. According to the method in the specification of a human anti-capture kit (GE, Cat # BR-1008-39), a Protein A biosensor chip (Cat # 29127556, GE) was used for affinity capture of an antibody to be detected, then soluble antigens with a series of concentration gradients flowed through the surface of the chip, and a

Biacore T200 instrument was used for real-time detection of reaction signals, so that a binding-dissociation curve was obtained. After dissociation was completed for each cycle, the biosensor chip was washed with a glycine-hydrochloric acid regeneration solution (pH 1.5, Cat # BR-1003-54, GE). The data obtained from the experiment were fitted to the data using BIAevaluation version 4.1, GE software using a (1:1) Langmuir model to obtain affinity values, and the experimental results are shown in Table 16.

The experimental results indicate that the domain engineered bispecific antibody disclosed herein fully retained the affinity of the two parent monoclonal antibodies to antigens thereof. In this experiment, included were antigens hRANKL (available from Sino biological, 11682-HNCH), hNGF (available from Sino biological, 11050-HNAC), hBAFF (available from Sino biological, 10056-HNCH), hP40 (available from Sino biological, 10052-H08H), hB7H3 (prepared in the laboratory, for the sequence, see SEQ ID NO: 111), and hCD3 (prepared in the laboratory, a heterodimer consisting of the δ subunit (for the sequence, see SEQ ID NO: 112) and the ϵ subunit (for the sequence, see SEQ ID NO: 113) of hCD3).

Table 16. Detection results of affinity of bispecific antibody

Antibody	Antigen	ka (1/Ms)	kd (1/s)	KD (M)
B0	hBAFF	1.77E+05	1.52E-04	8.55E-10
U0	hP40	1.44E+06	1.14E-04	7.93E-11
BU5	hBAFF	1.94E+05	7.62E-05	3.93E-10
	hP40	1.54E+06	1.02E-04	6.64E-11
BU1	hBAFF	3.38E+05	1.69E-04	4.99E-10
	hP40	1.38E+06	4.81E-05	3.49E-11
D0	hRANKL	2.36E+04	2.10E-04	8.89E-09
I0	hNGF	1.92E+06	1.19E-04	6.21E-11
DI-1	hRANKL	3.05E+04	9.36E-05	3.06E-09
	hNGF	2.56E+06	8.95E-05	3.50E-11
A0	hCD3	8.01E+04	4.92E-03	6.14E-08
F0	hB7H3	1.57E+05	2.06E-03	1.31E-08
FA-1	hCD3	7.06E+04	4.25E-03	6.02E-08
	hB7H3	1.58E+05	7.12E-03	4.50E-08

Test Example 7: Experiment for Simultaneous Binding of CH1-CL Domain-Engineered Diabodies to Two Target Antigens

The CH1-CL domain-engineered bispecific antibodies disclosed herein were verified to bind to two target antigens simultaneously by determining the affinity of the antibody to be detected to the antigenic protein using a Biacore T200 (GE) instrument. The specific experimental steps were as follows: the antibody BU5 was affinity-captured by using a Protein A biosensor chip (Cat # 29127556, GE), then the first antigen molecule hP40 (available from Sino biological, 10052-H08H) of the bispecific antibody flowed through the surface of the chip to reach saturation, and then a second antigen molecule hBAFF (available from Sino biological, 10056-HNCH) was injected at a certain concentration, and reaction signals were detected in real time by using a Biacore T200 instrument to

obtain a binding-dissociation curve. After dissociation was completed for each cycle, the biosensor chip was washed with a glycine-hydrochloric acid regeneration solution (pH 1.5, Cat # BR-1003-54, GE), and the data fitting model was obtained using BIAevaluation version 4.1, GE software using a (1:1) Langmuir model. Then, the antibody BU5 was affinity-captured by using a Protein A biosensor chip (Cat # 29127556, GE), the first antigen molecule hP40 (available from Sino biological, 10052-H08H) of the bispecific antibody flowed through the surface of the chip to reach saturation, a second antigen molecule hBAFF (available from Sino biological, 10056-HNCH) was then injected at a certain concentration, and the reaction signal was detected in real time by using a Biacore T200 instrument to obtain a binding-dissociation curve. After dissociation was completed for each cycle, the biosensor chip was washed with a glycine-hydrochloric acid regeneration solution (pH 1.5, Cat # BR-1003-54, GE), and the data fitting model was obtained using BIAevaluation version 4.1, GE software using a (1:1) Langmuir model. The experimental results are shown in Table 17, and the results showed that the bispecific antibody BU5 could continue to bind to the antigen hBAFF after binding to the antigen hP40 to reach saturation, and had the ability of rebinding to hBAFF comparable to the monoclonal antibody B0. Similarly, the bispecific antibody BU5 could continue to bind to the antigen hP40 after binding to the antigen hBAFF to reach saturation, and had the ability of rebinding to hP40 comparable to U0. This indicates that the bispecific antibody disclosed herein with CH1/CL substituted with a Titin-T chain/Obscurin-O chain had a dual-target feature and could bind to two target antigens simultaneously.

Table 17. Detection results of affinity of antibodies

Antibody	Antigen flowed through chip surface	Affinity detection data			
		Antigen	ka (1/Ms)	kd (1/s)	KD (M)
Bmab	hBAFF	hBAFF	1.77E+05	1.53E-04	8.64E-10
Umab	hP40	hP40	1.59E+06	1.09E-04	6.89E-11
BU5	Injecting hBAFF for binding to reach saturation, reinjecting hP40 antigen	hP40	1.57E+06	1.04E-04	6.61E-11
	Injecting hP40 for binding to reach saturation, reinjecting hBAFF antigen	hBAFF	1.57E+05	8.44E-05	5.37E-10

Test Example 8: Experiment of Osteoclast Differentiation of DI-1 Bispecific Antibody

Raw264.7 cells (the Chinese Academy of Cell Bank, SCSP-5036) were digested and counted in resuspension, plated in a 24-well cell culture plate (Corning, 3524) and cultured overnight in a cell incubator at 37 °C. The next day, the antibody solution was diluted to different concentrations and mixed homogeneously with RANKL (Sino biological, 11682-HNCH) in the cell culture plate to a final concentration of 50 ng/mL, and the cells were incubated at 37 °C. After 96 h, the solution in the 24-well plate was removed, 100 µL of cell lysate (Beyotime, P0013J) was added to each well, the mixture was pipetted and mixed homogeneously, the lysate was transferred to an EP tube and

centrifuged at 12000 g for 5 min, the supernatant was taken and measured using an anti-tartaric acid phosphatase test kit (Beyotime, P0332) according to the method described in the specification, and the absorption values at 405 nm were read using a microplate reader. The measured values were fitted to a curve by using software, and the IC₅₀ values were calculated. The experimental results are shown in FIG. 10, and the experimental results showed that the bispecific antibody DI-1 with substituted CH1/CL maintained good activity and effectively inhibited osteoclast differentiation.

Test Example 9: Experiment of TF1 Cell Proliferation of DI-1 Bispecific Antibody

The activity of the antibody at the cellular level was assessed in an NGF-induced TF-1 cell (ATCC, CRL-2003) proliferation experiment. The experimental method was as follows: TF1 cells were digested and collected, resuspended, then counted, plated in a 96-well plate (Corning, 3903), and incubated overnight in an incubator at 37 °C. The next day, the antibody solution was diluted to different concentrations and mixed homogeneously with NGF (Sino biological, 11050-HNAC) and added to the cell culture plate to a final concentration of 10 ng/mL, and the cells were incubated in the incubator. After 72 h, the cell culture plate was removed, 50 μL of Cell-titer Glo (Promega, G755B) assay solution was added to each well, the reaction solution was incubated on a shaker for 10 min and allowed to stand at room temperature for 10 min. Luminescence signals were detected using a microplate reader (PerkinElmer, Victor 3). The detected signal values were fitted to a graph using software, and the IC₅₀ values were calculated. The experimental results are shown in FIG. 11, and the results showed that the bispecific antibody DI-1 with substituted CH1/CL had good activity.

Test Example 10: Detection of Light and Heavy Chain Mispairing of Bispecific Antibody with CH1/CL Substituted with Different Domains

The following experiments were performed to analyze the light and heavy chain mispairing of bispecific antibodies with CH1/CL substituted with a Titin-T chain/Obseurin-O chain or with TCRα/TCRβ, and the specific experiments were as follows:

I. Experiment of light and heavy chain mispairing during co-expression of four chains of bispecific antibody

Bispecific antibodies HJ-1 and HJ-2 each consisting of four chains were constructed by substituting CH1/CL of H0 or J1 with TCRα/TCRβ, and bispecific antibodies HJ-3 and HJ-4 each consisting of four chains were constructed by substituting CH1/CL of H0 or J1 with the Titin-T chain/Obseurin-O chain; the schematic structural diagrams of the bispecific antibodies are shown in FIG. 12, and the full-length sequences of the bispecific antibodies are shown in Table 18:

Table 18. Bispecific antibody sequence listing

Name of diabody	Four-chain sequence of IgG-like bispecific antibody			
	Chain 1	Chain 3	Chain 2	Chain 4

HJ-1	Heavy chain of H0 (knob), and CH1 is substituted with TCR β	Light chain of H0, and CL is substituted with TCR α	Heavy chain of J1 (hole)	Light chain of J1
	HJ-1-H1: <u>EVQLVESGGGLVQPG</u> <u>GSLRLSCAASGFTFSH</u> <u>YYMAWVRQAPGKGL</u> <u>EWVTSISYEGDITYYG</u> <u>DSVKGRTISRDNSEN</u> <u>TLYLQMNSLRRAEDTA</u> <u>TYYCASQTLRESFDY</u> <u>WGQGTLLTVSSLEDL</u> <u>KNVFPPEVAVFEPSEA</u> <u>EISHTQKATLVCLATG</u> <u>FYPDHVELSWWVNG</u> <u>KEVHSGVCTDPQPLK</u> <u>EQPALQDSRYALSSRL</u> <u>RVSATFWQNP RNHFR</u> <u>CQVQFYGLSENDEWT</u> <u>QDRAKPVTQIVSAEA</u> <u>WGRASDKTHTCPPCP</u> <u>APEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCV</u> <u>VVDVSHEDPEVKFNW</u> <u>YVDGVEVHNAKTKPR</u> <u>EEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKC</u> <u>KVSNKALPAPIEKTISK</u> <u>AKGQPREPQVYTLPPC</u> <u>REEMTKNQVSLWCLV</u> <u>KGFPYSDIAVEWESNG</u> <u>QPENNYKTTTPVLDSD</u> <u>GSFFLYSKLTVDKSR</u> <u>WQOGNVFSCVMHE</u> <u>ALHNHYTQKSLSLSPG</u> <u>KHHHHHH</u> (SEQ ID NO: 114)	HJ-1-L1: <u>DIQMTQSPSSVS</u> <u>ASVGDRVTITCR</u> <u>ASQDIANYLSW</u> <u>YQOKPGKSPKL</u> <u>LIYGTSNLEVGV</u> <u>PSRFGSRSGTD</u> <u>FTLTISLQPEDF</u> <u>ATYYCLQDKEF</u> <u>PRTFGGGTKVEI</u> <u>KKPDIQNPDP</u> <u>YQLRDSKSSDKS</u> <u>VCLFTDFDSQTQ</u> <u>VSQKSDSDVYIT</u> <u>DKCVLDMRSM</u> <u>DFKSNSAVAWS</u> <u>QKSDFACANAF</u> <u>QNSIIPEDTFFPS</u> PESS (SEQ ID NO: 115)	HJ-1-H2: <u>EVQLVQSGAEVKKPGS</u> <u>SVKVSCKASGYTFSNY</u> <u>LIEWVRQAPGQGLEWI</u> <u>GVIDPGVGDITNYNENF</u> <u>KGRATLTADKSTSTAYI</u> <u>ELSSLRSEDTAVYYCAR</u> <u>EDNTGTAFDYWGQGT</u> <u>ITVSSASTKGPSVFPLA</u> <u>PSSKSTSGGTAALGCLV</u> <u>KDYFPEPVTVSWNSGA</u> <u>LTSGVHTFPAVLQSSGL</u> <u>YSLSSVVTVPSSSLGTQ</u> <u>TYICNVNHKPSNTKVD</u> <u>KKVEPKSCDKTHTCPPC</u> <u>PAPEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCV</u> <u>VDVSHEDPEVKFNWYV</u> <u>DGVEVHNAKTKPREEQ</u> <u>YNSTYRVVSVLTVLHQ</u> <u>DWLNGKEYKCKVSNK</u> <u>ALPAPIEKTISKAKGQP</u> <u>REPQVCTLPPSREEMTK</u> <u>NQVSLSCAVKGFYPSDI</u> <u>AVEWESNGQPENNYKT</u> <u>TPPVLDSDGSFFLVSKL</u> <u>TVDKSRWQQGNVFSCS</u> <u>VMHEALHNHYTQKSLS</u> <u>LSPGKDYKDDDDK</u> (SEQ ID NO: 116)	HJ-1-L2: <u>SIVMTQTPLS</u> <u>LSVTPGQPA</u> <u>SISCKASQSV</u> <u>SSDVTWYLO</u> <u>KPGQSPQLLI</u> <u>YYVSEHYTG</u> <u>VPDRFSGSG</u> <u>YGTDFTLKIS</u> <u>RVEAEDVG</u> <u>VYYCQQHH</u> <u>RFPLTFGQG</u> <u>TKLEIKRTV</u> <u>AAPSVFIFPP</u> <u>SDEQLKSGT</u> <u>ASVVCLLNN</u> <u>FYPREAKVQ</u> <u>WKVDNALQ</u> <u>SGNSQESVT</u> <u>EQDSKDSY</u> <u>LSSTLTLSK</u> <u>ADYEKHKV</u> <u>YACEVTHQ</u> <u>GLSSPVTKSF</u> <u>NRGEC</u> (SEQ ID NO: 117)
HJ-2	Heavy chain of H0 (hole)	Light chain of H0	Heavy chain of J1 (knob), and CH1 is substituted with TCR β	Light chain of J1, and CL is substituted with TCR α
	HJ-2-H1: <u>EVQLVESGGGLVQPG</u> <u>GSLRLSCAASGFTFSH</u> <u>YYMAWVRQAPGKGL</u> <u>EWVTSISYEGDITYYG</u> <u>DSVKGRTISRDNSEN</u> <u>TLYLQMNSLRRAEDTA</u> <u>TYYCASQTLRESFDY</u> <u>WGQGTLLTVSSASTK</u> <u>GPSVFPLAPSSKSTSG</u> <u>GTAALGCLVKDYFPE</u> <u>PVTVSWNSGALTSGV</u> <u>HTFPAVLQSSGLYSLS</u> <u>SVVTVPSSSLGTQTYI</u> <u>CNVNHKPSNTKVDKK</u> <u>VEPKSCDKTHTCPPCP</u> <u>APEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCV</u>	HJ-2-L1: <u>DIQMTQSPSSVS</u> <u>ASVGDRVTITCR</u> <u>ASQDIANYLSW</u> <u>YQOKPGKSPKL</u> <u>LIYGTSNLEVGV</u> <u>PSRFGSRSGTD</u> <u>FTLTISLQPEDF</u> <u>ATYYCLQDKEF</u> <u>PRTFGGGTKVEI</u> <u>KRTVAAPS</u> <u>PPSDEQLKSGTA</u> <u>SVVCLLNNFYPR</u> <u>EAKVQWKVDN</u> <u>ALQSGNSQESVT</u> <u>EQDSKDSYLS</u> <u>STLTLSKADYEK</u> <u>HKVYACEVTHQ</u>	HJ-2-H2: <u>EVQLVQSGAEVKKPGS</u> <u>SVKVSCKASGYTFSNY</u> <u>LIEWVRQAPGQGLEWI</u> <u>GVIDPGVGDITNYNENF</u> <u>KGRATLTADKSTSTAYI</u> <u>ELSSLRSEDTAVYYCAR</u> <u>EDNTGTAFDYWGQGT</u> <u>ITVSSLEDLKNVFPPE</u> <u>VAVFEPSEAEISHTQK</u> <u>ATLVCLATGFYPDHV</u> <u>ELSWWVNGKEVHSGV</u> <u>CTDPQPLKEQPALQDS</u> <u>RYALSSRLRVSATFWQ</u> <u>NPRNHFR</u> <u>SENDEWTQDRAPVT</u> <u>QIVSAEAWGRASDKTH</u> <u>TCPPCPAPEAAGGPSVF</u>	HJ-2-L2: <u>SIVMTQTPLS</u> <u>LSVTPGQPA</u> <u>SISCKASQSV</u> <u>SSDVTWYLO</u> <u>KPGQSPQLLI</u> <u>YYVSEHYTG</u> <u>VPDRFSGSG</u> <u>YGTDFTLKIS</u> <u>RVEAEDVG</u> <u>VYYCQQHH</u> <u>RFPLTFGQG</u> <u>TKLEIKKPD</u> <u>QNPDP</u> <u>QRLRDSKSSD</u> <u>KSVCLFTDF</u> <u>DSQTQVSQS</u> <u>KDS</u> <u>SDVYITD</u>

	<u>VVDVSHEDPEVKFNW</u> <u>YVDGVEVHNAKTKPR</u> <u>EEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKC</u> <u>KVSNKALPAPIEKTISK</u> <u>AKGQPREPQVCTLPPS</u> <u>REEMTKNQVSLSCAV</u> <u>KGFYPSDIAVEWESNG</u> <u>QPENNYKTTPPVLDSD</u> <u>GSFFLVSKLTVDKSR</u> <u>WQQGNVFSCSVMHE</u> <u>ALHNHYTQKSLSLSPG</u> <u>KDYKDDDDK (SEQ ID</u> <u>NO: 118)</u>	<u>GLSSPVTKSFNR</u> <u>GEC (SEQ ID NO:</u> <u>119)</u>	<u>LFPPKPKDTLMISRTPE</u> <u>VTCVVVDVSHEDPEVK</u> <u>FNWYVDGVEVHNAKT</u> <u>KPREEQYNSTYRVVSV</u> <u>LTVLHQDWLNGKEYK</u> <u>CKVSNKALPAPIEKTIS</u> <u>KAKGQPREPQVYTLPP</u> <u>CREEMTKNQVSLWCLV</u> <u>KGFYPSDIAVEWESNG</u> <u>QPENNYKTTPPVLDSD</u> <u>GSFFLVSKLTVDKSRW</u> <u>QQQNVFSCSVMHEALH</u> <u>NHYTQKSLSLSPGKHH</u> <u>HHHH (SEQ ID NO: 120)</u>	KCVLDMRS MDFKSNSA VAWSQKSD FACANAFQ NSIIPEDTFF PSPESS (SEQ ID NO: 121)
HJ-3	Heavy chain of H0 (knob), and CH1 is substituted with T.11	Light chain of H0, and CL is substituted with O.21	Heavy chain of J1 (hole)	Light chain of J1
	HJ-3-H1: <u>EVQLVESGGGLVQPG</u> <u>GSLRLSCAASGFTFSH</u> <u>YYMAWVRQAPGKGL</u> <u>EWVTSISYEGDITYYG</u> <u>DSVKGRFTISRDN SKN</u> <u>TLYLQMNSLR AEDTA</u> <u>TTYCASQTLRESFDY</u> <u>WGQGT LTVVSSGGG</u> GSGIPPKIECLPIDISI DEGKVLTVASAFTGE PTPEVTWSTGGRKIH SQEQGRFHIENTDDL TTLIKDVQKQDGGL YTLTLRNEFGSDSAT VNIHIRSIDKTHTCPPC PAPEAAGGPSVFLFPP KPKDTLMISRTPEVTC VVDVSHEDPEVKFN WYVDGVEVHNAKTK PREEQYNSTYRVVSVL TVLHQDWLNGKEYK CKVSNKALPAPIEKTIS KAKGQPREPQVYTLPP CREEMTKNQVSLWCL VKGFYPSDIAVEWESN GQPENNYKTTPPVLD DGSFFLVSKLTVDKSR WQQGNVFSCSVMHE ALHNHYTQKSLSLSPG KHHHHHH (SEQ ID NO: 122)	HJ-3-L1: <u>DIQMTQSPSSVS</u> <u>ASVGDRVTITCR</u> <u>ASQDIANYLSW</u> <u>YQQKPGKSPKL</u> <u>LIYGTSNLEVGV</u> <u>PSRFSGSRSGTD</u> <u>FTLTISSLQPEDF</u> <u>ATYYCLODKEF</u> <u>PRTFGGGTKVEI</u> KGGGGSSGAPR FLTRPLAFVVS VGKDATLSSQI VGNPTPQVSWE KDKQPVTAGA RFRLAQDGDLY RLKILDQLSD SGQYVSRARNA IGEAFACLGLQ VDAEA (SEQ ID NO: 123)	HJ-3-H2: <u>EVQLVQSGAEVKKPGS</u> <u>SVKVSCKASGYTFSNY</u> <u>LIEWVRQAPGQGLEWI</u> <u>GVIDPGVGD TNYNENF</u> <u>KGRATLTADKSTSTAYI</u> <u>ELSSLRSEDTAVYYCAR</u> <u>EDNTGTAFDYWGQGT</u> <u>VTVSSASTKGPSVFPLA</u> <u>PSSKSTSGGTAALGCLV</u> <u>KDYFPEPVT VSWNSGA</u> <u>LTSGVHTFPAVLQSSGL</u> <u>YSLSSVTVPSSSLGTQ</u> <u>TYICNVNHKPSNTKVD</u> <u>KKVEPKSCDKTHTCPPC</u> <u>PAPEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCVV</u> <u>VDVSHEDPEVKFNWYV</u> <u>DGVEVHNAKTKPREEQ</u> <u>YNSTYRVVSVLTVLHQ</u> <u>DWLNGKEYKCKVSNK</u> <u>ALPAPIEKTISKAKGQP</u> <u>REPQVCTLPPSREEMTK</u> <u>NQVSLSCAVKGFYPSDI</u> <u>AVEWESNGQPENNYKT</u> <u>TPPVLDSDGSFFLVSKL</u> <u>TVDKSRWQQGNVFSCS</u> <u>VMHEALHNHYTQKSLS</u> <u>LSPGKDYKDDDDK (SE</u> <u>Q ID NO: 116)</u>	HJ-3-L2: <u>SIVMTQTPLS</u> <u>LSVTPGQPA</u> <u>SISCKASQSV</u> <u>SSDVTWYLQ</u> <u>KPGQSPQLLI</u> <u>YYVSEHYTG</u> <u>VPDRFSGSG</u> <u>YGTDFTLKIS</u> <u>RVEAEDVG</u> <u>VYYCQQHH</u> <u>RFPLTFGQG</u> <u>TKLEIKRTV</u> <u>AAPSVFIFPP</u> <u>SDEQLKSGT</u> <u>ASVVCLLNN</u> <u>FYPREAKVQ</u> <u>WKVDNALQ</u> <u>SGNSQESVT</u> <u>EQDSKDSTY</u> <u>SLSSTLTLSK</u> <u>ADYEKHKV</u> <u>YACEVTHQ</u> <u>GLSSPVTKSF</u> <u>NRGEC (SEQ</u> <u>ID NO: 117)</u>
HJ-4	Heavy chain of H0 (hole)	Light chain of H0	Heavy chain of J1 (knob), and CH1 is substituted with T.11	Light chain of J1, and CL is substituted with O.21
	HJ-4-H1: <u>EVQLVESGGGLVQPG</u> <u>GSLRLSCAASGFTFSH</u> <u>YYMAWVRQAPGKGL</u> <u>EWVTSISYEGDITYYG</u> <u>DSVKGRFTISRDN SKN</u>	HJ-4-L1: <u>DIQMTQSPSSVS</u> <u>ASVGDRVTITCR</u> <u>ASQDIANYLSW</u> <u>YQQKPGKSPKL</u> <u>LIYGTSNLEVGV</u>	HJ-4-H2: <u>EVQLVQSGAEVKKPGS</u> <u>SVKVSCKASGYTFSNY</u> <u>LIEWVRQAPGQGLEWI</u> <u>GVIDPGVGD TNYNENF</u> <u>KGRATLTADKSTSTAYI</u>	HJ-4-L2: <u>SIVMTQTPLS</u> <u>LSVTPGQPA</u> <u>SISCKASQSV</u> <u>SSDVTWYLQ</u> <u>KPGQSPQLLI</u>

<u>TLYLQMNSLRAEDTA</u> <u>TYYCASQTLRESFDY</u> <u>WGQGTTLTVSSASTK</u> <u>GPSVFPLAPSSKSTSG</u> <u>GTAALGCLVKDYFPE</u> <u>PVTVSWNSGALTSGV</u> <u>HTFPAVLQSSGLYSLS</u> <u>SVVTVPSSSLGTQTYI</u> <u>CNVNHKPSNTKVDKK</u> <u>VEPKSCDKTHTCPPCP</u> <u>APEAAGGPSVFLFPPK</u> <u>PKDTLMISRTPEVTCV</u> <u>VVDVSHEDPEVKFNW</u> <u>YVDGVEVHNAKTKPR</u> <u>EEQYNSTYRVVSVLT</u> <u>VLHQDWLNGKEYKC</u> <u>KVSNKALPAIEKTISK</u> <u>AKGQPREPQVCTLPSP</u> <u>REEMTKNQVSLSCAV</u> <u>KGFYPSPDIAVEWESNG</u> <u>QPENNYKTTTPVLDS</u> <u>GSFFLYSKLTVDKSR</u> <u>WQQGNVFSCSVMHE</u> <u>ALHNHYTQKSLSLSPG</u> <u>KDYKDDDDK (SEQ ID</u> <u>NO: 118)</u>	<u>PSRFSGSRSGTD</u> <u>FTLTISSLQPEDF</u> <u>ATYYCLODKKEF</u> <u>PRTFGGGTKVEI</u> <u>KRTVAAPSVFIF</u> <u>PPSDEQLKSGTA</u> <u>SVVCLLNNFYPR</u> <u>EAKVQWKVDN</u> <u>ALQSGNSQESVT</u> <u>EQDSKDSTYSL</u> <u>STLTLSKADYEK</u> <u>HKVYACEVTHQ</u> <u>GLSSPVTKSFNR</u> <u>GEC (SEQ ID NO:</u> <u>119)</u>	<u>ELSSLRSEDTAVYYCAR</u> <u>EDNTGTAFDYWGQGT</u> <u>VTVSSGGGGSGIPPKIE</u> <u>CLPIDISIDEGKVLTV</u> <u>SAFTGEPTPEVTWSTG</u> <u>GRKIHSEQGRFHIE</u> <u>TDDLTTLLIKDVKQD</u> <u>GGLYTLTLRNEFGSDS</u> <u>ATVNIHIRSIDKTHTCP</u> <u>PCPAPEAAGGPSVFLFP</u> <u>PKPKDTLMISRTPEVTC</u> <u>VVDVSHEDPEVKFNW</u> <u>YVDGVEVHNAKTKPRE</u> <u>EQYNSTYRVVSVLTVL</u> <u>HQDWLNGKEYKCKVS</u> <u>NKALPAIEKTISKAKG</u> <u>QPREPQVYTLPPCREEM</u> <u>TKNQVSLWCLVKGFYP</u> <u>SDIAVEWESNGQPENN</u> <u>YKTPPVLDSDGSFFLY</u> <u>SKLTVDKSRWQQGNVF</u> <u>SCSVMHEALHNHYTQK</u> <u>SLSLSPGKHHHHHH</u> <u>(SEQ ID NO: 124)</u>	<u>YYVSEHYTG</u> <u>VPDRFSGSG</u> <u>YGTDFTLKIS</u> <u>RVEAEDVG</u> <u>VYYCQQHH</u> <u>RFPLTFGQG</u> <u>TKLEIKGGG</u> <u>GSSGAPRFL</u> <u>TRPLAFVVS</u> <u>VGKDATLSS</u> <u>QIVGNPTPQ</u> <u>VSWEKDKQ</u> <u>PVTAGARF</u> <u>RLAQDGD</u> <u>YRLKILDLO</u> <u>LSDSGQYVS</u> <u>RARNAIGEA</u> <u>FACLGLOV</u> <u>DAEA (SEQ</u> <u>ID NO: 125)</u>
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Note: In the sequence, the bold part is a substituted portion, the dotted underlined part is a constant region portion, and a single underlined part is a variable region.

Heavy chain of J1:

EVQLVQSGAEVKKPGSSVKVSCKASGYTFSNYLIEWVRQAPGQGLEWIGVIDP
5 GVGDTNYNENFKGRATLTADKSTSTAYIELSSLRSEDTAVYYCAREDNTGTAF
DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
10 EYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 126);

Light chain of J1:

15 SIVMTQTPLSLSVTPGQPASISCKASQSVSSDVTWYLQKPGQSPQLLIYYVSEHY
TGVPDRFSGSGYGTDFTLKISRVEAEDVGVYYCQQHHRFPLTFGQGTKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 117);

20 The four chains of HJ-1, HJ-2, HJ-3 and HJ-4 were co-transfected for expression respectively, and then mass spectrometry was carried out on the expression products (for the method, see Test Example 3 disclosed herein) to detect the presence of the light and heavy chain mispaired molecules. The experimental results are shown in FIGs. 13A to

13D and Table 19.

Table 19. Experimental results of mass spectrometry of expression of bispecific antibodies

Name of diabody	Co-transfected chains	Results of mass spectrometry		
		HJ (1+2+3+4)	Mispaired molecule 1 (1 + 2 + 3 + 3)	Mispaired molecule 2 (1 + 2 + 4 + 4)
HJ-1	1: HJ-1-H1	√	X	√
	2: HJ-1-H2			
	3: HJ-1-L1			
	4: HJ-1-L2			
HJ-2	1: HJ-2-H2	√	X	√
	2: HJ-2-H1			
	3: HJ-2-L2			
	4: HJ-2-L1			
HJ-3	1: HJ-3-H1	√	X	X
	2: HJ-3-H2			
	3: HJ-3-L1			
	4: HJ-3-L2			
HJ-4	1: HJ-4-H2	√	X	X
	2: HJ-4-H1			
	3: HJ-4-L2			
	4: HJ-4-L1			

Note: In the table, "√" indicates that the molecule was detected, "X" indicates that the molecule was undetectable, "HJ (1 + 2 + 3 + 4)" indicates a bispecific antibody formed by the four corresponding chains numbered 1, 2, 3 and 4 on the left side thereof, "mispaired molecule 1 (1 + 2 + 3 + 3)" indicates a mispaired molecule 1 formed by the four corresponding chains numbered 1, 2, 3 and 3 on the left side thereof; and "mispaired molecule 2 (1 + 2 + 4 + 4)" indicates a mispaired molecule 2 formed by the four corresponding chains numbered 1, 2, 4 and 4 on the left side thereof.

Experimental results showed that when four chains of the bispecific antibody with CH1/CL substituted with TCRβ/TCRα were co-transfected for expression, the light and heavy chains of the antibody were mispaired. However, the bispecific antibody with CH1/CL substituted with the Titin-T chain/Obseurin-O chain had no mispairing of light and heavy chains. This indicates that the bispecific antibody disclosed herein with CH1/CL substituted with the Titin-T chain/Obseurin-O chain had excellent ability of reducing the mispairing of light and heavy chains.

II. Experiment of three-chain co-expression of bispecific antibody

The experiment was performed by co-transfecting and expressing three chains (1 heavy chain with CH1 substituted with TCRβ or Titin-T chain, 1 heavy chain with CH1 not substituted, and 1 wild-type light chain (VL-CL) with CL not substituted, and specific sequences are shown in Table 18), then performing mass spectrometry on the expression product (for the method, see Test Example 3 disclosed herein) and detecting antibody

purity SEC (for the method, see Test Example 2 disclosed herein) to verify whether the wild-type light chain (VL-CL) and the heavy chain with CH1 substituted with TCRβ or Titin-T chain were bound to form a mispaired molecule. The experimental results are shown in FIG. 14A, FIG. 14B, FIG. 15A, FIG. 15B and Table 20.

5 Table 20. Experimental results of three-chain co-expression of bispecific antibody

Group	Co-transfected chains	Antibody purity SEC (%)	Results of mass spectrometry	
			Molecule (1 + 2 + 3)	Mispaired molecule (1 + 2 + 3 + 3)
1	1: HJ-1-H1	75.85	√	√
	2: HJ-1-H2			
	3: HJ-1-L2			
2	1: HJ-3-H1	96.82	√	X
	2: HJ-3-H2			
	3: HJ-3-L2			

Note: In the table, "√" indicates that the molecule was detected, "X" indicates that the molecule was undetectable, "molecule (1 + 2 + 3)" indicates a molecule formed by the three corresponding chains numbered 1, 2 and 3 on the left side thereof, and "mispaired molecule (1 + 2 + 3 + 3)" indicates a mispaired molecule formed by the four corresponding chains 1, 2, 3 and 3 on the left side thereof.

The experimental results showed that VL-CL was readily bound to the heavy chain with CH1 substituted with TCRβ to express a mispaired molecule with two identical light chains. However, the VL-CL light chain did not bind to the heavy chain with CH1 substituted with the Titin-T chain to form a mispaired molecule with two identical light chains, which further indirectly indicated that the bispecific antibody with CH1 of heavy chain substituted with the Titin-T chain disclosed herein had more excellen ability of reducing the mispairing of light and heavy chains compared to the bispecific antibody with CH1 of heavy chain substituted with TCRβ.

CLAIMS

1. A polypeptide complex, comprising a first antigen-binding moiety comprising:
 - A) a first polypeptide, comprising a first heavy chain variable domain (VH1) from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a Titin-T chain, and
 - a second polypeptide, comprising a first light chain variable domain (VL1) from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a domain capable of interacting with a Titin-T chain;
 - or,
 - B) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a domain capable of interacting with a Titin-T chain, and
 - a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a Titin-T chain;
 - or,
 - C) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising an Obscurin-O chain or an Obscurin-like-O chain, and
 - a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising a domain capable of interacting with an Obscurin-O chain or an Obscurin-like-O chain;
 - or,
 - D) a first polypeptide, comprising a VH1 from an N-terminus to a C-terminus, the VH1 being operably linked to a first domain comprising a domain capable of interacting with an Obscurin-O chain or an Obscurin-like-O chain, and
 - a second polypeptide, comprising a VL1 from an N-terminus to a C-terminus, the VL1 being operably linked to a second domain comprising an Obscurin-O chain or an Obscurin-like-O chain;
 - wherein the first antigen-binding moiety specifically binds to a first antigen, and the first domain and the second domain are capable of forming a dimer.
2. The polypeptide complex according to claim 1, wherein,
 - the domain capable of interacting with an Obscurin-O chain or an Obscurin-like-O chain is a Titin-T chain, and
 - the domain capable of interacting with a Titin-T chain is an Obscurin-O chain or an Obscurin-like-O chain.
3. The polypeptide complex according to claim 1 or 2, wherein the VH1 and the VL1 of the first antigen-binding moiety form a first antigen-binding site specifically binding to the first antigen; the C-terminus of the VH1 is operably linked to an N-terminus of the

first domain, and the C-terminus of the VL1 is operably linked to an N-terminus of the second domain.

4. The polypeptide complex according to any one of claims 1 to 3, wherein the first domain and the second domain form a dimer through natural inter-chain bonds and/or non-natural inter-chain bonds;
preferably, the first domain and the second domain form a dimer through natural inter-chain bonds;
more preferably, one or more residues selected from the group consisting of positions 7-15, 19-24, 26, 55, 59 and 60 on the Titin-T chain and one or more residues selected from the group consisting of positions 3-6, 9, 41, 73, 75 and 80-90 on the Obscurin-O chain are linked to each other; or
one or more residues selected from the group consisting of positions 1, 7-10, 13-16, 19-26, 59-60 and 96 on the Titin-T chain and one or more residues selected from the group consisting of positions 4-5, 10, 12-13, 74, 76, 78 and 82-91 on the Obscurin-like-O chain are linked to each other;
the residue position in the Titin-T chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 32; the residue position in the Obscurin-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 33; the residue position in the Obscurin-like-O chain is a natural sequence numbering position relative to a sequence SEQ ID NO: 34.

5. The polypeptide complex according to any one of claims 1 to 4, wherein the first domain and the second domain form a dimer through at least one non-natural inter-chain bonds;
preferably, the non-natural inter-chain bond is formed between a particular mutated residue of the first domain and a particular mutated residue of the second domain;
more preferably, at least one pair of the mutated residues is cysteine residues;
most preferably, the non-natural inter-chain bond is a disulfide bond;
more preferably, wherein the dimer comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 non-natural inter-chain bonds.

6. The polypeptide complex according to claim 5, wherein the particular mutated residue of the first domain and the particular mutated residue of the second domain are selected from the group consisting of the following mutations:
(A) the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-O chain has one or more amino acid residue mutations on positions selected from the group consisting of 3, 9, 25, 76 and 88; or
(B) the Titin-T chain has one or more amino acid residue mutations on positions selected from the group consisting of 8, 20, 22, 25, 26 and 39, and/or the Obscurin-like-O chain

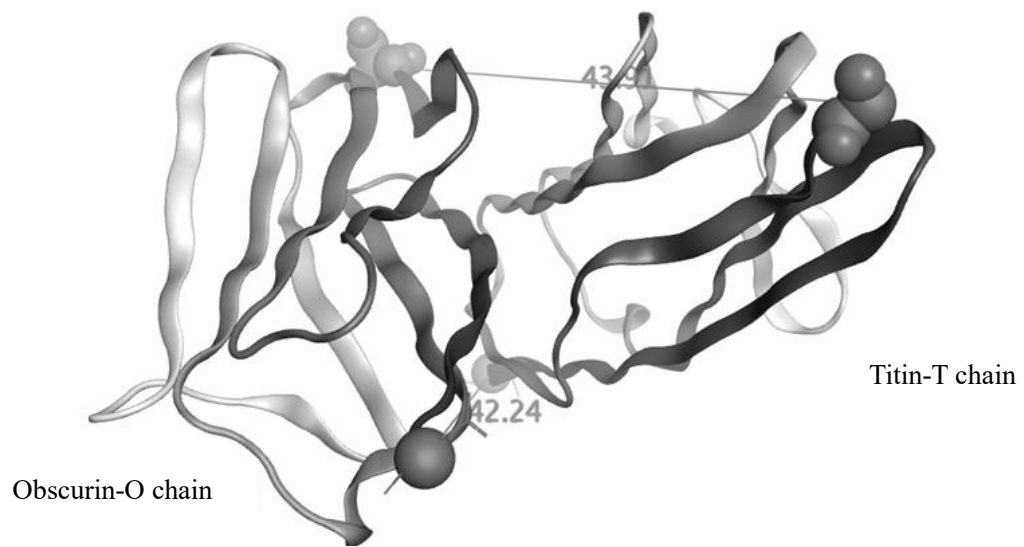


FIG. 1A

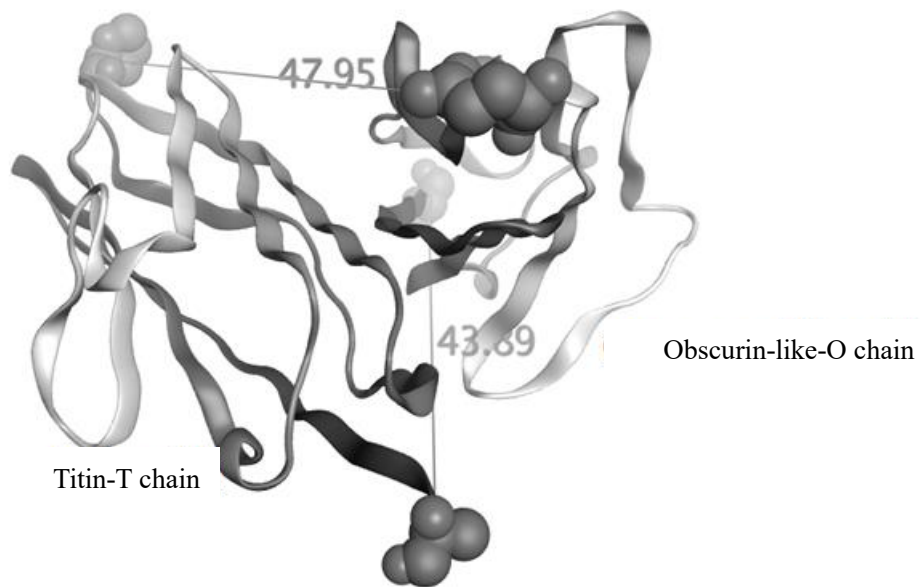


FIG. 1B

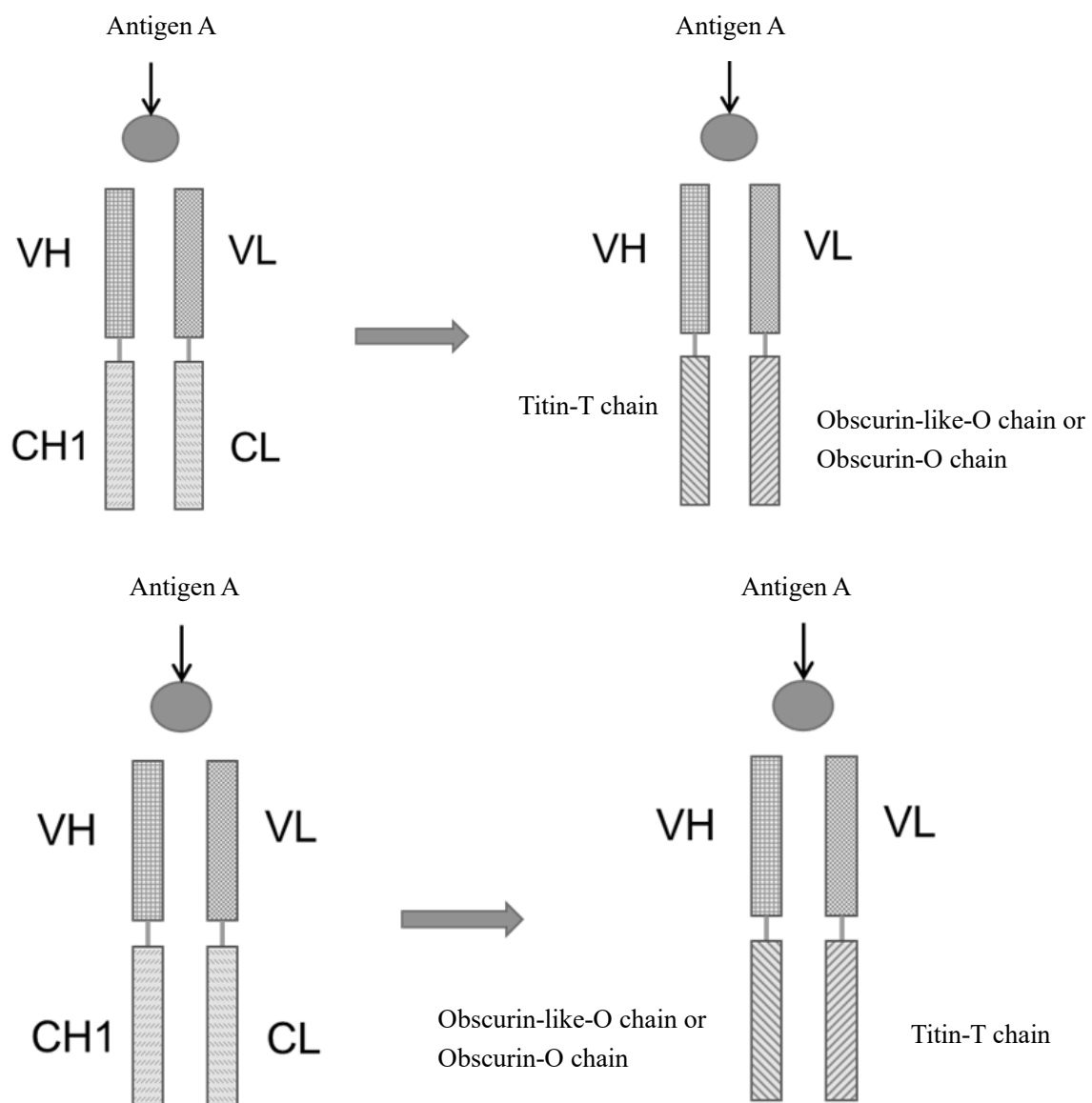


FIG. 2

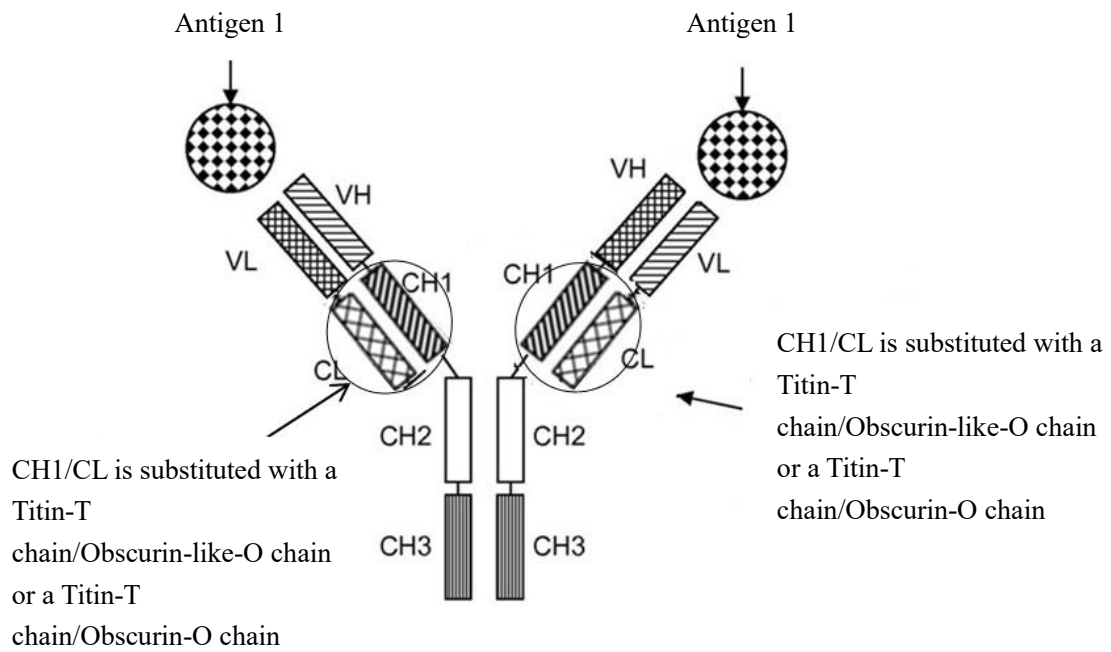


FIG. 3

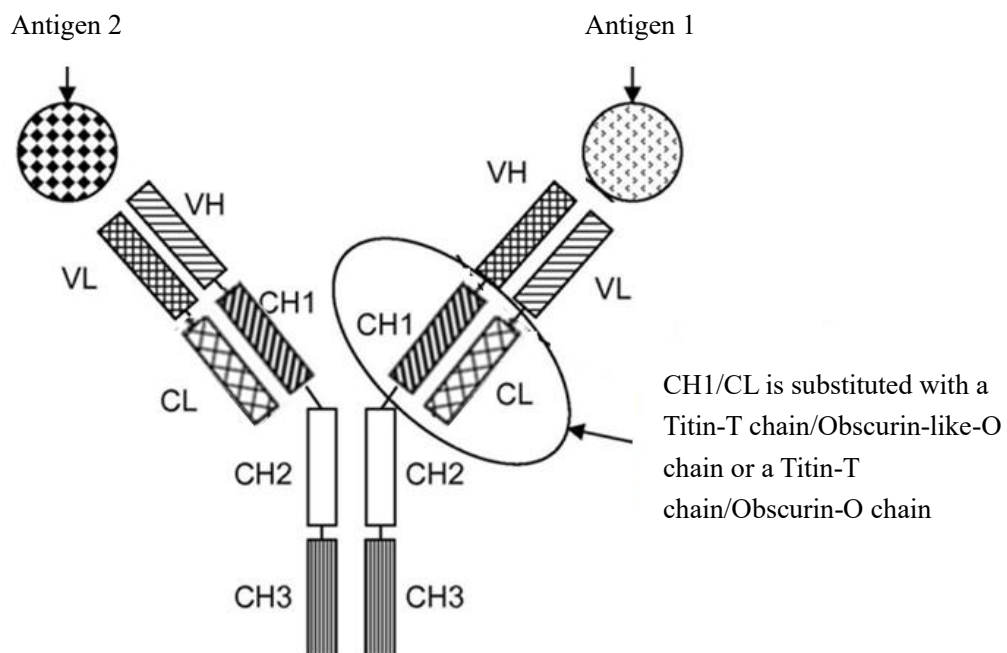


FIG. 4

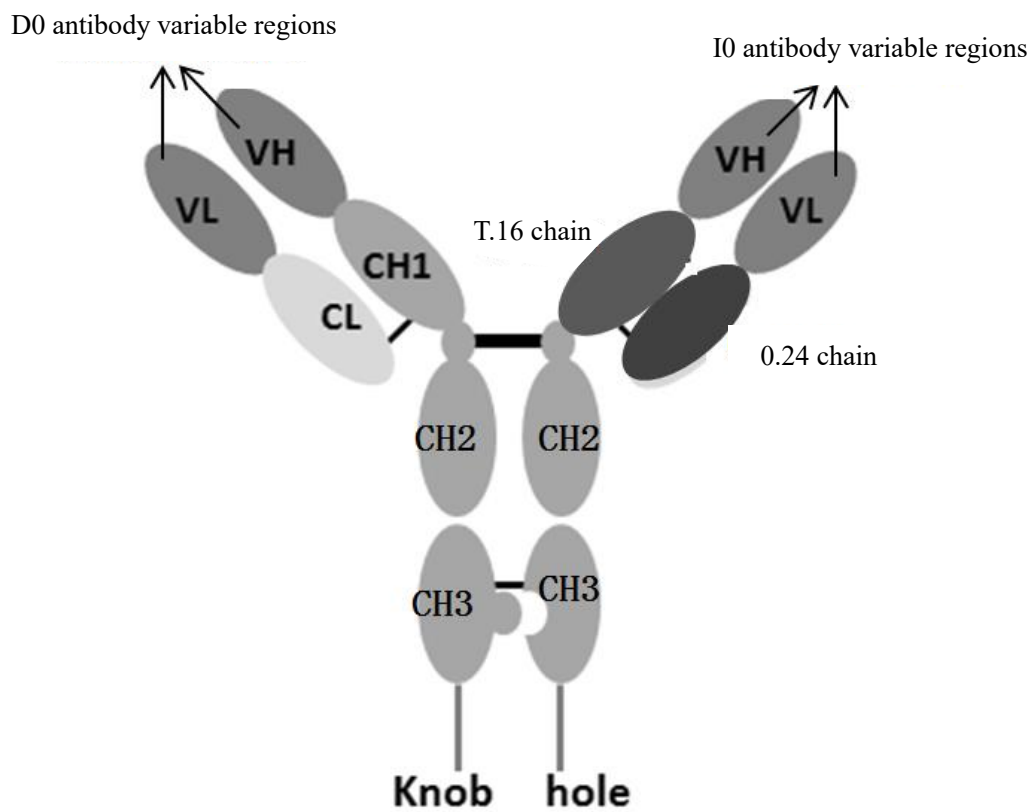


FIG. 5

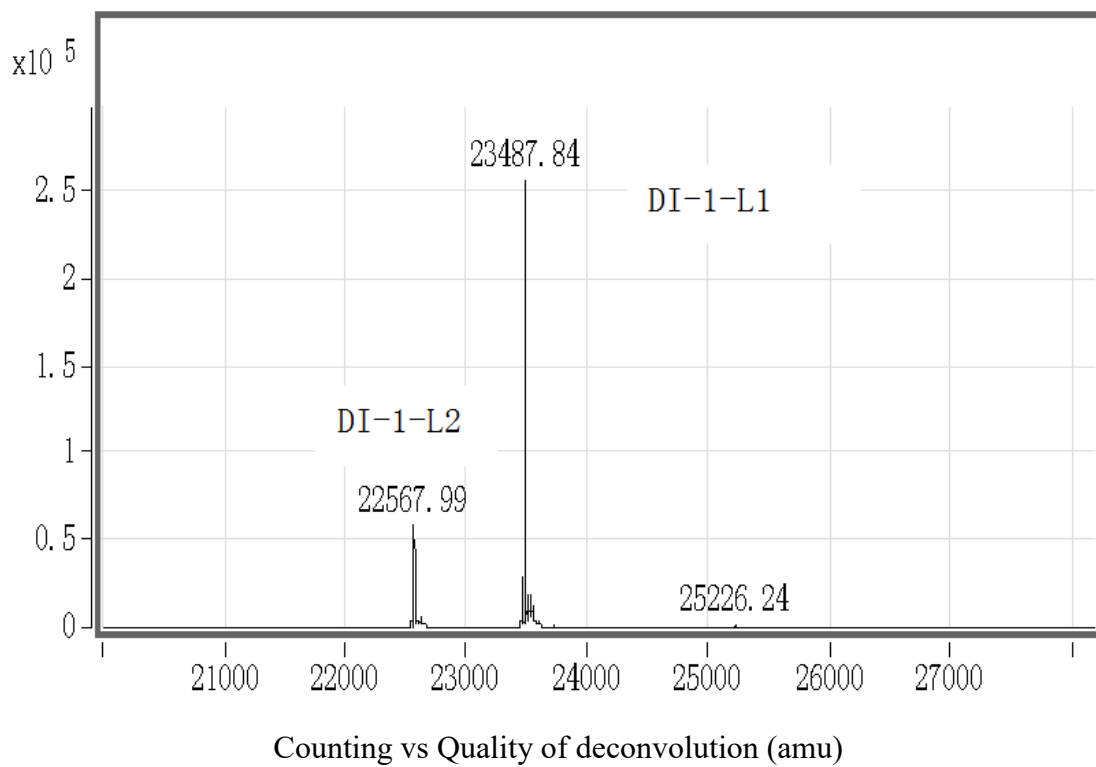


FIG. 6A

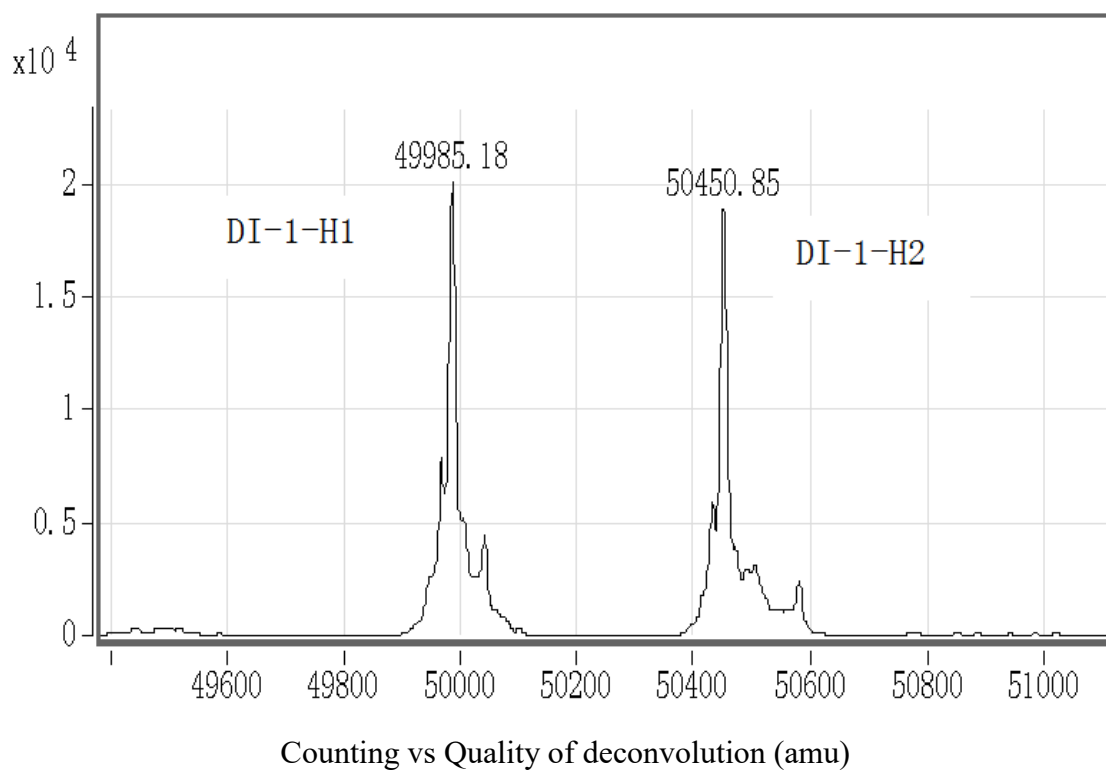


FIG. 6B

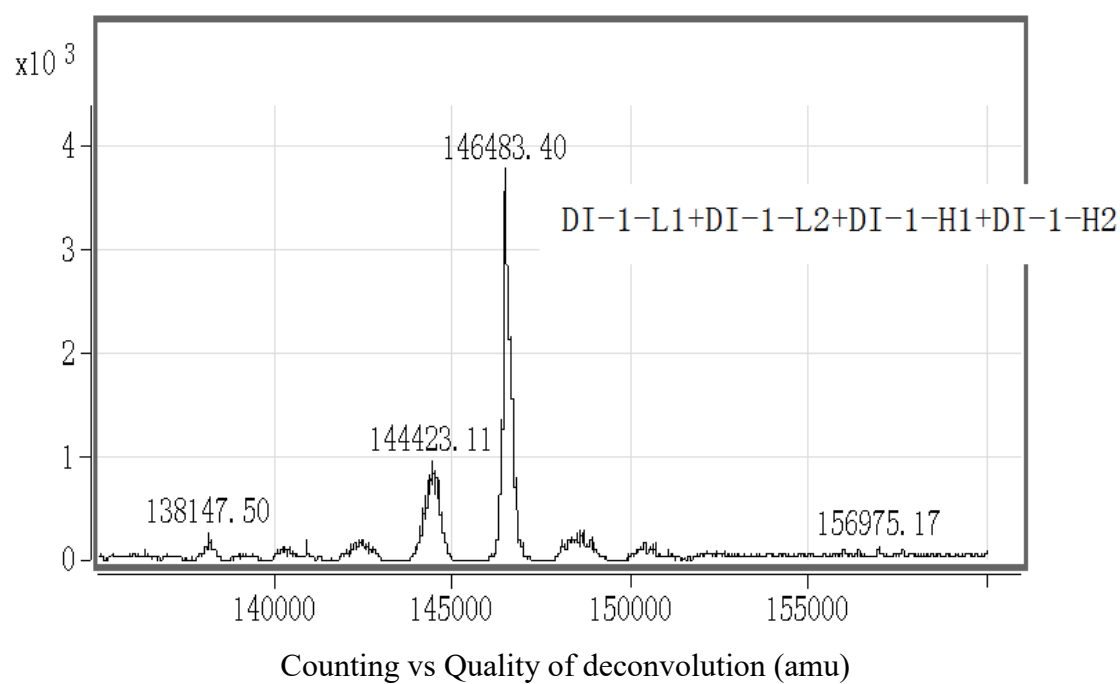


FIG. 6C

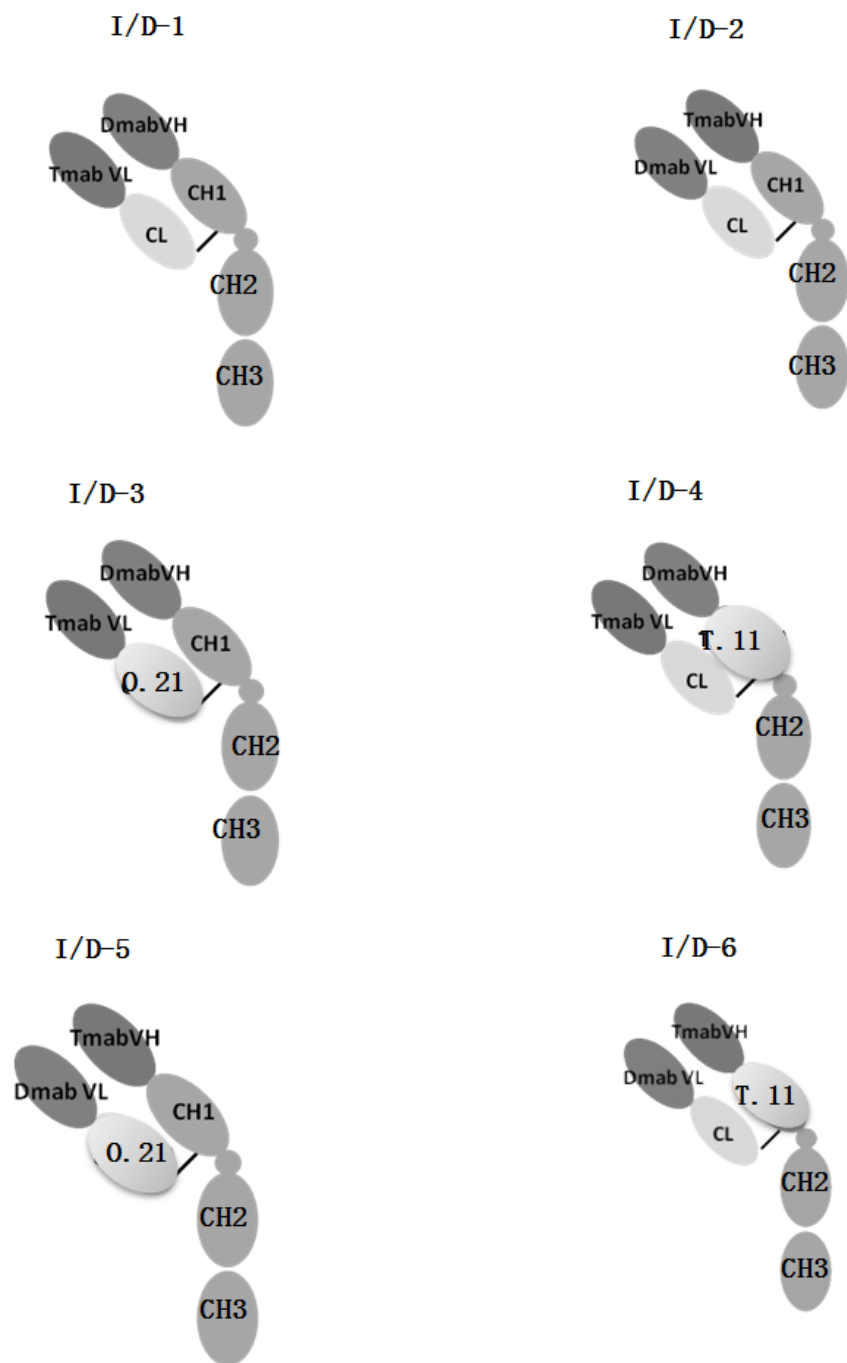


FIG. 7

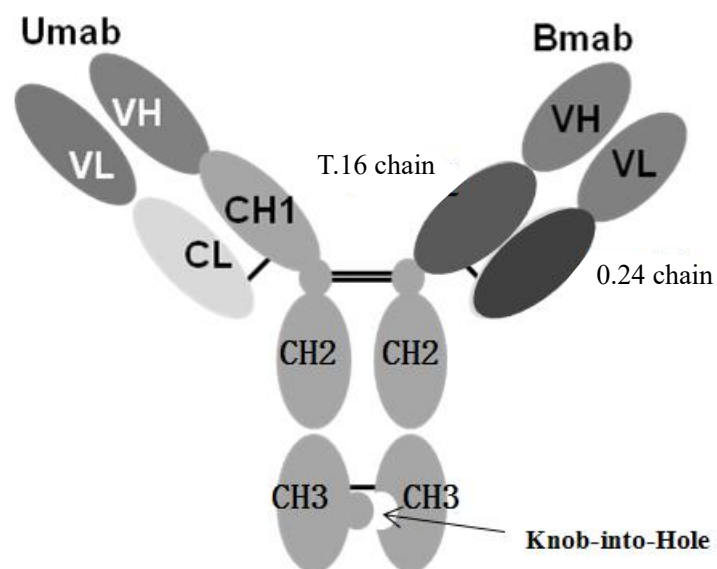
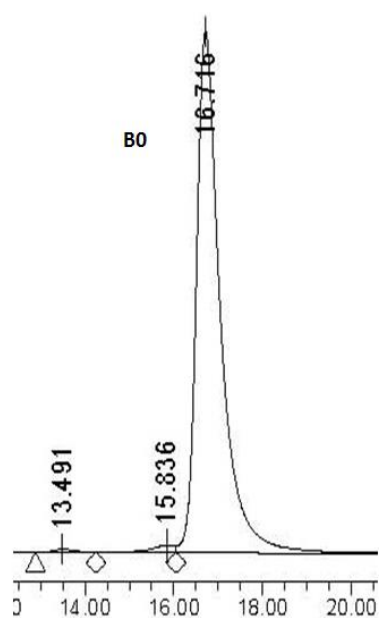
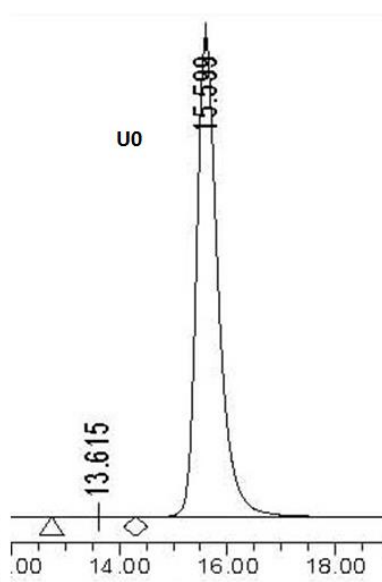


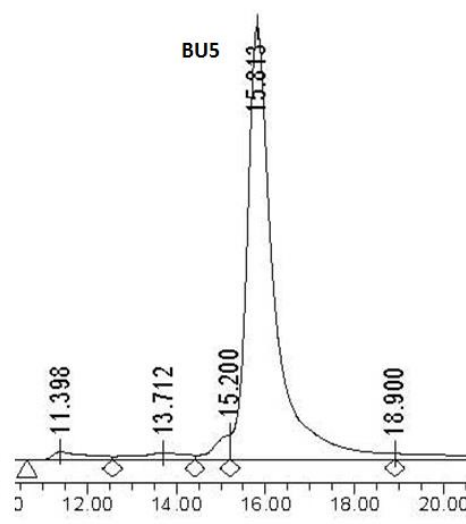
FIG. 8



Min
FIG. 9A



Min
FIG. 9B



Min
FIG. 9C

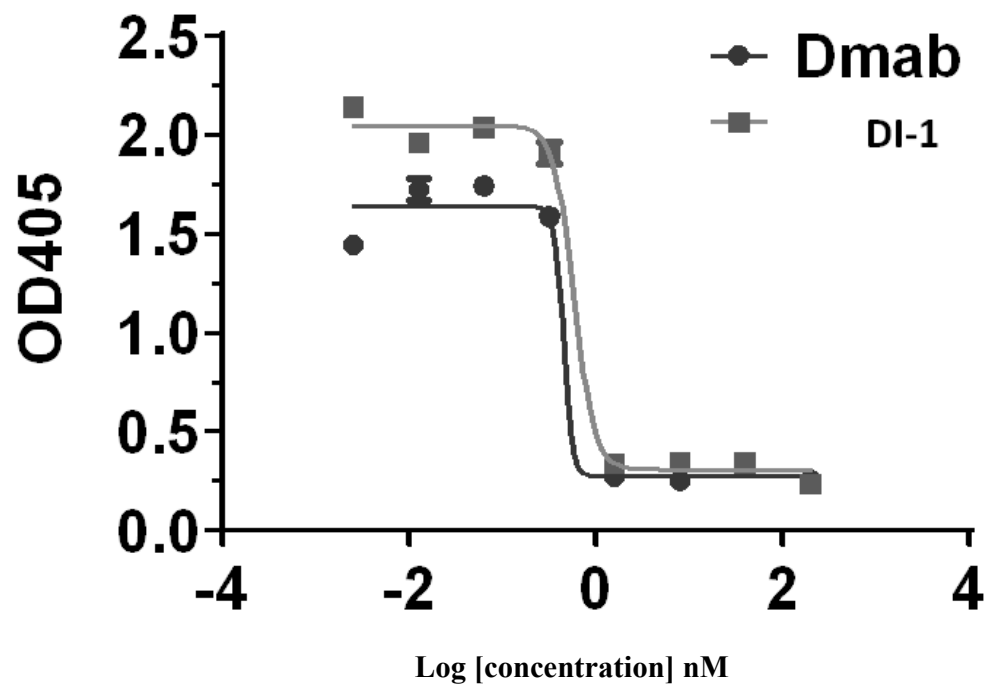


FIG. 10

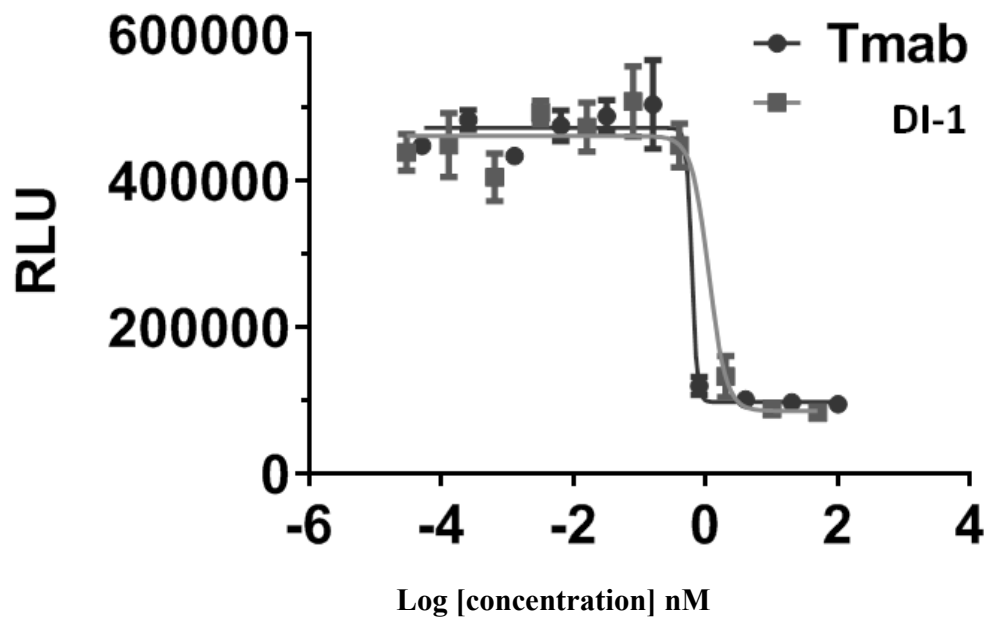


FIG. 11

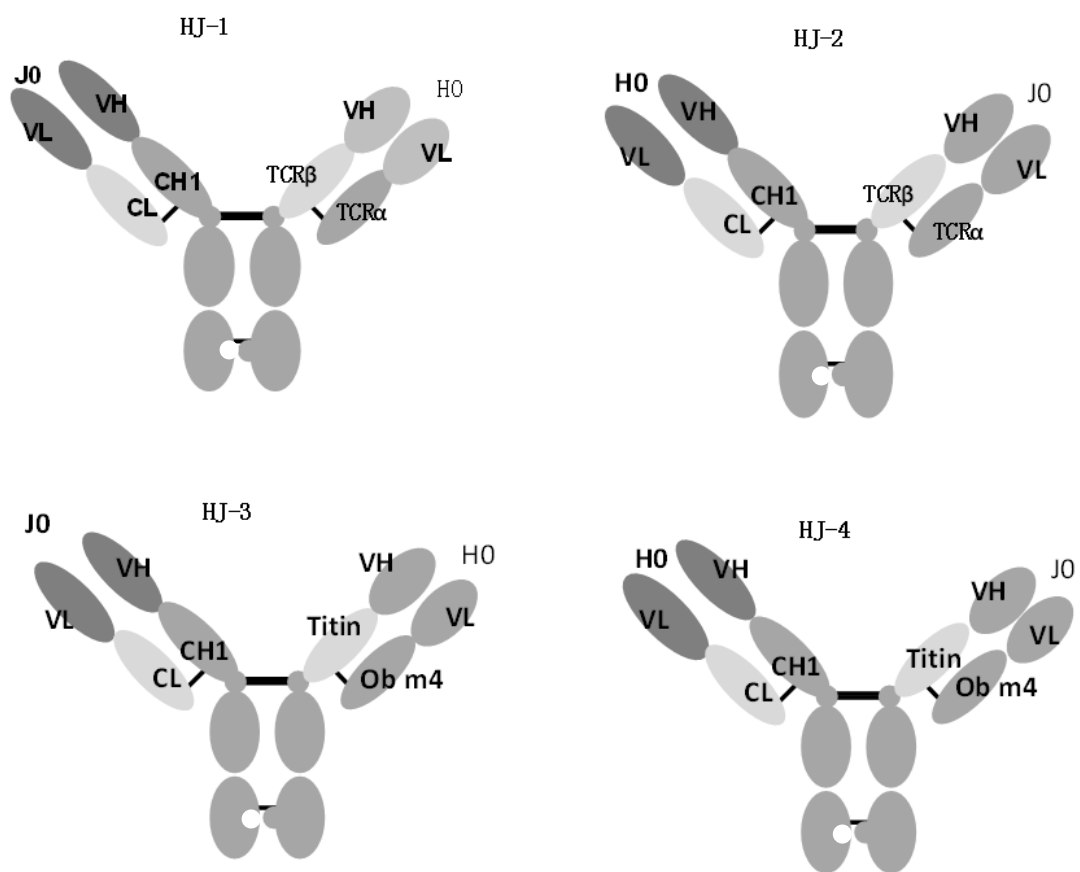
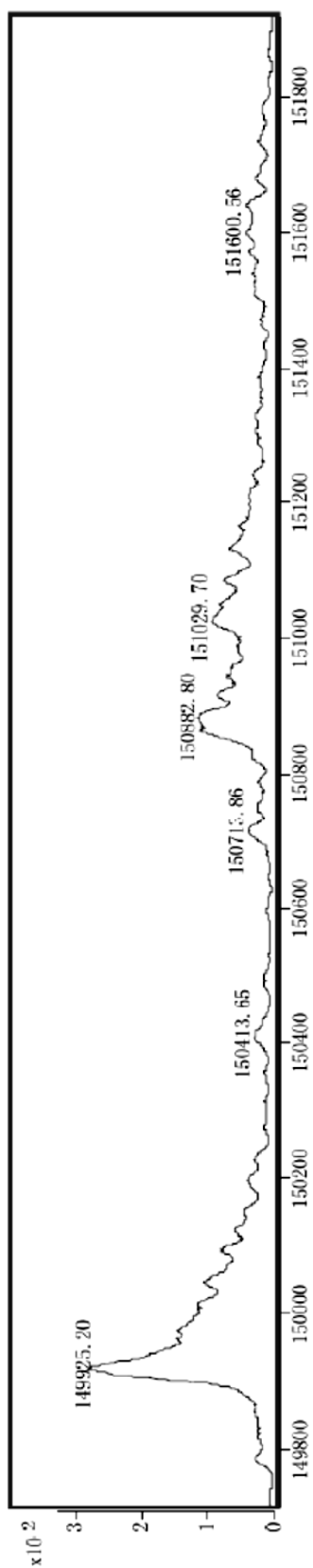


FIG. 12

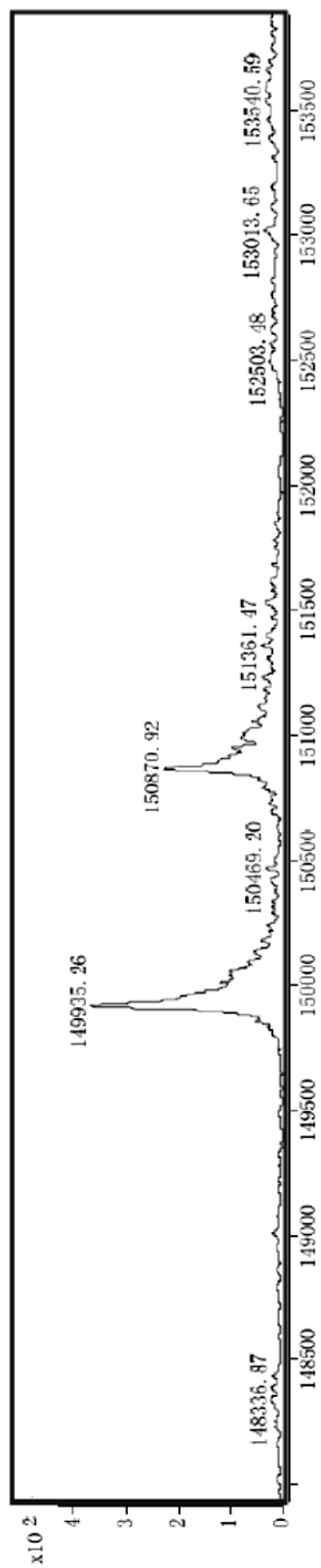
HJ-1



Counting vs Quality of deconvolution (amu)

FIG. 13A

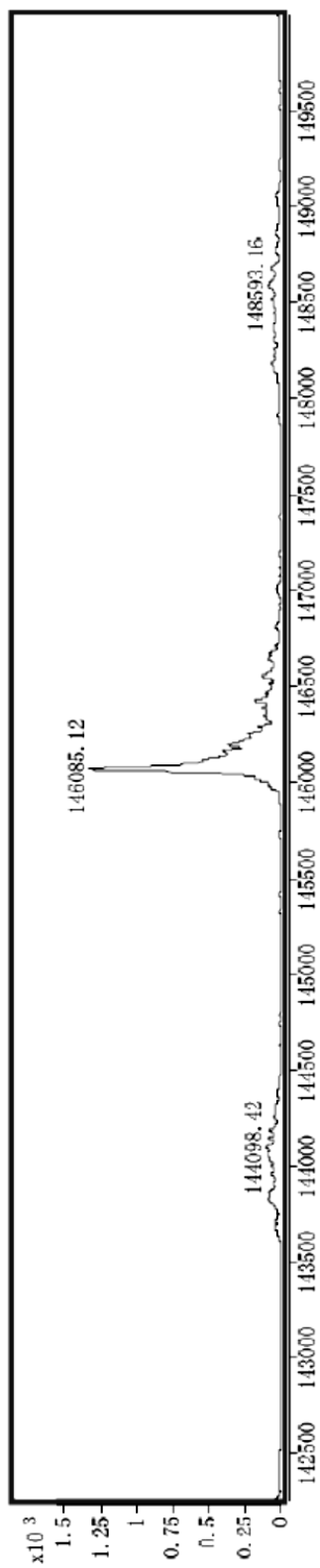
HJ-2



Counting vs Quality of deconvolution (amu)

FIG. 13B

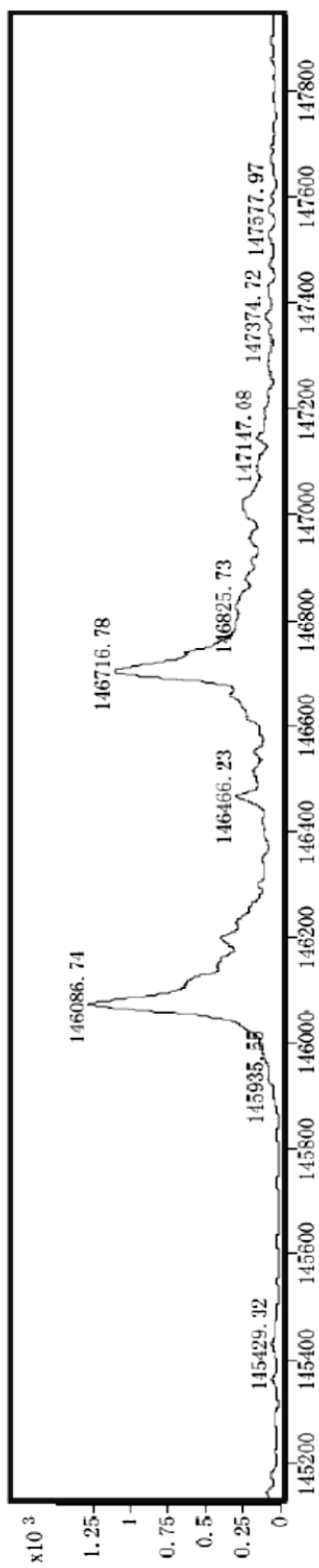
HJ-3



Counting vs Quality of deconvolution (amu)

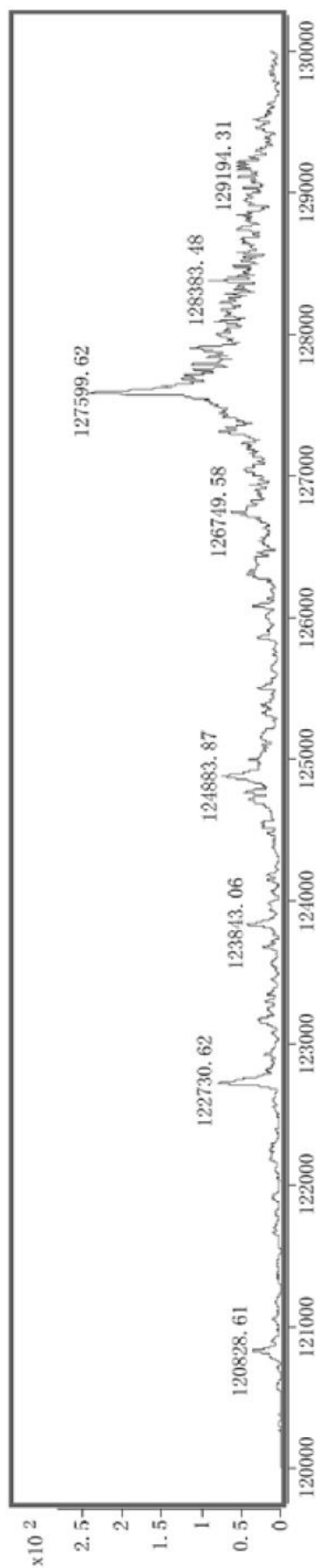
FIG. 13C

HJ-4



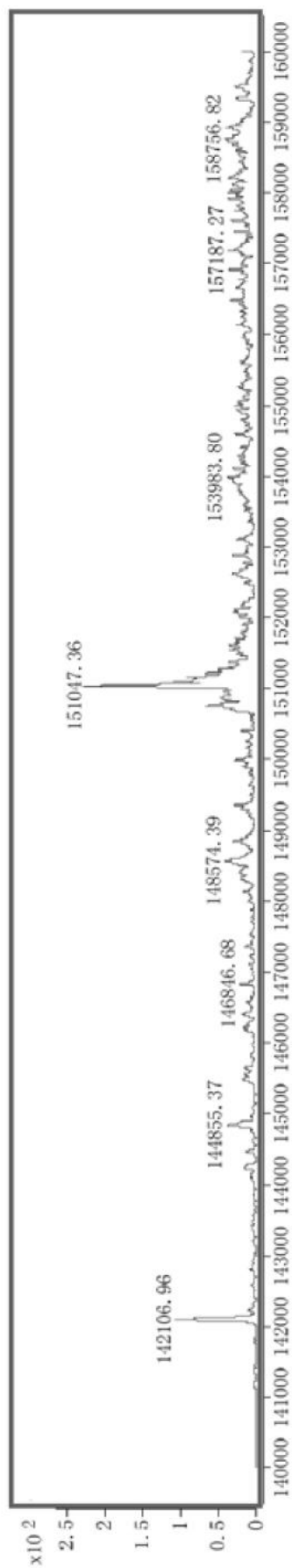
Counting vs Quality of deconvolution (amu)

FIG. 13D



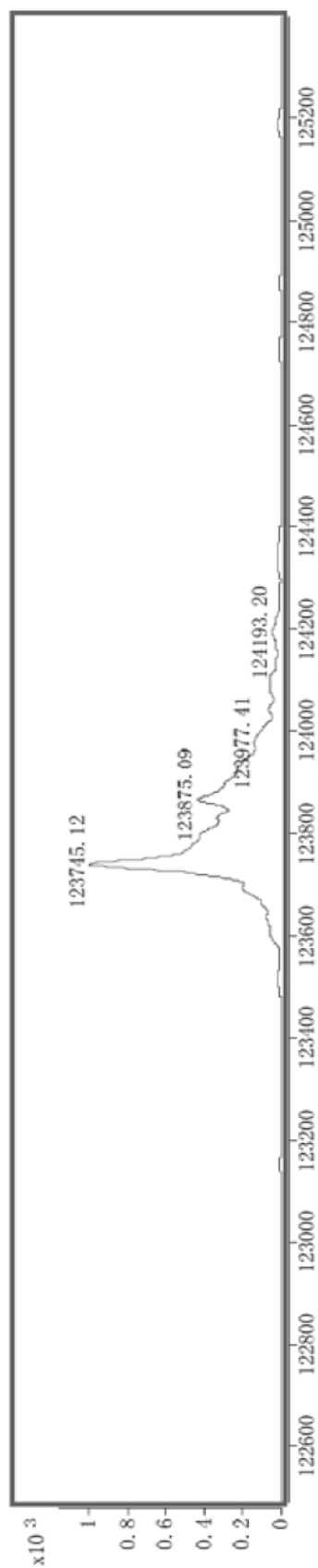
Counting vs Quality of deconvolution (amu)

FIG. 14A



Counting vs Quality of deconvolution (amu)

FIG. 14B



Counting vs Quality of deconvolution (amu)

FIG. 15A



Counting vs Quality of deconvolution (amu)

FIG. 15B

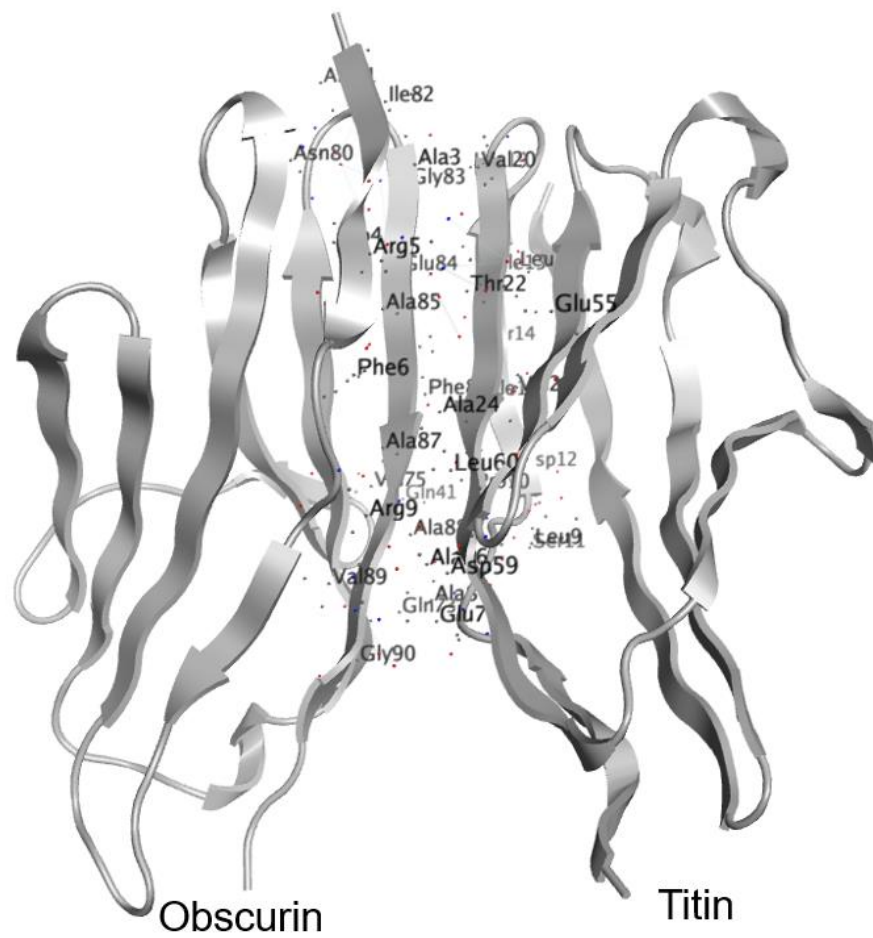


FIG. 16A

SEQUENCE LISTING

<110> Jiangsu Hengrui Medicine Co., Ltd.
Shanghai Hengrui Pharmaceutical Co., Ltd.

<120> New polypeptide complex

<130> 702150CPCT

<140> PCT/CN2021/070832

<141> 2021-01-08

<150> CN202010020878.7

<151> 2020-01-09

<160> 126

<170> PatentIn 3.5

<210> 1

<211> 330

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 heavy chain constant region

<400> 1

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Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70				75					80	
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90						95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
			115				120						125		

Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
130						135					140				
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
145					150					155					160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
			165						170					175	
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
			180				185						190		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
		195				200					205				
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
210						215					220				
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
225					230					235					240
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
			245						250					255	
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
		260					265					270			
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
		275					280					285			
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
290						295					300				
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
305					310					315					320
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
			325						330						

<210> 2

<211> 330

<212> PRT

<213> Artificial Sequence

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<223> knob-IgG1 heavy chain constant region

<400> 2

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Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20					25					30			
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35				40					45				
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
50						55					60				

Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	65	70	75	80
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	85	90	95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	100	105	110	
Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	115	120	125	
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	130	135	140	
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	145	150	155	160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	165	170	175	
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	180	185	190	
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	195	200	205	
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	210	215	220	
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg	Glu	Glu	225	230	235	240
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	245	250	255	
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	260	265	270	
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	275	280	285	
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	290	295	300	
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	305	310	315	320
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys							325	330		

<210> 3

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<212> PRT

<213> Artificial Sequence

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<223> hole-IgG 1 heavy chain constant region

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Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70					75					80
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
		115					120					125			
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
	130					135					140				
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
145					150					155					160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
			165						170					175	
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
			180					185					190		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
		195					200					205			
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
	210					215					220				
Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu
225					230					235					240
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr
			245						250					255	
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
			260					265					270		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
		275					280					285			
Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
	290					295					300				
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
305					310					315					320
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
				325					330						

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20 25 30
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80
Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

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1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Ser Ser
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ala Arg Leu Tyr Ala Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Ala Leu Val Thr Val Ser Ser
115

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<212> PRT
<213> Artificial Sequence

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<400> 7
Asp Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
His Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Met

		35					40					45					
Leu	Ile	Tyr	Asn	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Asp	Arg	Phe		
	50					55					60						
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala		
65					70					75					80		
Gln	Ala	Asp	Asp	Glu	Ser	Asp	Tyr	Tyr	Cys	Ala	Ile	His	Val	Asp	Arg		
				85					90					95			
Asp	Ile	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
			100					105					110				

<210> 8

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of N0 antibody

<400> 8

Asp	Val	Gln	Leu	Val	Gln	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5				10						15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Gly	Ser	Gly	Phe	Thr	Ser	Ser	Leu	Ser		
			20					25					30				
Trp	Met	Ser	Trp	Leu	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35				40						45					
Ala	Asn	Ile	Asn	Gln	Asp	Gly	Ser	Glu	Lys	Asn	Tyr	Val	Asp	Ser	Val		
	50				55					60							
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Gln	Asn	Ser	Leu	Tyr		
65					70				75					80			
Leu	Gln	Met	Ser	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85				90					95				
Ala	Arg	Gly	Leu	Trp	Thr	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu	Leu		
			100					105					110				
Thr	Val	Ser	Pro														
			115														

<210> 9

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of N0 antibody

<400> 9
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Ile Asn Asn Arg
 20 25 30
 Phe Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Ala Ala Ser Ser Arg Ala Thr Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Ala Glu Asp Phe Ala Met Tyr His Cys Gln Gln Tyr Gly Ser Phe Pro
 85 90 95
 Arg Thr Phe Gly Gln Gly Thr Met Val Asp Ile Lys
 100 105

<210> 10
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH amino acid sequence of S0 antibody

<400> 10
 Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Gly Gly
 1 5 10 15
 Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Val Phe Ser Ser Tyr
 20 25 30
 Asp Met Ser Trp Val Arg Gln Thr Pro Glu Arg Gly Leu Glu Trp Val
 35 40 45
 Ala Tyr Ile Ser Ser Gly Gly Gly Ile Thr Tyr Ala Pro Ser Thr Val
 50 55 60
 Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Ala His Tyr Phe Gly Ser Ser Gly Pro Phe Ala Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 11

<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> VL amino acid sequence of S0 antibody

<400> 11

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ser	Ala	Ser	Val	Gly	
1				5					10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Glu	Asn	Ile	Phe	Ser	Tyr	
		20						25					30			
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Leu	Leu	Val	
		35					40					45				
Tyr	Asn	Thr	Arg	Thr	Leu	Ala	Glu	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
	50					55					60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Ser	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
65					70					75				80		
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	His	Tyr	Gly	Thr	Pro	Phe	
				85					90					95		
Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
			100					105								

<210> 12

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of V0 antibody

<400> 12

Gln	Val	Gln	Leu	Gln	Gln	Ser	Ala	Ala	Glu	Leu	Ala	Arg	Pro	Gly	Ala	
1				5					10					15		
Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Ser	Tyr	
		20						25					30			
Thr	Ile	His	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	
		35					40					45				
Gly	Tyr	Ile	Asn	Pro	Asn	Ser	Arg	Asn	Thr	Asp	Tyr	Asn	Gln	Lys	Phe	
	50					55					60					
Lys	Asp	Glu	Thr	Thr	Leu	Thr	Ala	Asp	Arg	Ser	Ser	Ser	Thr	Ala	Tyr	
65					70					75				80		
Met	Gln	Leu	Ile	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	

				85					90					95			
Ala	Arg	Tyr	Ser	Gly	Ser	Thr	Pro	Tyr	Trp	Tyr	Phe	Asp	Val	Trp	Gly		
			100					105					110				
Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser									
		115					120										

<210> 13

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of V0 antibody

<400> 13

Gln	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ile	Leu	Ser	Ala	Ser	Pro	Gly		
1			5					10					15				
Glu	Lys	Val	Thr	Met	Thr	Cys	Arg	Ala	Ser	Ser	Ser	Val	Ser	Tyr	Met		
		20					25					30					
Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Ser	Ser	Pro	Lys	Pro	Trp	Ile	Tyr		
	35					40					45						
Ala	Thr	Ser	Asn	Leu	Ala	Ser	Gly	Val	Pro	Ala	Arg	Phe	Ser	Val	Ser		
	50				55					60							
Val	Ser	Gly	Thr	Ser	His	Ser	Leu	Thr	Ile	Ser	Arg	Val	Glu	Ala	Glu		
65				70					75					80			
Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Trp	Ser	Ser	Asn	Pro	Leu	Thr		
		85					90					95					
Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys								
		100				105											

<210> 14

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of J0 antibody

<400> 14

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Lys	Pro	Gly	Gly		
1			5					10					15				
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr		
		20					25					30					

Trp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	His	Ile	Lys	Ser	Lys	Thr	Asp	Ala	Gly	Thr	Thr	Asp	Tyr	Ala	Ala
	50					55					60				
Pro	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
65					70					75					80
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
				85					90					95	
Tyr	Cys	Ala	Arg	Glu	Ile	Tyr	Tyr	Tyr	Ala	Phe	Asp	Ser	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115					120								

<210> 15

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of J0 antibody

<400> 15

Ser	Tyr	Glu	Leu	Thr	Gln	Pro	Leu	Ser	Val	Ser	Val	Ala	Leu	Gly	Gln
1				5					10					15	
Thr	Ala	Arg	Ile	Thr	Cys	Ser	Gly	Asp	Asn	Ile	Gly	Ser	Lys	Tyr	Val
			20					25					30		
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35					40					45			
Gly	Asp	Asn	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50					55					60				
Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Arg	Ala	Gln	Ala	Gly
65					70					75					80
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ala	Ala	Asp	Trp	Val	Asp	Phe	Tyr
			85					90						95	
Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
			100					105							

<210> 16

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of H0 antibody

<400>	16															
Glu Val Gln Leu	Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly															
1	5				10							15				
Ser Leu Arg Leu	Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr															
20				25							30					
Tyr Met Ala Trp	Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val															
35				40							45					
Thr Ser Ile Ser	Tyr Glu Gly Asp Ile Thr Tyr Tyr Gly Asp Ser Val															
50				55							60					
Lys Gly Arg Phe	Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr															
65	70				75							80				
Leu Gln Met Asn	Ser Leu Arg Ala Glu Asp Thr Ala Thr Tyr Tyr Cys															
85				90							95					
Ala Ser Gln Thr	Leu Arg Glu Ser Phe Asp Tyr Trp Gly Gln Gly Thr															
100				105							110					
Leu Val Thr Val	Ser Ser															
115																

<211> 107

<213> Artificial Sequence

<223> VL amino acid sequence of H0 antibody

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ala	Asn	Tyr
			20					25					30		
Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Gly	Thr	Ser	Asn	Leu	Glu	Val	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					
Ser	Arg	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Asp	Lys	Glu	Phe	Pro	Arg
			85						90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 18
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> VH amino acid sequence of R0 antibody

<400> 18
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Ser Leu Thr Ser Asn
20 25 30
Ser Val Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Gly Leu Ile Trp Ser Asn Gly Asp Thr Asp Tyr Asn Ser Ala Ile Lys
50 55 60
Ser Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Ser Thr Val Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Glu Tyr Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 19
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL amino acid sequence of R0 antibody

<400> 19
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Glu Gly Ile Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Asn Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser	Gly	Ser	Ala	Thr	Asp	Tyr	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Lys	Phe	Pro	Asn
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Val	Lys					
			100					105							

<210> 20
 <211> 123
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH amino acid sequence of B0 antibody

<400> 20															
Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1			5					10					15		
Ser	Val	Arg	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Asn	Asn
			20				25						30		
Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35				40					45				
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe
	50				55				60						
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser
65					70				75						80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90						95	
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro
			100				105						110		
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser					
			115				120								

<210> 21
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL amino acid sequence of B0 antibody

<400> 21															
Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln

1				5					10					15		
Thr	Val	Arg	Val	Thr	Cys	Gln	Gly	Asp	Ser	Leu	Arg	Ser	Tyr	Tyr	Ala	
			20					25					30			
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
		35					40					45				
Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
	50					55				60						
Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu	
65					70				75						80	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His	
			85					90						95		
Trp	Val	Phe	Gly	Gly	Gly	Thr	Glu	Leu	Thr	Val	Leu					
			100					105								

<210> 22

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of U0 antibody

<400> 22

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu	
1				5				10					15			
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Thr	Tyr	
			20				25					30				
Trp	Leu	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Asp	Trp	Ile	
		35				40					45					
Gly	Ile	Met	Ser	Pro	Val	Asp	Ser	Asp	Ile	Arg	Tyr	Ser	Pro	Ser	Phe	
	50					55			60							
Gln	Gly	Gln	Val	Thr	Met	Ser	Val	Asp	Lys	Ser	Ile	Thr	Thr	Ala	Tyr	
65					70				75						80	
Leu	Gln	Trp	Asn	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	
			85					90						95		
Ala	Arg	Arg	Arg	Pro	Gly	Gln	Gly	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly	
			100					105					110			
Thr	Leu	Val	Thr	Val	Ser	Ser										
			115													

<210> 23

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of U0 antibody

<400> 23

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	
1				5				10						15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp	
			20					25					30			
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Glu	Lys	Ala	Pro	Lys	Ser	Leu	Ile	
			35				40					45				
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
	50					55				60						
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
65					70					75					80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ile	Tyr	Pro	Tyr	
				85					90					95		
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
			100					105								

<210> 24

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of D0 antibody

<400> 24

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5				10						15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
			20					25					30			
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35				40					45				
Ser	Gly	Ile	Thr	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	
	50					55				60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65					70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85						90					95		
Ala	Lys	Asp	Pro	Gly	Thr	Thr	Val	Ile	Met	Ser	Trp	Phe	Asp	Pro	Trp	
			100					105					110			

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 25

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of D0 antibody

<400> 25

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Arg	Gly	Arg
			20					25					30		
Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
		35					40					45			
Ile	Tyr	Gly	Ala	Ser	Ser	Arg	Ala	Thr	Gly	Ile	Pro	Asp	Arg	Phe	Ser
	50					55					60				
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Arg	Leu	Glu
65					70				75					80	
Pro	Glu	Asp	Phe	Ala	Val	Phe	Tyr	Cys	Gln	Gln	Tyr	Gly	Ser	Ser	Pro
			85						90					95	
Arg	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys				
			100					105							

<210> 26

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of I0 antibody

<400> 26

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ile	Gly	Tyr
			20					25					30		
Asp	Leu	Asn	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Ile	Ile	Trp	Gly	Asp	Gly	Thr	Thr	Asp	Tyr	Asn	Ser	Ala	Val	Lys

50		55		60											
Ser	Arg	Val	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu
65					70					75					80
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85					90					95	
Arg	Gly	Gly	Tyr	Trp	Tyr	Ala	Thr	Ser	Tyr	Tyr	Phe	Asp	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

<210> 27

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of I0 antibody

<400> 27

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Asn	Asn
			20					25					30		
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Tyr	Thr	Ser	Arg	Phe	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Glu	His	Thr	Leu	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
			100					105							

<210> 28

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of C0 antibody

<400> 28

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr
			20					25						30	
His	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Arg	Leu	Glu	Trp	Met
		35					40					45			
Gly	Asp	Ile	Asn	Pro	Asp	Ile	Gly	Gly	Thr	Ser	Tyr	Asn	Gln	Asn	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Arg	Asp	Thr	Ser	Ala	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Trp	Asp	Phe	Asp	Ser	Phe	Ala	Asn	Trp	Gly	Gln	Gly	Thr	Leu
			100					105					110		
Val	Thr	Val	Ser	Ser											
			115												

<210> 29

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of C0 antibody

<400> 29

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Glu	Ser	Val	Ser	Ile	Ile
			20					25						30	
Gly	Thr	Asn	Leu	Ile	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35				40						45			
Lys	Leu	Leu	Ile	Tyr	His	Ala	Ser	Asn	Leu	Glu	Thr	Gly	Val	Pro	Asp
	50					55				60					
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
65					70					75					80
Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Leu	Gln	Ser	Arg
				85					90					95	
Lys	Ile	Pro	Tyr	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	
			100					105					110		

<210> 30

<211> 104

<212> PRT

<213> Artificial Sequence

<220>

<223> IL6Ra.0 chain sequence

<400> 30

Gly	Ile	Leu	Gln	Pro	Asp	Pro	Pro	Ala	Asn	Ile	Thr	Val	Thr	Ala	Val	
1				5				10						15		
Ala	Arg	Asn	Pro	Arg	Trp	Leu	Ser	Val	Thr	Trp	Gln	Asp	Pro	His	Ser	
			20					25					30			
Trp	Asn	Ser	Ser	Phe	Tyr	Arg	Leu	Arg	Phe	Glu	Leu	Arg	Tyr	Arg	Ala	
		35					40					45				
Glu	Arg	Ser	Lys	Thr	Phe	Thr	Thr	Trp	Met	Val	Lys	Asp	Leu	Gln	His	
	50					55					60					
His	Cys	Val	Ile	His	Asp	Ala	Trp	Ser	Gly	Leu	Arg	His	Val	Val	Gln	
65					70					75					80	
Leu	Arg	Ala	Gln	Glu	Glu	Phe	Gly	Gln	Gly	Glu	Trp	Ser	Glu	Trp	Ser	
			85						90					95		
Pro	Glu	Ala	Met	Gly	Thr	Pro	Trp									
			100													

<210> 31

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> IL6Rb.0 chain sequence

<400> 31

Phe	Asp	Pro	Val	Tyr	Lys	Val	Lys	Pro	Asn	Pro	Pro	His	Asn	Leu	Ser	
1				5				10						15		
Val	Ile	Asn	Ser	Glu	Glu	Leu	Ser	Ser	Ile	Leu	Lys	Leu	Thr	Trp	Thr	
			20					25					30			
Asn	Pro	Ser	Ile	Lys	Ser	Val	Ile	Ile	Leu	Lys	Tyr	Asn	Ile	Gln	Tyr	
		35					40					45				
Arg	Thr	Lys	Asp	Ala	Ser	Thr	Trp	Ser	Gln	Ile	Pro	Pro	Glu	Asp	Thr	
	50					55					60					
Ala	Ser	Thr	Arg	Ser	Ser	Phe	Thr	Val	Gln	Asp	Leu	Lys	Pro	Phe	Thr	
65					70					75					80	
Glu	Tyr	Val	Phe	Arg	Ile	Arg	Cys	Met	Lys	Glu	Asp	Gly	Lys	Gly	Tyr	
			85						90					95		
Trp	Ser	Asp	Trp	Ser	Glu	Glu	Ala	Ser	Gly	Ile	Thr					

100

105

<210> 32
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.0 chain sequence

<400> 32
 Gly Ile Pro Pro Lys Ile Glu Ala Leu Pro Ser Asp Ile Ser Ile Asp
 1 5 10 15
 Glu Gly Lys Val Leu Thr Val Ala Cys Ala Phe Thr Gly Glu Pro Thr
 20 25 30
 Pro Glu Val Thr Trp Ser Cys Gly Gly Arg Lys Ile His Ser Gln Glu
 35 40 45
 Gln Gly Arg Phe His Ile Glu Asn Thr Asp Asp Leu Thr Thr Leu Ile
 50 55 60
 Ile Met Asp Val Gln Lys Gln Asp Gly Gly Leu Tyr Thr Leu Ser Leu
 65 70 75 80
 Gly Asn Glu Phe Gly Ser Asp Ser Ala Thr Val Asn Ile His Ile Arg
 85 90 95
 Ser Ile

<210> 33
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.0 chain sequence

<400> 33
 Ser Gly Ala Pro Arg Phe Leu Thr Arg Pro Lys Ala Phe Val Val Ser
 1 5 10 15
 Val Gly Lys Asp Ala Thr Leu Ser Cys Gln Ile Val Gly Asn Pro Thr
 20 25 30
 Pro Gln Val Ser Trp Glu Lys Asp Gln Gln Pro Val Ala Ala Gly Ala
 35 40 45
 Arg Phe Arg Leu Ala Gln Asp Gly Asp Leu Tyr Arg Leu Thr Ile Leu
 50 55 60

Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Ala	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	
Ala															

<210> 34
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.0 chain sequence

<400> 34															
Gln	Gly	Ser	Pro	Pro	Cys	Phe	Leu	Arg	Phe	Pro	Arg	Pro	Val	Arg	Val
1				5					10					15	
Val	Ser	Gly	Ala	Glu	Ala	Glu	Leu	Lys	Cys	Val	Val	Leu	Gly	Glu	Pro
			20					25					30		
Pro	Pro	Val	Val	Val	Trp	Glu	Lys	Gly	Gly	Gln	Gln	Leu	Ala	Ala	Ser
			35				40					45			
Glu	Arg	Leu	Ser	Phe	Pro	Ala	Asp	Gly	Ala	Glu	His	Gly	Leu	Leu	Leu
	50					55					60				
Thr	Ala	Ala	Leu	Pro	Thr	Asp	Ala	Gly	Val	Tyr	Val	Cys	Arg	Ala	Arg
65					70					75					80
Asn	Ala	Ala	Gly	Glu	Ala	Tyr	Ala	Ala	Ala	Ala	Val	Thr	Val	Leu	Glu
				85					90					95	
Pro	Pro														

<210> 35
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.1 chain sequence

<400> 35															
Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
1				5					10					15	
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr

			20					25					30			
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	
		35					40					45				
Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	
	50					55					60					
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Ser	Leu	
65					70					75					80	
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	
				85					90					95		
Ser	Ile															

<210> 36
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.2 chain sequence

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Ala	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp	
1				5				10					15			
Glu	Gly	Lys	Cys	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	
			20					25				30				
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	
		35					40					45				
Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	
	50					55					60					
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Ser	Leu	
65					70					75					80	
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	
				85					90					95		
Ser	Ile															

<210> 37
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.3 chain sequence

<400> 37

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Ala	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
1				5				10						15	
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Cys	Phe	Thr	Gly	Glu	Pro	Thr
			20					25					30		
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu
		35					40					45			
Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile
	50					55					60				
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Ser	Leu
65					70					75					80
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
				85					90					95	

Ser Ile

<210> 38

<211> 98

<212> PRT

<213> Artificial Sequence

<220>

<223> T.4 chain sequence

<400> 38

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Ala	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
1				5				10						15	
Glu	Gly	Lys	Val	Leu	Cys	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr
			20					25					30		
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu
		35					40					45			
Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile
	50					55					60				
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Ser	Leu
65					70					75					80
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
				85					90					95	

Ser Ile

<210> 39

<211> 103

<212> PRT

<210> 41
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.7 chain sequence

<400> 41
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Pro Pro Lys Ile
 1 5 10 15
 Glu Cys Leu Pro Ser Asp Ile Ser Ile Asp Glu Gly Lys Val Leu Thr
 20 25 30
 Val Ala Ser Ala Phe Thr Gly Glu Pro Thr Pro Glu Val Thr Trp Ser
 35 40 45
 Thr Gly Gly Arg Lys Ile His Ser Gln Glu Gln Gly Arg Phe His Ile
 50 55 60
 Glu Asn Thr Asp Asp Leu Thr Thr Leu Ile Ile Met Asp Val Gln Lys
 65 70 75 80
 Gln Asp Gly Gly Leu Tyr Thr Leu Ser Leu Gly Asn Glu Phe Gly Ser
 85 90 95
 Asp Ser Ala Thr Val Asn Ile His Ile Arg Ser Ile
 100 105

<210> 42
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.1 chain sequence

<400> 42
 Ser Gly Ala Pro Arg Phe Leu Thr Arg Pro Lys Ala Phe Val Val Ser
 1 5 10 15
 Val Gly Lys Asp Ala Thr Leu Ser Cys Gln Ile Val Gly Asn Pro Thr
 20 25 30
 Pro Gln Val Ser Trp Glu Lys Asp Gln Gln Pro Val Ala Ala Gly Ala
 35 40 45
 Arg Phe Arg Leu Ala Gln Asp Gly Asp Leu Tyr Arg Leu Thr Ile Leu
 50 55 60

Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	
Ala															

<210> 43
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.2 chain sequence

<400> 43															
Ser	Gly	Cys	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Lys	Ala	Phe	Val	Val	Ser
1				5					10					15	
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Cys	Gln	Ile	Val	Gly	Asn	Pro	Thr
			20					25					30		
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala
		35					40					45			
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu
	50				55						60				
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Ala	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	
Ala															

<210> 44
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.3 chain sequence

<400> 44															
Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Cys	Pro	Lys	Ala	Phe	Val	Val	Ser
1				5					10					15	
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Cys	Gln	Ile	Val	Gly	Asn	Pro	Thr

			20					25					30				
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala		
		35					40					45					
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu		
	50					55					60						
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Arg	Asn		
65					70					75					80		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Ala	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu		
			85					90					95				
Ala																	

<210> 45
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.4 chain sequence

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Lys	Ala	Phe	Val	Val	Ser		
1			5					10					15				
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr		
		20						25				30					
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala		
		35					40					45					
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu		
	50					55					60						
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn		
65					70					75					80		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu		
			85					90					95				
Ala																	

<210> 46
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.5 chain sequence

<400> 46

Ser	Gly	Cys	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Lys	Ala	Phe	Val	Val	Ser
1				5					10					15	
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
			20					25					30		
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala
		35					40					45			
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu
	50					55					60				
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Ala	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	

Ala

<210> 47

<211> 97

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.6 chain sequence

<400> 47

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Cys	Pro	Lys	Ala	Phe	Val	Val	Ser
1				5					10					15	
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
			20					25					30		
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala
		35					40					45			
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu
	50					55					60				
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Ala	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	

Ala

<210> 48

<211> 97

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.7 chain sequence

<400> 48

[illegible]

<210> 49

<211> 97

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.8 chain sequence

<400> 49

[illegible]

<210> 50
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> 0.9 chain sequence

<400> 50
Ser Gly Ala Pro Arg Phe Leu Thr Arg Pro Leu Ala Phe Val Val Ser
1 5 10 15
Val Gly Lys Asp Ala Thr Leu Ser Ser Gln Ile Val Gly Asn Pro Thr
20 25 30
Pro Gln Val Ser Trp Glu Lys Asp Gln Gln Pro Val Ala Ala Gly Ala
35 40 45
Arg Phe Arg Leu Ala Gln Asp Gly Asp Leu Tyr Arg Leu Lys Ile Leu
50 55 60
Asp Leu Ala Leu Gly Asp Ser Gly Gln Tyr Val Ser Arg Ala Arg Asn
65 70 75 80
Ala Ile Gly Glu Ala Phe Ala Cys Val Gly Leu Gln Val Asp Ala Glu
85 90 95
Ala

<210> 51
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> 0.10 chain sequence

<400> 51
Ser Gly Ala Pro Arg Phe Leu Thr Arg Pro Leu Ala Phe Val Val Ser
1 5 10 15
Val Gly Lys Asp Ala Thr Leu Ser Ser Gln Ile Val Gly Asn Pro Thr
20 25 30
Pro Gln Val Ser Trp Glu Lys Asp Gln Gln Pro Val Ala Ala Gly Ala
35 40 45
Arg Phe Arg Leu Ala Gln Asp Gly Asp Leu Tyr Arg Leu His Ile Leu
50 55 60

Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	

Ala

<210> 52
 <211> 102
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.11 chain sequence

<400> 52

Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Lys
1				5					10					15	
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile
			20					25					30		
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro
		35				40						45			
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr
	50				55					60					
Arg	Leu	Thr	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val
65					70				75						80
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu
				85					90					95	

Gln Val Asp Ala Glu Ala
 100

<210> 53
 <211> 102
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.12 chain sequence

<400> 53

Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Lys	Thr	Arg	Pro	Lys
1				5					10					15	
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile

			20					25					30			
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	
		35					40					45				
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	
	50					55					60					
Arg	Leu	Lys	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	
65					70					75					80	
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	
				85				90						95		
Gln	Val	Asp	Ala	Glu	Ala											
			100													

<210> 54
 <211> 102
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.13 chain sequence

<400> 54																
Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Lys	Thr	Arg	Pro	Lys	
1			5					10						15		
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	
		20						25					30			
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	
	35					40						45				
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	
	50					55					60					
Arg	Leu	His	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	
65					70					75					80	
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	
				85				90						95		
Gln	Val	Asp	Ala	Glu	Ala											
			100													

<210> 55
 <211> 102
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.14 chain sequence

<400> 55

Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Arg	Thr	Arg	Pro	Lys
1				5					10					15	
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile
			20					25					30		
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro
		35					40					45			
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr
	50					55					60				
Arg	Leu	Lys	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val
65					70					75					80
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu
				85					90					95	
Gln	Val	Asp	Ala	Glu	Ala										
				100											

<210> 56

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.15 chain sequence

<400> 56

Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Arg	Thr	Arg	Pro	Lys
1				5					10					15	
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile
			20					25					30		
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro
		35					40					45			
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr
	50					55					60				
Arg	Leu	His	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val
65					70					75					80
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu
				85					90					95	
Gln	Val	Asp	Ala	Glu	Ala										
				100											

<210> 57

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.16 chain sequence

<400> 57

Gly	Gly	Gly	Gly	Ser	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Lys	
1				5					10					15		
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	
			20					25						30		
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	
		35					40					45				
Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	
	50					55					60					
Arg	Leu	Thr	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	
65					70					75					80	
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	
				85					90					95		
Gln	Val	Asp	Ala	Glu	Ala											
				100												

<210> 58

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.17 chain sequence

<400> 58

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ser	Gly	Ala	Pro	Arg	Phe	
1				5					10					15		
Leu	Thr	Arg	Pro	Lys	Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	
			20						25					30		
Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	
		35					40					45				
Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	
	50					55					60					
Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Thr	Ile	Leu	Asp	Leu	Ala	Leu	Gly	Asp	
65					70					75					80	
Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	
				85					90					95		
Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu	Ala						

100

105

<210> 59
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.1 chain sequence

<400> 59
 Gln Gly Ser Pro Pro Glu Phe Leu Arg Phe Pro Arg Pro Val Arg Val
 1 5 10 15
 Val Ser Gly Ala Glu Ala Glu Leu Lys Cys Val Val Leu Gly Glu Pro
 20 25 30
 Pro Pro Val Val Val Trp Glu Lys Gly Gly Gln Gln Leu Ala Ala Ser
 35 40 45
 Glu Arg Leu Ser Phe Pro Ala Asp Gly Ala Glu His Gly Leu Leu Leu
 50 55 60
 Thr Ala Ala Leu Pro Thr Asp Ala Gly Cys Tyr Val Cys Arg Ala Arg
 65 70 75 80
 Asn Ala Ala Gly Glu Ala Tyr Ala Ala Ala Val Thr Val Leu Glu
 85 90 95
 Pro Pro

<210> 60
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.2 chain sequence

<400> 60
 Gln Gly Ser Pro Pro Glu Phe Leu Arg Phe Pro Arg Pro Val Arg Val
 1 5 10 15
 Val Ser Gly Ala Glu Ala Glu Leu Lys Cys Val Val Leu Gly Glu Pro
 20 25 30
 Pro Pro Val Val Val Trp Glu Lys Gly Gly Gln Gln Leu Ala Ala Ser
 35 40 45
 Glu Arg Leu Ser Phe Pro Ala Asp Gly Ala Glu His Gly Leu Leu Leu
 50 55 60

Thr	Ala	Ala	Leu	Pro	Thr	Asp	Ala	Gly	Val	Tyr	Val	Cys	Arg	Ala	Arg
65					70					75					80
Asn	Ala	Ala	Cys	Glu	Ala	Tyr	Ala	Ala	Ala	Ala	Val	Thr	Val	Leu	Glu
				85					90					95	
Pro	Pro														

<210> 61
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.3 chain sequence

<400> 61															
Gln	Gly	Ser	Pro	Pro	Glu	Phe	Leu	Arg	Phe	Pro	Arg	Pro	Val	Arg	Val
1				5					10					15	
Val	Ser	Gly	Ala	Glu	Ala	Glu	Leu	Lys	Cys	Val	Val	Leu	Gly	Glu	Pro
			20					25					30		
Pro	Pro	Val	Val	Val	Trp	Glu	Lys	Gly	Gly	Gln	Gln	Leu	Ala	Ala	Ser
			35				40					45			
Glu	Arg	Leu	Ser	Phe	Pro	Ala	Asp	Gly	Ala	Glu	His	Gly	Leu	Leu	Leu
	50					55					60				
Thr	Ala	Ala	Leu	Pro	Thr	Asp	Ala	Gly	Val	Tyr	Val	Cys	Arg	Ala	Arg
65					70					75					80
Asn	Ala	Ala	Gly	Glu	Cys	Tyr	Ala	Ala	Ala	Ala	Val	Thr	Val	Leu	Glu
				85					90					95	
Pro	Pro														

<210> 62
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.4 chain sequence

<400> 62															
Gln	Gly	Ser	Pro	Pro	Glu	Phe	Leu	Arg	Phe	Pro	Arg	Pro	Val	Arg	Val
1				5					10					15	
Val	Ser	Gly	Ala	Glu	Ala	Glu	Leu	Lys	Ser	Val	Val	Leu	Gly	Glu	Pro

			20					25					30			
Pro	Pro	Val	Val	Val	Trp	Glu	Lys	Gly	Gly	Gln	Gln	Leu	Ala	Ala	Ser	
		35					40					45				
Glu	Arg	Leu	Ser	Phe	Pro	Ala	Asp	Gly	Ala	Glu	His	Gly	Leu	Leu	Leu	
	50					55					60					
Thr	Ala	Ala	Leu	Pro	Thr	Asp	Ala	Gly	Cys	Tyr	Val	Ser	Arg	Ala	Arg	
65					70					75					80	
Asn	Ala	Ala	Gly	Glu	Ala	Tyr	Ala	Ala	Ala	Ala	Val	Thr	Val	Leu	Glu	
			85					90						95		
Pro	Pro															

<210> 63
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.5 chain sequence

<400> 63																
Gln	Gly	Ser	Pro	Pro	Glu	Phe	Leu	Arg	Phe	Pro	Arg	Pro	Val	Arg	Val	
1			5					10					15			
Val	Ser	Gly	Ala	Glu	Ala	Glu	Leu	Lys	Ser	Val	Val	Leu	Gly	Glu	Pro	
		20					25					30				
Pro	Pro	Val	Val	Val	Trp	Glu	Lys	Gly	Gly	Gln	Gln	Leu	Ala	Ala	Ser	
		35				40						45				
Glu	Arg	Leu	Ser	Phe	Pro	Ala	Asp	Gly	Ala	Glu	His	Gly	Leu	Leu	Leu	
	50				55					60						
Thr	Ala	Ala	Leu	Pro	Thr	Asp	Ala	Gly	Val	Tyr	Val	Ser	Arg	Ala	Arg	
65					70					75					80	
Asn	Ala	Ala	Cys	Glu	Ala	Tyr	Ala	Ala	Ala	Ala	Val	Thr	Val	Leu	Glu	
			85					90						95		
Pro	Pro															

<210> 64
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> OL.6 chain sequence

<400> 64
 Gln Gly Ser Pro Pro Glu Phe Leu Arg Phe Pro Arg Pro Val Arg Val
 1 5 10 15
 Val Ser Gly Ala Glu Ala Glu Leu Lys Ser Val Val Leu Gly Glu Pro
 20 25 30
 Pro Pro Val Val Val Trp Glu Lys Gly Gly Gln Gln Leu Ala Ala Ser
 35 40 45
 Glu Arg Leu Ser Phe Pro Ala Asp Gly Ala Glu His Gly Leu Leu Leu
 50 55 60
 Thr Ala Ala Leu Pro Thr Asp Ala Gly Val Tyr Val Ser Arg Ala Arg
 65 70 75 80
 Asn Ala Ala Gly Glu Cys Tyr Ala Ala Ala Val Thr Val Leu Glu
 85 90 95
 Pro Pro

<210> 65
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.8 chain sequence

<400> 65
 Gly Ile Pro Pro Lys Ile Glu Cys Leu Pro Ser Asp Ile Ser Ile Asp
 1 5 10 15
 Glu Gly Lys Val Leu Thr Val Ala Ser Ala Phe Thr Gly Glu Pro Thr
 20 25 30
 Pro Glu Val Thr Trp Ser Thr Gly Gly Arg Lys Ile His Ser Gln Glu
 35 40 45
 Gln Gly Arg Phe His Ile Glu Asn Thr Asp Asp Leu Thr Thr Leu Ile
 50 55 60
 Ile Ser Asp Val Gln Lys Gln Asp Gly Gly Leu Tyr Ser Leu Ser Leu
 65 70 75 80
 Gly Asn Glu Phe Gly Ser Asp Ser Ala Thr Val Asn Ile His Ile Arg
 85 90 95
 Ser Ile

<210> 66
 <211> 98
 <212> PRT

<213> Artificial Sequence

<220>

<223> T.9 chain sequence

<400> 66

[illegible]

<210> 67

<211> 98

<212> PRT

<213> Artificial Sequence

<220>

<223> T.10 chain sequence

<400> 67

[illegible]

<210> 68
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> T.11 chain sequence

<400> 68
Gly Ile Pro Pro Lys Ile Glu Cys Leu Pro Ile Asp Ile Ser Ile Asp
1 5 10 15
Glu Gly Lys Val Leu Thr Val Ala Ser Ala Phe Thr Gly Glu Pro Thr
20 25 30
Pro Glu Val Thr Trp Ser Thr Gly Gly Arg Lys Ile His Ser Gln Glu
35 40 45
Gln Gly Arg Phe His Ile Glu Asn Thr Asp Asp Leu Thr Thr Leu Ile
50 55 60
Ile Lys Asp Val Gln Lys Gln Asp Gly Gly Leu Tyr Thr Leu Thr Leu
65 70 75 80
Arg Asn Glu Phe Gly Ser Asp Ser Ala Thr Val Asn Ile His Ile Arg
85 90 95
Ser Ile

<210> 69
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> T.12 chain sequence

<400> 69
Gly Ile Pro Pro Lys Ile Glu Cys Leu Pro Ser Asp Ile Ser Ile Asp
1 5 10 15
Glu Gly Lys Val Leu Thr Val Ala Ser Ala Phe Thr Gly Glu Pro Thr
20 25 30
Pro Glu Val Thr Trp Ser Thr Ser Gly Lys Lys Ile Ser Ser Glu Glu
35 40 45
Gly Gly Arg Phe His Ile Glu Ser Thr Glu Asp Leu Thr Thr Leu Ile
50 55 60

Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Val	Tyr	Thr	Leu	Ser	Leu
65					70					75					80
Gly	Asn	Asp	Leu	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
				85					90					95	

Ser Ile

<210> 70
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.13 chain sequence

<400> 70

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
1				5				10						15	
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr
			20					25					30		
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Glu	Glu
			35				40					45			
Gly	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile
	50				55					60					
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Val	Tyr	Thr	Leu	Ser	Leu
65					70					75					80
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
				85					90					95	

Ser Ile

<210> 71
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.14 chain sequence

<400> 71

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
1				5				10						15	
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr

			20					25					30			
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	
		35					40					45				
Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile	
	50					55					60					
Ile	Met	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Val	Tyr	Thr	Leu	Ser	Leu	
65					70					75					80	
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	
				85					90					95		
Ser	Ile															

<210> 72
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.15 chain sequence

Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp	
1				5				10						15		
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	
			20					25					30			
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	
		35					40					45				
Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile	
	50					55					60					
Ile	Ser	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Ser	Leu	Ser	Leu	
65					70					75					80	
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	
				85					90					95		
Ser	Ile															

<210> 73
 <211> 103
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> T.16 chain sequence

<400> 73

Gly	Gly	Gly	Gly	Ser	Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ile	
1				5					10					15		
Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	
			20					25					30			
Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	
		35					40					45				
Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	
	50					55					60					
Leu	Thr	Thr	Leu	Ile	Ile	Lys	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	
65					70					75					80	
Tyr	Thr	Leu	Thr	Leu	Arg	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	
				85					90					95		
Asn	Ile	His	Ile	Arg	Ser	Ile										
			100													

<210> 74

<211> 103

<212> PRT

<213> Artificial Sequence

<220>

<223> T.17 chain sequence

<400> 74

Lys	Ala	Gly	Ile	Arg	Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	
1				5					10					15		
Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	
			20					25					30			
Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	
		35					40					45				
Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	
	50					55					60					
Leu	Thr	Thr	Leu	Ile	Ile	Ser	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	
65					70					75					80	
Tyr	Ser	Leu	Ser	Leu	Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	
				85					90					95		
Asn	Ile	His	Ile	Arg	Ser	Ile										
			100													

<210> 75

<211> 108

<212> PRT

<210> 77
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.18 chain sequence

<400> 77
 Ser Gly Ala Pro Arg Phe Leu Thr Arg Pro Lys Ser Tyr Thr Val Ser
 1 5 10 15
 Val Gly Lys Asp Ala Ser Leu Ser Ser Gln Ile Val Gly Asn Pro Thr
 20 25 30
 Pro Gln Val Ser Trp Glu Lys Asp Gln Gln Pro Val Ala Ala Gly Ala
 35 40 45
 Arg Phe Arg Leu Ala Gln Asp Gly Asp Leu Tyr Arg Leu Lys Ile Leu
 50 55 60
 Asp Leu Ala Leu Gly Asp Ser Gly Gln Tyr Val Ser Arg Ala Arg Asn
 65 70 75 80
 Ala Ile Gly Glu Ala Phe Ala Cys Val Gly Leu Gln Val Asp Ala Glu
 85 90 95
 Ala

<210> 78
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.19 chain sequence

<400> 78
 Ser Glu Ala Pro Arg Phe Leu Thr Arg Pro Leu Ala Phe Val Val Ser
 1 5 10 15
 Glu Gly Lys Asp Ala Thr Leu Ser Ser Gln Ile Val Gly Asp Pro Pro
 20 25 30
 Pro Glu Val Thr Trp Glu Lys Asp Gln Gln Pro Ile Thr Ala Gly Ala
 35 40 45
 Arg Phe Arg Leu Ala Gln Asp Gly Asp Val Tyr Arg Leu Glu Ile Leu
 50 55 60

Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	

Gly

<210> 79
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.20 chain sequence

<400> 79

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser
1				5				10					15		
Val	Gly	Lys	Leu	Ala	Met	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
			20					25					30		
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Gln	Pro	Val	Ala	Ala	Gly	Ala
			35				40					45			
Arg	Phe	Arg	Leu	Leu	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu
	50				55					60					
Asp	Leu	Ala	Leu	Gly	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Gln	Val	Asp	Ala	Glu
				85					90					95	

Ala

<210> 80
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.21 chain sequence

<400> 80

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser
1				5				10					15		
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr

			20					25					30				
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr	Ala	Gly	Ala		
		35					40					45					
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu		
	50					55					60						
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn		
65					70					75					80		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val	Asp	Ala	Glu		
			85						90					95			
Ala																	

<210> 81
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.22 chain sequence

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser		
1			5					10					15				
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr		
		20						25				30					
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Leu	Pro	Val	Thr	Ala	Gly	Ala		
	35						40				45						
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu		
	50					55				60							
Asp	Leu	Thr	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn		
65					70					75					80		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Glu	Val	Gly	Ala	Glu		
			85						90					95			
Ala																	

<210> 82
 <211> 97
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.23 chain sequence

<400> 82

Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ser	Tyr	Val	Val	Ser
1				5					10					15	
Val	Gly	Lys	Asp	Ala	Ser	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
			20					25					30		
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Leu	Pro	Val	Thr	Ala	Gly	Ala
		35					40					45			
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu
	50					55					60				
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
65					70					75					80
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Glu	Val	Gly	Ala	Glu
				85					90					95	

Ala

<210> 83

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.24 chain sequence

<400> 83

Gly	Gly	Gly	Gly	Ser	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu
1				5					10					15	
Ala	Phe	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile
			20					25					30		
Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro
		35					40					45			
Val	Thr	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr
	50					55					60				
Arg	Leu	Lys	Ile	Leu	Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val
65					70					75					80
Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu
				85					90					95	

Gln Val Asp Ala Glu Ala

100

<210> 84

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.25 chain sequence

<400> 84

[illegible]

<210> 85

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> 0.26 chain sequence

<400> 85

[illegible]

<210> 86
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 0.27 chain sequence

<400> 86
 Gly Gly Gly Gly Ser Asp Gln Pro Gln Phe Ser Gly Ala Pro Arg Phe
 1 5 10 15
 Leu Thr Arg Pro Leu Ser Tyr Val Val Ser Val Gly Lys Asp Ala Ser
 20 25 30
 Leu Ser Ser Gln Ile Val Gly Asn Pro Thr Pro Gln Val Ser Trp Glu
 35 40 45
 Lys Asp Gln Leu Pro Val Thr Ala Gly Ala Arg Phe Arg Leu Ala Gln
 50 55 60
 Asp Gly Asp Leu Tyr Arg Leu Lys Ile Leu Asp Leu Gln Leu Ser Asp
 65 70 75 80
 Ser Gly Gln Tyr Val Ser Arg Ala Arg Asn Ala Ile Gly Glu Ala Phe
 85 90 95
 Ala Cys Val Gly Leu Glu Val Gly Ala Glu Ala
 100 105

<210> 87
 <211> 452
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Amino acid sequence of DI-1 chain 1 (DI-1-H1)

<400> 87
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Asp	Pro	Gly	Thr	Thr	Val	Ile	Met	Ser	Trp	Phe	Asp	Pro	Trp
			100					105					110		
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
		115					120					125			
Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
	130					135					140				
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
145					150					155					160
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
			165						170					175	
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
			180					185					190		
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
		195					200					205			
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
	210					215					220				
Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala
225					230					235					240
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
			245						250					255	
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
			260					265					270		
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
	275						280					285			
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
	290					295					300				
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
305					310					315					320
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
			325						330					335	
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
			340					345					350		
Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val
		355					360					365			
Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val
	370					375					380				
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro
385					390					395					400
Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr
			405						410					415	
Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val

<210> 89
 <211> 451
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Amino acid sequence of DI-1 chain 3 (DI-1-H2)

<400> 89

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ile	Gly	Tyr
			20					25					30		
Asp	Leu	Asn	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Ile	Ile	Trp	Gly	Asp	Gly	Thr	Thr	Asp	Tyr	Asn	Ser	Ala	Val	Lys
	50					55					60				
Ser	Arg	Val	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu
65					70					75					80
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85					90					95	
Arg	Gly	Gly	Tyr	Trp	Tyr	Ala	Thr	Ser	Tyr	Tyr	Phe	Asp	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ile
		115					120					125			
Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ile	Asp	Ile	Ser	Ile	Asp	Glu	Gly
	130					135					140				
Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	Pro	Glu
145					150					155					160
Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	Gln	Gly
				165					170					175	
Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	Ile	Lys
		180					185					190			
Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Thr	Leu	Arg	Asn
	195					200					205				
Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	Ser	Ile
	210					215					220				
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly
225					230					235					240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			245						250					255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
		260					265					270			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val

		275					280					285			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
	290					295					300				
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
305					310					315					320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			325						330					335	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		340						345					350		
Cys	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
	355						360					365			
Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
370						375					380				
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
385					390					395					400
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val
			405					410						415	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
			420					425					430		
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	435						440					445			
Pro	Gly	Lys													
	450														

<210> 90

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of DI-1 chain 4 (DI-1-L2)

<400> 90

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Asn	Asn
		20					25					30			
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35					40					45				
Tyr	Tyr	Thr	Ser	Arg	Phe	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55			60							
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70				75						80	
Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Glu	His	Thr	Leu	Pro	Tyr

				85					90					95			
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser		
			100					105					110				
Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser		
		115					120					125					
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr		
	130					135					140						
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr	Ala	Gly	Ala		
145					150				155						160		
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu		
				165				170						175			
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn		
		180					185					190					
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val	Asp	Ala	Glu		
	195						200					205					

Ala

<210> 91

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU1 chain 1 (BU1-H1)

<400> 91

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser		
1			5					10					15				
Ser	Val	Arg	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Asn	Asn		
		20					25					30					
Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
	35					40					45						
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe		
	50				55				60								
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser		
65				70				75						80			
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85				90					95					
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro		
		100					105					110					
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly		
	115				120						125						
Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly		

130		135		140											
Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
145					150					155					160
Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
				165						170					175
Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
			180					185					190		
Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val
		195					200					205			
Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys
	210					215					220				
Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala
225					230					235					240
Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
				245					250					255	
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
			260					265					270		
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val
	275						280					285			
Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser
	290					295					300				
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
305					310					315					320
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala
				325					330					335	
Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro
			340					345					350		
Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln
	355						360					365			
Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
	370					375					380				
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr
385					390					395					400
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu
				405					410					415	
Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser
		420						425					430		
Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser
	435						440					445			
Leu	Ser	Pro	Gly	Lys											
450															

<210> 92
 <211> 214
 <212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU1 chain 2 (BU1-L1)

<400> 92

Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln	
1				5					10					15		
Thr	Val	Arg	Val	Thr	Cys	Gln	Gly	Asp	Ser	Leu	Arg	Ser	Tyr	Tyr	Ala	
			20					25					30			
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
		35					40					45				
Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
	50					55					60					
Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu	
65					70					75					80	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His	
				85					90					95		
Trp	Val	Phe	Gly	Gly	Gly	Thr	Glu	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	
			100					105					110			
Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	
		115					120					125				
Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	
	130					135					140					
Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	
145					150					155					160	
Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	
				165					170					175		
Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser	
			180					185					190			
Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	
		195					200					205				
Ala	Pro	Thr	Glu	Cys	Ser											
																210

<210> 93

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU1 chain 3 (BU1-H2)

<400> 93

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Thr	Tyr
			20					25					30		
Trp	Leu	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Asp	Trp	Ile
		35					40					45			
Gly	Ile	Met	Ser	Pro	Val	Asp	Ser	Asp	Ile	Arg	Tyr	Ser	Pro	Ser	Phe
	50					55					60				
Gln	Gly	Gln	Val	Thr	Met	Ser	Val	Asp	Lys	Ser	Ile	Thr	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Asn	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
			85						90				95		
Ala	Arg	Arg	Arg	Pro	Gly	Gln	Gly	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ile	Pro	Pro
		115					120					125			
Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val
	130					135					140				
Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr
145					150					155					160
Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe
			165					170					175		
His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile	Ile	Ser	Asp	Val
		180					185						190		
Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Ser	Leu	Ser	Leu	Gly	Asn	Glu	Phe
	195						200					205			
Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	Ser	Ile	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
225					230					235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
			245						250				255		
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260				265						270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
	275						280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
	290					295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325					330					335		
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr
			340					345					350		

Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser
		355					360					365			
Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370					375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
		435					440					445			

Lys

<210> 94

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU1 chain 4 (BU1-L2)

<400> 94

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
			20				25						30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Glu	Lys	Ala	Pro	Lys	Ser	Leu	Ile
		35				40						45			
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ile	Tyr	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser
			100					105					110		
Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ser	Tyr	Val	Val	Ser
		115					120					125			
Val	Gly	Lys	Asp	Ala	Ser	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
	130					135					140				
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Leu	Pro	Val	Thr	Ala	Gly	Ala
145					150					155					160

Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu
				165					170					175	
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
			180					185					190		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly	Leu	Glu	Val	Gly	Ala	Glu
		195					200					205			

Ala

<210> 95

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU2 chain 1 (BU2-H1)/BU4 chain 1 (BU4-H1)/BU5 chain 3 (BU5-H2)

<400> 95

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Thr	Tyr
			20					25					30		
Trp	Leu	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Asp	Trp	Ile
		35					40					45			
Gly	Ile	Met	Ser	Pro	Val	Asp	Ser	Asp	Ile	Arg	Tyr	Ser	Pro	Ser	Phe
	50					55				60					
Gln	Gly	Gln	Val	Thr	Met	Ser	Val	Asp	Lys	Ser	Ile	Thr	Thr	Ala	Tyr
65					70				75						80
Leu	Gln	Trp	Asn	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Arg	Arg	Pro	Gly	Gln	Gly	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
		115					120					125			
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
	130					135					140				
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
145					150				155						160
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
			165						170					175	
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180				185						190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro

	195					200					205				
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
225					230					235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
			245						250					255	
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260					265					270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275					280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
	290					295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325						330					335	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			340					345					350		
Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp
		355					360					365			
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370					375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
	435						440					445			

Lys

<210> 96

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU2 chain 2 (BU2-L1) /BU3 chain 4 (BU3-L2)/BU4 chain 2 (BU4-L1)/BU5 chain 4 (BU5-L2)

<400> 96

Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe
50						55					60				
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro
			100					105					110		
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser
		115					120					125			
Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
130						135					140				
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr
145					150					155					160
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu
				165					170					175	
Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile
			180					185					190		
Ile	Ser	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Ser	Leu	Ser	Leu
		195					200					205			
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
210						215					220				
Ser	Ile	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala
225					230					235					240
Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
				245					250					255	
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
			260					265					270		
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val
		275					280					285			
Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser
290						295					300				
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
305					310					315					320
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala
				325					330					335	
Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro
			340					345					350		
Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln
		355					360					365			
Val	Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
370						375					380				
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr
385					390					395					400
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu

210

215

<210> 99

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU3 chain 1 (BU3-H1)

<400> 99

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1			5						10					15	
Ser	Val	Arg	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Asn	Asn
			20					25					30		
Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe
	50					55					60				
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro
			100					105					110		
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser
		115				120						125			
Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	Asp	Ile	Ser	Ile	Asp
	130					135					140				
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr
145					150					155					160
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu
				165					170					175	
Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	Leu	Thr	Thr	Leu	Ile
			180					185					190		
Ile	Ser	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Ser	Leu	Ser	Leu
		195				200						205			
Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg
	210					215					220				
Ser	Ile	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala
225					230					235					240
Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
				245				250						255	
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val

			260					265				270					
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val		
		275					280					285					
Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser		
	290					295					300						
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu		
305					310					315					320		
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala		
			325						330					335			
Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro		
		340						345					350				
Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln		
	355						360					365					
Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala		
	370					375					380						
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr		
385					390					395					400		
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu		
			405					410						415			
Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser		
		420					425					430					
Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser		
	435					440					445						
Leu	Ser	Pro	Gly	Lys													
	450																

<210> 100

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU3 chain 2 (BU3-L1)/BU4 chain 4 (BU4-L2)

<400> 100

Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln		
1			5					10					15				
Thr	Val	Arg	Val	Thr	Cys	Gln	Gly	Asp	Ser	Leu	Arg	Ser	Tyr	Tyr	Ala		
		20					25					30					
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr		
	35					40				45							
Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser		
	50					55					60						

Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu
65					70					75					80
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His
			85						90					95	
Trp	Val	Phe	Gly	Gly	Gly	Thr	Glu	Leu	Thr	Val	Leu	Gly	Gly	Gly	Gly
			100					105					110		
Ser	Asp	Gln	Pro	Gln	Phe	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro
		115					120					125			
Leu	Ser	Tyr	Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Ser	Leu	Ser	Ser	Gln
	130					135					140				
Ile	Val	Gly	Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Gln	Leu
145					150					155					160
Pro	Val	Thr	Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu
				165				170						175	
Tyr	Arg	Leu	Lys	Ile	Leu	Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr
			180					185					190		
Val	Ser	Arg	Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Val	Gly
		195					200					205			
Leu	Glu	Val	Gly	Ala	Glu	Ala									
	210					215									

<210> 101

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU3 chain 3 (BU3-H2)

<400> 101

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Thr	Tyr
			20					25					30		
Trp	Leu	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Asp	Trp	Ile
		35					40					45			
Gly	Ile	Met	Ser	Pro	Val	Asp	Ser	Asp	Ile	Arg	Tyr	Ser	Pro	Ser	Phe
	50					55				60					
Gln	Gly	Gln	Val	Thr	Met	Ser	Val	Asp	Lys	Ser	Ile	Thr	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Asn	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Arg	Arg	Pro	Gly	Gln	Gly	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly
			100					105					110		

[illegible]

<210> 102
 <211> 458
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Amino acid sequence of BU4 chain 3 (BU4-H2)

<400> 102

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	1	5	10	15
Ser	Val	Arg	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Asn	Asn	20	25	30	
Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	35	40	45	
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe	50	55	60	
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser	65	70	75	80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro	100	105	110	
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	115	120	125	
Lys	Ala	Gly	Ile	Arg	Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ser	130	135	140	
Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	145	150	155	160
Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	165	170	175	
Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe	His	Ile	Glu	Ser	Thr	Glu	Asp	180	185	190	
Leu	Thr	Thr	Leu	Ile	Ile	Ser	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	195	200	205	
Tyr	Ser	Leu	Ser	Leu	Gly	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	210	215	220	
Asn	Ile	His	Ile	Arg	Ser	Ile	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	225	230	235	240
Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	245	250	255	
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	260	265	270	
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp				

	275					280						285					
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu		
	290					295					300						
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu		
305					310					315					320		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn		
			325						330					335			
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly		
			340					345					350				
Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu		
	355						360					365					
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr		
	370					375					380						
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn		
385					390					395					400		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe		
			405					410						415			
Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn		
			420					425					430				
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr		
	435						440					445					
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
	450					455											

<210> 103

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU5 chain 1 (BU5-H1)

<400> 103

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser		
1			5				10						15				
Ser	Val	Arg	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Asn	Asn		
		20					25					30					
Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
		35				40					45						
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Ala	Lys	Tyr	Ser	Gln	Asn	Phe		
	50				55						60						
Gln	Gly	Arg	Val	Ala	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Gly	Thr	Ala	Ser		
65					70				75						80		
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		

				85					90				95				
Ala	Arg	Ser	Arg	Asp	Leu	Leu	Leu	Phe	Pro	His	His	Ala	Leu	Ser	Pro		
			100					105					110				
Trp	Gly	Arg	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser		
		115					120					125					
Gly	Ile	Pro	Pro	Lys	Ile	Glu	Cys	Leu	Pro	Ile	Asp	Ile	Ser	Ile	Asp		
	130					135					140						
Glu	Gly	Lys	Val	Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr		
145					150					155					160		
Pro	Glu	Val	Thr	Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu		
				165					170					175			
Gln	Gly	Arg	Phe	His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile		
			180				185						190				
Ile	Lys	Asp	Val	Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Thr	Leu		
	195						200					205					
Arg	Asn	Glu	Phe	Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg		
	210					215					220						
Ser	Ile	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala		
225					230					235				240			
Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr		
				245					250					255			
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val		
			260				265						270				
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val		
	275						280					285					
Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser		
	290					295					300						
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu		
305					310					315				320			
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala		
				325					330					335			
Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro		
			340				345						350				
Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln		
	355						360					365					
Val	Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala		
	370					375					380						
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr		
385					390					395				400			
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu		
				405					410					415			
Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser		
			420				425					430					
Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser		
		435					440					445					

Leu Ser Pro Gly Lys

450

<210> 104

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of BU5 chain 2 (BU5-L1)

<400> 104

Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln
1				5					10					15	
Thr	Val	Arg	Val	Thr	Cys	Gln	Gly	Asp	Ser	Leu	Arg	Ser	Tyr	Tyr	Ala
			20					25					30		
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35					40					45			
Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser
	50					55					60				
Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu
65					70					75					80
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His
				85					90					95	
Trp	Val	Phe	Gly	Gly	Gly	Thr	Glu	Leu	Thr	Val	Leu	Gly	Gly	Gly	Gly
			100					105					110		
Ser	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val
		115					120					125			
Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro
	130					135					140				
Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr	Ala	Gly
145					150					155					160
Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile
				165					170					175	
Leu	Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg
			180					185					190		
Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val	Asp	Ala
		195					200					205			
Glu	Ala														
															210

<210> 105

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> VH amino acid sequence of A0 antibody

<400> 105

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr		
			20					25					30				
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp		
	50					55					60						
Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr		
65					70					75					80		
Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr		
			85					90						95			
Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Glu	Tyr	Ile	Ser	Tyr	Trp		
			100					105						110			
Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
		115					120					125					

<210> 106

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> VL amino acid sequence of A0 antibody

<400> 106

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly		
1				5					10					15			
Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly		
			20					25					30				
Asn	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly		
		35					40					45					
Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe		
	50					55					60						
Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val		
65					70					75					80		
Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn		

				85					90				95
Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	
			100					105					

<210> 107

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of FA-1 chain 1 (FA-1-H1)

<400> 107

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Thr
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Ile	Phe	Ser	Ser	Ser
			20					25					30		
Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Val	Ile	Ser	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Val	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Ser	Ala	Arg	Leu	Tyr	Ala	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Ala	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ile	Pro	Pro
		115					120					125			
Lys	Ile	Glu	Cys	Leu	Pro	Ile	Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val
	130					135					140				
Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr
145					150					155					160
Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe
			165						170					175	
His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	Ile	Lys	Asp	Val
			180					185					190		
Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Thr	Leu	Arg	Asn	Glu	Phe
		195					200					205			
Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	Ser	Ile	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
225					230					235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser

				245					250					255			
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp		
			260						265				270				
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn		
		275						280				285					
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val		
	290					295					300						
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu		
305					310				315						320		
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys		
			325						330					335			
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr		
			340					345					350				
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser		
		355					360					365					
Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu		
	370					375					380						
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu		
385					390				395						400		
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys		
			405						410					415			
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu		
		420						425					430				
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly		
	435						440					445					

Lys

<210> 108

<211> 212

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of FA-1 chain 2 (FA-1-L1)

<400> 108

Asp	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly		
1				5					10					15			
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser		
			20					25					30				
His	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Met		
	35					40						45					
Leu	Ile	Tyr	Asn	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Asp	Arg	Phe		

50		55		60											
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala
65					70					75					80
Gln	Ala	Asp	Asp	Glu	Ser	Asp	Tyr	Tyr	Cys	Ala	Ile	His	Val	Asp	Arg
				85					90					95	
Asp	Ile	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gly
			100					105						110	
Gly	Gly	Ser	Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe
		115					120					125			
Val	Val	Ser	Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly
	130					135					140				
Asn	Pro	Thr	Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr
145					150					155					160
Ala	Gly	Ala	Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu
			165					170						175	
Lys	Ile	Leu	Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg
			180					185					190		
Ala	Arg	Asn	Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val
		195					200					205			
Asp	Ala	Glu	Ala												
	210														

<210> 109

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of FA-1 chain 3 (FA-1-H2)

<400> 109

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5					10					15		
Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr
			20				25					30			
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35				40					45				
Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
	50				55				60						
Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
65				70					75					80	
Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
			85				90						95		
Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Glu	Tyr	Ile	Ser	Tyr	Trp

			100					105					110					
Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr			
			115					120					125					
Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser			
			130					135					140					
Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu			
145				150					155					160				
Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His			
			165					170					175					
Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser			
			180					185					190					
Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys			
			195					200					205					
Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu			
			210					215					220					
Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro			
225				230					235					240				
Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys			
			245					250					255					
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val			
			260					265					270					
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp			
			275					280					285					
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr			
			290					295					300					
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp			
305				310					315					320				
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu			
			325					330					335					
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg			
			340					345					350					
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys			
			355					360					365					
Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp			
			370					375					380					
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys			
385				390					395					400				
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser			
			405					410					415					
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser			
			420					425					430					
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser			
			435					440					445					
Leu	Ser	Leu	Ser	Pro	Gly	Lys												
			450					455										

<210> 110
 <211> 216
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Amino acid sequence of FA-1 chain 4 (FA-1-L2)

<400> 110
 Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
 1 5 10 15
 Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30
 Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45
 Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60
 Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80
 Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
 85 90 95
 Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Thr Val
 100 105 110
 Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
 115 120 125
 Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
 130 135 140
 Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
 145 150 155 160
 Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
 165 170 175
 Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
 180 185 190
 Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
 195 200 205
 Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 111
 <211> 447
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Sequence of hB7H3 antigen protein

<400> 111

Leu	Glu	Val	Gln	Val	Pro	Glu	Asp	Pro	Val	Val	Ala	Leu	Val	Gly	Thr
1				5					10					15	
Asp	Ala	Thr	Leu	Cys	Cys	Ser	Phe	Ser	Pro	Glu	Pro	Gly	Phe	Ser	Leu
			20					25					30		
Ala	Gln	Leu	Asn	Leu	Ile	Trp	Gln	Leu	Thr	Asp	Thr	Lys	Gln	Leu	Val
		35					40					45			
His	Ser	Phe	Ala	Glu	Gly	Gln	Asp	Gln	Gly	Ser	Ala	Tyr	Ala	Asn	Arg
	50					55					60				
Thr	Ala	Leu	Phe	Pro	Asp	Leu	Leu	Ala	Gln	Gly	Asn	Ala	Ser	Leu	Arg
65					70					75				80	
Leu	Gln	Arg	Val	Arg	Val	Ala	Asp	Glu	Gly	Ser	Phe	Thr	Cys	Phe	Val
			85						90					95	
Ser	Ile	Arg	Asp	Phe	Gly	Ser	Ala	Ala	Val	Ser	Leu	Gln	Val	Ala	Ala
			100					105						110	
Pro	Tyr	Ser	Lys	Pro	Ser	Met	Thr	Leu	Glu	Pro	Asn	Lys	Asp	Leu	Arg
	115						120					125			
Pro	Gly	Asp	Thr	Val	Thr	Ile	Thr	Cys	Ser	Ser	Tyr	Gln	Gly	Tyr	Pro
	130					135					140				
Glu	Ala	Glu	Val	Phe	Trp	Gln	Asp	Gly	Gln	Gly	Val	Pro	Leu	Thr	Gly
145					150					155					160
Asn	Val	Thr	Thr	Ser	Gln	Met	Ala	Asn	Glu	Gln	Gly	Leu	Phe	Asp	Val
				165					170					175	
His	Ser	Ile	Leu	Arg	Val	Val	Leu	Gly	Ala	Asn	Gly	Thr	Tyr	Ser	Cys
			180					185					190		
Leu	Val	Arg	Asn	Pro	Val	Leu	Gln	Gln	Asp	Ala	His	Ser	Ser	Val	Thr
	195						200					205			
Ile	Thr	Pro	Gln	Arg	Ser	Pro	Thr	Gly	Ala	Val	Glu	Val	Gln	Val	Pro
	210					215					220				
Glu	Asp	Pro	Val	Val	Ala	Leu	Val	Gly	Thr	Asp	Ala	Thr	Leu	Arg	Cys
225					230					235					240
Ser	Phe	Ser	Pro	Glu	Pro	Gly	Phe	Ser	Leu	Ala	Gln	Leu	Asn	Leu	Ile
				245					250					255	
Trp	Gln	Leu	Thr	Asp	Thr	Lys	Gln	Leu	Val	His	Ser	Phe	Thr	Glu	Gly
			260					265					270		
Arg	Asp	Gln	Gly	Ser	Ala	Tyr	Ala	Asn	Arg	Thr	Ala	Leu	Phe	Pro	Asp
	275						280					285			
Leu	Leu	Ala	Gln	Gly	Asn	Ala	Ser	Leu	Arg	Leu	Gln	Arg	Val	Arg	Val
	290					295					300				
Ala	Asp	Glu	Gly	Ser	Phe	Thr	Cys	Phe	Val	Ser	Ile	Arg	Asp	Phe	Gly
305					310					315					320

Ser	Ala	Ala	Val	Ser	Leu	Gln	Val	Ala	Ala	Pro	Tyr	Ser	Lys	Pro	Ser
				325					330					335	
Met	Thr	Leu	Glu	Pro	Asn	Lys	Asp	Leu	Arg	Pro	Gly	Asp	Thr	Val	Thr
			340					345					350		
Ile	Thr	Cys	Ser	Ser	Tyr	Arg	Gly	Tyr	Pro	Glu	Ala	Glu	Val	Phe	Trp
		355					360					365			
Gln	Asp	Gly	Gln	Gly	Val	Pro	Leu	Thr	Gly	Asn	Val	Thr	Thr	Ser	Gln
	370					375					380				
Met	Ala	Asn	Glu	Gln	Gly	Leu	Phe	Asp	Val	His	Ser	Val	Leu	Arg	Val
385					390					395					400
Val	Leu	Gly	Ala	Asn	Gly	Thr	Tyr	Ser	Cys	Leu	Val	Arg	Asn	Pro	Val
				405					410					415	
Leu	Gln	Gln	Asp	Ala	His	Gly	Ser	Val	Thr	Ile	Thr	Gly	Gln	Pro	Met
			420					425					430		
Thr	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	His	His	His	His	His	His	
		435					440					445			

<210> 112

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Sequence of delta subunit of hCD3 antigen

<400> 112

Phe	Lys	Ile	Pro	Ile	Glu	Glu	Leu	Glu	Asp	Arg	Val	Phe	Val	Asn	Cys
1				5					10					15	
Asn	Thr	Ser	Ile	Thr	Trp	Val	Glu	Gly	Thr	Val	Gly	Thr	Leu	Leu	Ser
			20					25					30		
Asp	Ile	Thr	Arg	Leu	Asp	Leu	Gly	Lys	Arg	Ile	Leu	Asp	Pro	Arg	Gly
		35					40					45			
Ile	Tyr	Arg	Cys	Asn	Gly	Thr	Asp	Ile	Tyr	Lys	Asp	Lys	Glu	Ser	Thr
	50					55					60				
Val	Gln	Val	His	Tyr	Arg	Met	Cys	Gln	Ser	Cys	Val	Glu	Leu	Asp	Pro
65					70					75					80
Ala	Thr	Val	Ala	Ser	Ala	Glu	Asn	Ala	Gln	Cys	Glu	Lys	Glu	Leu	Gln
				85					90					95	
Ala	Leu	Glu	Lys	Glu	Asn	Ala	Gln	Leu	Glu	Trp	Glu	Leu	Gln	Ala	Leu
			100					105					110		
Glu	Lys	Glu	Leu	Ala	Gln	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys		
		115					120					125			

<210> 113

<211> 143
<212> PRT
<213> Artificial Sequence

<220>

<223> Sequence of epsilon subunit of hCD3 antigen

<400> 113

Asp	Gly	Asn	Glu	Glu	Met	Gly	Gly	Ile	Thr	Gln	Thr	Pro	Tyr	Lys	Val	
1				5					10					15		
Ser	Ile	Ser	Gly	Thr	Thr	Val	Ile	Leu	Thr	Cys	Pro	Gln	Tyr	Pro	Gly	
			20					25					30			
Ser	Glu	Ile	Leu	Trp	Gln	His	Asn	Asp	Lys	Asn	Ile	Gly	Gly	Asp	Glu	
		35					40					45				
Asp	Asp	Lys	Asn	Ile	Gly	Ser	Asp	Glu	Asp	His	Leu	Ser	Leu	Lys	Glu	
	50					55					60					
Phe	Ser	Glu	Leu	Glu	Gln	Ser	Gly	Tyr	Tyr	Val	Cys	Tyr	Pro	Arg	Gly	
65					70					75					80	
Ser	Lys	Pro	Glu	Asp	Ala	Asn	Phe	Tyr	Leu	Tyr	Leu	Arg	Ala	Arg	Val	
				85					90					95		
Cys	Glu	Asn	Cys	Met	Glu	Met	Asp	Ala	Lys	Asn	Ala	Gln	Cys	Lys	Lys	
			100					105					110			
Lys	Leu	Gln	Ala	Leu	Lys	Lys	Lys	Asn	Ala	Gln	Leu	Lys	Trp	Lys	Leu	
		115					120					125				
Gln	Ala	Leu	Lys	Lys	Lys	Leu	Ala	Gln	His	His	His	His	His	His		
	130					135					140					

<210> 114

<211> 482

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-1-H1

<400> 114

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	His	Tyr	
			20					25					30			
Tyr	Met	Ala	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Thr	Ser	Ile	Ser	Tyr	Glu	Gly	Asp	Ile	Thr	Tyr	Tyr	Gly	Asp	Ser	Val	

50						55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
				85					90					95	
Ala	Ser	Gln	Thr	Leu	Arg	Glu	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Leu	Glu	Asp	Leu	Lys	Asn	Val	Phe	Pro	Pro
		115					120					125			
Glu	Val	Ala	Val	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile	Ser	His	Thr	Gln
	130					135					140				
Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr	Pro	Asp	His	Val
145					150					155					160
Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Cys
			165					170						175	
Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu	Gln	Asp	Ser	Arg
			180					185					190		
Tyr	Ala	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr	Phe	Trp	Gln	Asn
	195						200					205			
Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr	Gly	Leu	Ser	Glu
	210					215					220				
Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val	Thr	Gln	Ile	Val
225					230					235					240
Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro
			245					250						255	
Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
			260					265					270		
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
		275					280					285			
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
	290					295					300				
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
305					310					315					320
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr
			325					330						335	
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
			340					345					350		
Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
		355				360						365			
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys	Arg
	370					375					380				
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly
385					390					395					400
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
			405					410						415	

Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
			420					425					430		
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln
		435					440					445			
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
	450					455					460				
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	His	His	His	His
465					470					475					480
His	His														

<210> 115
 <211> 203
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HJ-1-L1

<400> 115

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ala	Asn	Tyr
			20					25					30		
Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Gly	Thr	Ser	Asn	Leu	Glu	Val	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					
Ser	Arg	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Asp	Lys	Glu	Phe	Pro	Arg
			85						90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Lys	Pro	Asp	Ile	Gln
			100					105					110		
Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser	Lys	Ser	Ser	Asp
		115					120					125			
Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln	Thr	Gln	Val	Ser
	130					135					140				
Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys	Cys	Val	Leu	Asp
145					150					155					160
Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val	Ala	Trp	Ser	Gln
			165						170					175	
Lys	Ser	Asp	Phe	Ala	Cys	Ala	Asn	Ala	Phe	Gln	Asn	Ser	Ile	Ile	Pro
			180					185					190		

Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser
 195 200

<210> 116
 <211> 457
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HJ-1-H2 and HJ-3-H2

<400> 116
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Tyr
 20 25 30
 Leu Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Val Ile Asp Pro Gly Val Gly Asp Thr Asn Tyr Asn Glu Asn Phe
 50 55 60
 Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Ile Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Glu Asp Asn Thr Gly Thr Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125
 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140
 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160
 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175
 Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190
 Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205
 Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220
 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260					265					270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275					280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
	290					295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325					330						335	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr
			340					345					350		
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser
		355					360					365			
Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370					375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
		435					440					445			
Lys	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys							
	450					455									

<210> 117
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HJ-1-L2 and HJ-3-L2

<400> 117															
Ser	Ile	Val	Met	Thr	Gln	Thr	Pro	Leu	Ser	Leu	Ser	Val	Thr	Pro	Gly
1			5					10					15		
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Lys	Ala	Ser	Gln	Ser	Val	Ser	Ser	Asp
		20						25				30			
Val	Thr	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Gln	Leu	Leu	Ile
		35					40					45			
Tyr	Tyr	Val	Ser	Glu	His	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Tyr	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	Ser	Arg	Val	Glu	Ala
65					70					75					80
Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Gln	Gln	His	His	Arg	Phe	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
			100					105					110		
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
		115					120					125			
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130					135					140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150					155					160
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			
Phe	Asn	Arg	Gly	Glu	Cys										
			210												

<210> 118

<211> 456

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-2-H1 and HJ-4-H1

<400> 118

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	His	Tyr
			20					25					30		
Tyr	Met	Ala	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Thr	Ser	Ile	Ser	Tyr	Glu	Gly	Asp	Ile	Thr	Tyr	Tyr	Gly	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
			85						90					95	
Ala	Ser	Gln	Thr	Leu	Arg	Glu	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		

Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	115	120	125
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	130	135	140
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	145	150	155
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	165	170	175
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	180	185	190
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	195	200	205
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	210	215	220
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	225	230	235
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	245	250	255
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	260	265	270
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	275	280	285
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	290	295	300
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	305	310	315
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	325	330	335
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr	Leu	340	345	350
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser	Cys	355	360	365
Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	370	375	380
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	385	390	395
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	405	410	415
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	420	425	430
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	435	440	445
Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys									450	455	

<210> 119
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HJ-2-L1 and HJ-4-L1

<400> 119
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asn Tyr
 20 25 30
 Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile
 35 40 45
 Tyr Gly Thr Ser Asn Leu Glu Val Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Lys Glu Phe Pro Arg
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> 120
 <211> 483
 <212> PRT
 <213> Artificial Sequence

<220>

<223> HJ-1-H2

<400> 120

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Ser	Asn	Tyr
			20					25					30		
Leu	Ile	Glu	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Val	Ile	Asp	Pro	Gly	Val	Gly	Asp	Thr	Asn	Tyr	Asn	Glu	Asn	Phe
	50					55					60				
Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70				75					80	
Ile	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Asp	Asn	Thr	Gly	Thr	Ala	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Thr	Val	Thr	Val	Ser	Ser	Leu	Glu	Asp	Leu	Lys	Asn	Val	Phe	Pro
		115					120					125			
Pro	Glu	Val	Ala	Val	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile	Ser	His	Thr
	130					135					140				
Gln	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr	Pro	Asp	His
145					150					155				160	
Val	Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val
				165					170					175	
Cys	Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu	Gln	Asp	Ser
			180					185					190		
Arg	Tyr	Ala	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr	Phe	Trp	Gln
		195					200					205			
Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr	Gly	Leu	Ser
	210					215					220				
Glu	Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val	Thr	Gln	Ile
225					230					235				240	
Val	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Ser	Asp	Lys	Thr	His	Thr	Cys
				245					250					255	
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu
			260				265						270		
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
		275					280					285			
Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
	290					295					300				
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
305					310					315				320	
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu

				325					330					335			
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys		
			340					345					350				
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys		
		355					360					365					
Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys		
	370					375					380						
Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys		
385					390				395						400		
Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln		
			405					410					415				
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly		
		420					425					430					
Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln		
	435					440				445							
Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn		
	450				455					460							
His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	His	His	His		
465				470				475							480		
His	His	His															

<210> 121
 <211> 203
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HJ-2-L2

<400> 121																	
Ser	Ile	Val	Met	Thr	Gln	Thr	Pro	Leu	Ser	Leu	Ser	Val	Thr	Pro	Gly		
1			5				10					15					
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Lys	Ala	Ser	Gln	Ser	Val	Ser	Ser	Asp		
		20					25					30					
Val	Thr	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Gln	Leu	Leu	Ile		
	35					40					45						
Tyr	Tyr	Val	Ser	Glu	His	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly		
	50					55				60							
Ser	Gly	Tyr	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	Ser	Arg	Val	Glu	Ala		
65				70					75						80		
Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Gln	Gln	His	His	Arg	Phe	Pro	Leu		
			85					90						95			
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Lys	Pro	Asp	Ile	Gln		

			100					105				110			
Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser	Lys	Ser	Ser	Asp
		115					120					125			
Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln	Thr	Gln	Val	Ser
	130					135					140				
Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys	Cys	Val	Leu	Asp
145					150					155					160
Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val	Ala	Trp	Ser	Gln
			165					170						175	
Lys	Ser	Asp	Phe	Ala	Cys	Ala	Asn	Ala	Phe	Gln	Asn	Ser	Ile	Ile	Pro
		180					185						190		
Glu	Asp	Thr	Phe	Phe	Pro	Ser	Pro	Glu	Ser	Ser					
	195						200								

<210> 122

<211> 454

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-3-H1

<400> 122

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	His	Tyr
		20					25					30			
Tyr	Met	Ala	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40					45				
Thr	Ser	Ile	Ser	Tyr	Glu	Gly	Asp	Ile	Thr	Tyr	Tyr	Gly	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70				75						80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
			85					90						95	
Ala	Ser	Gln	Thr	Leu	Arg	Glu	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
		100						105				110			
Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ile	Pro	Pro	Lys
	115						120					125			
Ile	Glu	Cys	Leu	Pro	Ile	Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val	Leu
	130					135					140				
Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr	Trp
145					150					155					160
Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe	His

				165					170					175		
Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	Ile	Lys	Asp	Val	Gln	
			180					185					190			
Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Thr	Leu	Arg	Asn	Glu	Phe	Gly	
		195					200					205				
Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	Ser	Ile	Asp	Lys	Thr	
	210					215					220					
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	
225					230				235						240	
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	
				245					250						255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	
			260					265					270			
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
		275					280					285				
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
	290					295					300					
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	
305					310				315						320	
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
				325					330					335		
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	
			340					345					350			
Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	
		355					360					365				
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	
	370					375					380					
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
385					390				395						400	
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	
				405					410					415		
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	
		420					425					430				
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	
		435				440						445				
His	His	His	His	His	His											
	450															

<210> 123

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-3-L1

<400> 123

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ala	Asn	Tyr
			20					25					30		
Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Gly	Thr	Ser	Asn	Leu	Glu	Val	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Arg	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Asp	Lys	Glu	Phe	Pro	Arg
			85						90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser
			100					105					110		
Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser
		115					120					125			
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
	130					135					140				
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr	Ala	Gly	Ala
145					150				155						160
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu
			165					170						175	
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
			180					185					190		
Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val	Asp	Ala	Glu
		195					200					205			

Ala

<210> 124

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-4-H2

<400> 124

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5				10						15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Ser	Asn	Tyr

			20					25				30					
Leu	Ile	Glu	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile		
		35					40					45					
Gly	Val	Ile	Asp	Pro	Gly	Val	Gly	Asp	Thr	Asn	Tyr	Asn	Glu	Asn	Phe		
	50					55					60						
Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr		
65					70					75					80		
Ile	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90					95			
Ala	Arg	Glu	Asp	Asn	Thr	Gly	Thr	Ala	Phe	Asp	Tyr	Trp	Gly	Gln	Gly		
			100						105				110				
Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ile	Pro	Pro		
		115					120					125					
Lys	Ile	Glu	Cys	Leu	Pro	Ile	Asp	Ile	Ser	Ile	Asp	Glu	Gly	Lys	Val		
	130					135					140						
Leu	Thr	Val	Ala	Ser	Ala	Phe	Thr	Gly	Glu	Pro	Thr	Pro	Glu	Val	Thr		
145					150					155					160		
Trp	Ser	Thr	Gly	Gly	Arg	Lys	Ile	His	Ser	Gln	Glu	Gln	Gly	Arg	Phe		
			165						170					175			
His	Ile	Glu	Asn	Thr	Asp	Asp	Leu	Thr	Thr	Leu	Ile	Ile	Lys	Asp	Val		
			180					185					190				
Gln	Lys	Gln	Asp	Gly	Gly	Leu	Tyr	Thr	Leu	Thr	Leu	Arg	Asn	Glu	Phe		
	195					200						205					
Gly	Ser	Asp	Ser	Ala	Thr	Val	Asn	Ile	His	Ile	Arg	Ser	Ile	Asp	Lys		
	210					215					220						
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro		
225					230					235					240		
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser		
			245						250					255			
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp		
			260					265					270				
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn		
	275					280						285					
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val		
	290					295					300						
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu		
305					310					315					320		
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys		
			325					330						335			
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr		
			340					345					350				
Leu	Pro	Pro	Cys	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp		
	355					360						365					
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu		
	370					375					380						

Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
				405					410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
		435					440					445			
Lys	His	His	His	His	His	His									
	450					455									

<210> 125

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<223> HJ-4-L2

<400> 125

Ser	Ile	Val	Met	Thr	Gln	Thr	Pro	Leu	Ser	Leu	Ser	Val	Thr	Pro	Gly
1				5				10						15	
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Lys	Ala	Ser	Gln	Ser	Val	Ser	Ser	Asp
			20					25					30		
Val	Thr	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Gln	Leu	Leu	Ile
		35					40					45			
Tyr	Tyr	Val	Ser	Glu	His	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Tyr	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	Ser	Arg	Val	Glu	Ala
65					70					75					80
Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Gln	Gln	His	His	Arg	Phe	Pro	Leu
				85				90						95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser
			100					105					110		
Ser	Gly	Ala	Pro	Arg	Phe	Leu	Thr	Arg	Pro	Leu	Ala	Phe	Val	Val	Ser
		115					120					125			
Val	Gly	Lys	Asp	Ala	Thr	Leu	Ser	Ser	Gln	Ile	Val	Gly	Asn	Pro	Thr
	130					135					140				
Pro	Gln	Val	Ser	Trp	Glu	Lys	Asp	Lys	Gln	Pro	Val	Thr	Ala	Gly	Ala
145					150					155					160
Arg	Phe	Arg	Leu	Ala	Gln	Asp	Gly	Asp	Leu	Tyr	Arg	Leu	Lys	Ile	Leu
				165				170						175	
Asp	Leu	Gln	Leu	Ser	Asp	Ser	Gly	Gln	Tyr	Val	Ser	Arg	Ala	Arg	Asn
			180					185					190		

Ala	Ile	Gly	Glu	Ala	Phe	Ala	Cys	Leu	Gly	Leu	Gln	Val	Asp	Ala	Glu
		195					200					205			

Ala

<210> 126
 <211> 449
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> J1 heavy chain

<400> 126

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Ser	Asn	Tyr
			20					25					30		
Leu	Ile	Glu	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Val	Ile	Asp	Pro	Gly	Val	Gly	Asp	Thr	Asn	Tyr	Asn	Glu	Asn	Phe
	50					55					60				
Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Ile	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Asp	Asn	Thr	Gly	Thr	Ala	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
		115					120					125			
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
	130					135					140				
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
145					150					155					160
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
				165					170					175	
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180					185					190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
		195					200					205			
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
225					230					235					240

[illegible]