Description

Title of Invention

FUSION PROTEIN COMPRISING DUAL FUNCTIONAL DOMAIN AND USES THEREOF

Technical Field

The present invention relates to a fusion protein comprising a dual functional domain and uses thereof. Specifically, the present invention relates to a fusion protein comprising: a first domain comprising a site that specifically binds to a first target; and a second domain comprising a site that specifically binds to an immune modulator or a second target; wherein the first target is a protein that is overexpressed in vascular cells or basal cells at a disease site, and the second target is a protein that is overexpressed or secreted on the surface of cancer cells or immune cells.

Background Art

Antibody-based therapeutic agents are widely used in fields such as various cancers, inflammatory diseases, infectious diseases, and immune diseases. However, clinically, there are problems such as reduced efficacy due to low drug delivery rates and side effects caused by drug activation in normal tissues rather than at the disease site. Currently, many studies are being conducted to develop drugs that are specifically delivered to and activated at the disease site in order to overcome the above problems.

In particular, research is actively being conducted on developing systems to overcome side effects caused by drug activation at a non-disease site by binding to proteins overexpressed in vascular cells surrounding the disease site, thereby enabling disease site-specific delivery and activation of the drug.

However, despite these efforts, no visible disease site-specific drug delivery system or activation technology has yet been developed, so further research is needed.

Detailed Description of Invention

Technical Problem

Accordingly, the present inventors have conducted repeated research to increase disease site-specific drug delivery efficiency without affecting normal tissues. As a result, the present inventors have found that a fusion protein of a dual domain structure comprising a first domain that binds to a protein specifically overexpressed in vascular cells or basal cells at a disease site and a second domain that binds to a protein specifically expressed in disease target cells accumulates specifically in the disease site and exhibits drug activity specific to the disease site. Based on the above, the present inventors have completed the present invention.

Solution to Problem

In order to achieve the above object, in one aspect of the present invention, there is provided a fusion protein comprising: a first domain comprising a site that specifically binds to a first target; and a second domain comprising a site that specifically binds to an immune modulator or a second target; and a fusion protein dimer comprising the same. In this case, the first target may be a protein that is overexpressed in vascular cells or basal cells at a disease site, and the second target may be a protein that is overexpressed or secreted on the surface of cancer cells or immune cells.

In another aspect of the present invention, there is provided a polynucleotide encoding the fusion protein or a fusion protein dimer comprising the same, a vector comprising the polynucleotide, and a cell transformed with the vector.

In another aspect of the present invention, there is provided a method for producing a fusion protein or a fusion protein dimer, the method comprising the steps of: culturing the transformed cells; and obtaining a fusion protein or a fusion protein dimer comprising the same from the culture solution.

In another aspect of the present invention, there is provided the fusion protein, a fusion protein dimer comprising the same, or a drug conjugate thereof (fusion protein-drug conjugate, fusion protein dimer-drug conjugate) and a pharmaceutical composition for the prevention or treatment of a disease, comprising the same as an active ingredient.

In another aspect of the present invention, there is provided a cleavable peptide comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 159, 160, 173 to 176, and combinations thereof.

In another aspect of the present invention, there is provided a use of the fusion protein, a fusion protein dimer comprising the same, or a drug conjugate thereof (fusion protein-drug conjugate, fusion protein dimer-drug conjugate) for the prevention or treatment of a disease.

In another aspect of the present invention, there is provided a method for the prevention or treatment of a disease, comprising administering the fusion protein, a fusion protein dimer comprising the same, or a drug conjugate thereof (fusion protein-drug conjugate, fusion protein dimer-drug conjugate) to a subject.

Effects of Invention

ReleaDome (Figure 1), a dual functional domain structure according to the present invention, has a structure in which a first domain and a second domain are linked via a linker. In this case, the first domain can bind to a protein that is specifically expressed or exposed to vascular cells or basal cells at a disease site, and the second domain can bind to a protein that is overexpressed in target cells at a disease site. In addition, the linker comprises a substrate sequence that can be cleaved by a specific proteolytic enzyme that is specifically expressed in

the microenvironment of the disease site. Therefore, the structure is a novel structure that can be specifically activated at the disease site and can efficiently exert a therapeutic effect. In addition, a multispecific fusion protein comprising the dual functional domain structure can be designed in various forms to include various functions. Therefore, the dual functional domain structure and the multispecific fusion protein comprising the same according to the present invention can be used for various applications as alternatives to conventional antibodies.

Brief Description of Drawings

Figure 1 is a schematic diagram of a structure of a dual functional domain (ReleaDome).

Figure 2 is a schematic diagram of a multispecific fusion protein comprising a ReleaDome. Figure 2a is a schematic diagram of a basic form multispecific fusion protein composed of minimal components, and Figures 2b and 2c are schematic diagrams of a multispecific fusion protein with an extended structure.

Figure 3 is a schematic diagram showing one example of a multispecific fusion protein comprising a ReleaDome. Figure 3a is a schematic diagram of a DVD-Ig type multispecific fusion protein comprising a ReleaDome and a variant thereof, Figure 3b is a schematic diagram of a ReleaBody type multispecific fusion protein comprising a ReleaDome and a variant thereof, and Figure 3c is a schematic diagram of various types of multispecific fusion proteins comprising a ReleaDome.

Figure 4 shows the results obtained by analyzing a DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2], which is one embodiment of the present invention, and a variant thereof. Figures 4a to 4e show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC (size-exclusion-UPLC) of a DVD-Ig type multispecific fusion protein and a variant molecule thereof. Figures 4f and 4g show the results obtained by staining a DVD-Ig type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 5 shows the results obtained by analyzing a DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47], which is one embodiment of the present invention, and a variant thereof. Figures 5a and 5b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a DVD-Ig type multispecific fusion protein and a variant molecule thereof. Figure 5c shows the results obtained by staining a DVD-Ig type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 6 shows the results obtained by analyzing a DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR], which is one embodiment of the present invention, and a variant thereof. Figures 6a to 6c show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a DVD-Ig type multispecific fusion

protein and a variant molecule thereof. Figures 6d and 6e show the results obtained by staining a DVD-Ig type multispecific fusion protein and a variant molecule thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 7 shows the results obtained by analyzing a DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-DLK1], which is one embodiment of the present invention, and a variant thereof. Figures 7a and 7b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a DVD-Ig type multispecific fusion protein and a variant molecule thereof. Figure 7c shows the results obtained by staining a DVD-Ig type multispecific fusion protein and a variant molecule thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 8 shows the results obtained by analyzing a ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2], which is one embodiment of the present invention, and a variant thereof. Figures 8a and 8b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a ReleaBody type multispecific fusion protein and a variant molecule thereof. Figure 8c shows the results obtained by staining a ReleaBody type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 9 shows the results obtained by analyzing a ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CTLA4], which is one embodiment of the present invention, and a variant thereof. Figures 9a and 9b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a ReleaBody type multispecific fusion protein and a variant molecule thereof. Figure 9c shows the results obtained by staining a ReleaBody type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 10 shows the results obtained by analyzing a ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47], which is one embodiment of the present invention, and a variant thereof. Figures 10a and 10b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a ReleaBody type multispecific fusion protein and a variant molecule thereof. Figure 10c shows the results obtained by staining a ReleaBody type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 11 shows the results obtained by analyzing a ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR], which is one embodiment of the present invention, and a variant thereof. Figures 11a and 11b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a ReleaBody type multispecific fusion protein and a variant molecule thereof. Figure 11c shows the results obtained by staining a ReleaBody type multispecific fusion protein and a variant molecule

thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 12 shows the results obtained by analyzing a ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-B7H3], which is one embodiment of the present invention, and a variant thereof. Figures 12a and 12b show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a ReleaBody type multispecific fusion protein and a variant molecule thereof. Figure 12c shows the results obtained by staining a ReleaBody type multispecific fusion protein and a variant thereof with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 13 shows the results obtained by analyzing a variant [DVD-IgG CrossMab, KIH, single arm-cleavable] of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR], which is one embodiment of the present invention. Figure 13a is a schematic diagram of a variant [DVD-IgG CrossMab, KIH, single arm-cleavable] of a multispecific fusion protein. Figures 13b and 13c show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a variant [DVD-IgG CrossMab, KIH, single arm-cleavable] of a multispecific fusion protein. Figure 13d shows the results obtained by staining a variant [DVD-IgG CrossMab, KIH, single arm-cleavable] of a multispecific fusion protein with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 14 shows the results obtained by analyzing a variant [DVD-IgG asymmetric] of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR], which is one embodiment of the present invention. Figure 14a is a schematic diagram of a variant [DVD-IgG asymmetric] of a multispecific fusion protein. Figures 14b and 14c show the results obtained by analyzing the productivity, property, and purity via SEC-UPLC of a variant [DVD-IgG asymmetric] of a multispecific fusion protein. Figure 14d shows the results obtained by staining a variant [DVD-IgG asymmetric] of a multispecific fusion protein with Coomassie Brilliant Blue after SDS-PAGE under reducing conditions.

Figure 15 shows the results obtained by analyzing the drug-antibody conjugation ratio (DAR, drug-antibody ratio) from a multispecific fusion protein-drug conjugate comprising a ReleaDome. Figures 15a and 15b show an example of the results analyzed using the reversed phase chromatography (RP-UPLC) method, and Figures 15c to 15g show an example of the results analyzed using the reduced RP-UPLC (rRP-UPLC) method.

Figure 16 shows the results of SDS-PAGE under reducing conditions on five proteolytic enzymes.

Figures 17a to 17c show the results obtained by analyzing the cleavage efficiency (cleavable activity) of a multispecific fusion protein comprising a ReleaDome by an MT-SP1 proteolytic enzyme using SDS-PAGE under reducing conditions.

Figure 18 shows the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein comprising a ReleaDome by a uPA proteolytic enzyme using SDS-

PAGE under reducing conditions.

Figure 19 shows the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein comprising a ReleaDome by a human MMP-2 (hMMP-2) proteolytic enzyme using SDS-PAGE under reducing conditions.

Figure 20 shows the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein comprising a ReleaDome by an MMP-9 proteolytic enzyme using SDS-PAGE under reducing conditions. Figure 20a shows an example of the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein by a human MMP-9 (hMMP-9) proteolytic enzyme using SDS-PAGE under reducing conditions. Figure 20b shows an example of the results obtained by analyzing the concentration-dependent cleavage efficiency of a hMMP-9 proteolytic enzyme using SDS-PAGE under reducing conditions. Figure 20c shows the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein by a mouse MMP-9 (mMMP-9) proteolytic enzyme using SDS-PAGE under reducing conditions.

Figure 21 shows the results obtained by analyzing the cleavage efficiency of a multispecific fusion protein comprising a ReleaDome using SDS-PAGE under reducing conditions when hMMP-2 and hMMP-9 proteolytic enzymes were used in combination. Figure 21a shows the results obtained by analyzing the cleavage efficiency using SDS-PAGE under reducing conditions when the multispecific fusion protein, hMMP-2 and hMMP-9 (hMMP-2&-9) were reacted in a ratio of 1:0.02:0.02. Figure 21b shows the results obtained by analyzing the cleavage efficiency using SDS-PAGE under reducing conditions when the multispecific fusion protein, hMMP-2 and hMMP-9 were reacted in a ratio of 1:0.02:0.06. Figure 21c shows the results obtained by analyzing the cleavage efficiency using SDS-PAGE under reducing conditions when the multispecific fusion protein, hMMP-2 and hMMP-9 were reacted in a ratio of 1:0.02:0.02 or 1:0.02:0.06.

Figure 22 shows the results obtained by analyzing the antigen binding avidity of a multispecific fusion protein comprising a ReleaDome using ELISA. Figures 22a to 22d shows the results obtained by confirming the changes in antigen [HER2] binding ability depending on the concentration of each multispecific fusion protein comprising a ReleaDome and the presence or absence of treatment with a proteolytic enzyme [MT-SP1]. Figure 22e shows the results obtained by confirming the binding avidity of each multispecific fusion protein to each antigen [ANXA1, HER2].

Figure 23 shows an example of the results obtained by mapping the antigen binding site of each UNIT1 having binding affinity to ANXA1 using ELISA.

Figure 24 shows the results obtained by analyzing the binding avidity of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2], which is one embodiment of the present invention, to each tumor cell (SK-OV-3 cell, NCI-N87 cell, BT-474 cell) using flow cytometry (Fc). Figure 24a shows the results obtained by confirming the antigen binding ability

depending on the concentration of BA-0102-001 comprising a ReleaDome and the presence or absence of treatment with a proteolytic enzyme [MT-SP1] in SK-OV-3 cells expressing HER2. Figure 24b shows the results obtained by confirming the antigen binding ability of each multispecific fusion protein comprising a ReleaDome at different concentrations in NCI-N87 cells expressing HER2. Figure 24c shows the results obtained by confirming the antigen binding ability of each multispecific fusion protein comprising a ReleaDome at different concentrations in BT-474 cells expressing HER2.

Figure 25 shows the results obtained by confirming the binding avidity of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47] to each cell (CT-26 cell, MDA-MB-231 cell) using flow cytometry. Figures 25a and 25b show the results obtained by confirming the antigen [CD47] binding ability of a fusion protein of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47] at different concentrations in CT-26 cells expressing mouse CD47. Figures 25c to 25f show the results obtained by confirming the antigen [CD47] binding ability of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47] at different concentrations in MDA-MB-231 cells expressing human CD47.

Figure 26 shows the results obtained by confirming the binding avidity of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR], which is one embodiment of the present invention, to each tumor cell line (MDA-MB-231 cell, MDA-MB-453 cell) using flow cytometry. Figures 26a to 26d shows the results obtained by confirming the antigen [EGFR] binding ability of each multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR] at different concentrations in MDA-MB-231 cells expressing human EGFR. Figure 26e shows the results obtained by confirming the antigen binding avidity of each fusion protein in MDA-MB-453 cells in which human EGFR is hardly expressed.

Figure 27 shows the results obtained by analyzing the transport capacity (in vitro transcytosis) of the first domain (UNIT1) of ReleaDome, which exhibits binding affinity to ANXA1, using ELISA. Figure 27a shows the results obtained by analyzing the transport capacity of single antibodies comprising the respective first domain (UNIT1) under co-culture conditions of EA.hy926 cells and MCF-7 cells. Figure 27b shows the results obtained by analyzing the transport capacity of single antibodies comprising the respective first domain (UNIT1) under co-culture conditions of HUVEC cells and MCF-7 cells. Figure 27c shows the results obtained by analyzing the transport capacity of single antibodies and multispecific fusion proteins, respectively, under co-culture conditions of HUVEC cells and MCF-7 cells.

Figure 28 shows the results obtained by analyzing the cytotoxicity (in vitro cytotoxicity) of each multispecific fusion protein-drug conjugate comprising a ReleaDome upon treatment with proteolytic enzymes. Figure 28a shows the results obtained by confirming the cytotoxicity in NCI-N87 cells expressing HER2 after treatment with TD-0102-001.017 or (+)TD-0102-001.017, in which the first domain is cleaved by a proteolytic enzyme (MT-SP1 and uPA), at

different concentrations. Figure 28b shows the results obtained by confirming the cytotoxicity in BT-474 cells expressing HER2 after treatment with TD-0102-001.017 or (+)TD-0102-001.017, in which the first domain is cleaved by a proteolytic enzyme (MT-SP1), at different concentrations. Figure 28c shows the results obtained by confirming the cytotoxicity in SK-BR-3 cells expressing HER2 after treatment with TD-0102-001.017 or (+)TD-0102-001.017, in which the first domain is cleaved by a proteolytic enzyme (MT-SP1), at different concentrations. Figure 28d shows the results obtained by confirming the cytotoxicity in JIMT-1 cells expressing HER2 after treatment with TD-0102-001.017 or (+)TD-0102-001.017, in which the first domain is cleaved by a proteolytic enzyme (MT-SP1), at different concentrations. Figure 28e shows the results obtained by confirming the cytotoxicity in SK-OV-3 cells expressing HER2 after treatment with TD-0102-001.017 or (+)TD-0102-001.017, in which the first domain is cleaved by a proteolytic enzyme (MT-SP1), at different concentrations.

Figure 29 shows the results obtained by confirming the cytotoxicity in MDA-MB-231 cells expressing EGFR after treatment with each multispecific fusion protein-drug conjugate comprising a ReleaDome at different concentrations.

Figures 30a to 30j show an example of the results obtained by analyzing the thermal stability (differential scanning fluorimetry) of a multispecific fusion protein comprising a ReleaDome.

Figure 31 shows the results obtained by analyzing the stability in human plasma (stability in species plasma) of each multispecific fusion protein comprising a ReleaDome using SDS-PAGE under reducing conditions. Figure 31a shows the results obtained by confirming each multispecific fusion protein conjugated with a fluorescent dye. Figures 31b to 31c show the results obtained by analyzing the stability of each multispecific fusion protein conjugated with a fluorescent dye by mixing it with human plasma and reacting it at 37 °C on a daily basis.

Figure 32 shows the results obtained by analyzing the pharmacokinetics (PK) of each multispecific fusion protein comprising a ReleaDome, which is one embodiment of the present invention, using a mouse. Figure 32a is a graph showing the results obtained by analyzing the pharmacokinetics of BA-0109-012 (4 mg/kg), Figure 32b is a graph showing the results obtained by analyzing the pharmacokinetics of BA-0109-016 (4 mg/kg), and Figure 32c is a graph showing the results obtained by analyzing the pharmacokinetics of BA-0109-018 (4 mg/kg).

Figure 33 shows the results obtained by analyzing the distribution of a multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2], which is one embodiment of the present invention, within cancer tissue in a tumor cell line transplanted tumor mouse model via optical tomographic imaging (IVIS®). Figure 33a shows the results obtained by confirming the in vivo distribution 4 hours after administration of each multispecific fusion protein in a HER2-expressing NCI-N87 (human gastric cancer cell) xenograft (CDX, cell-derived xenograft) mouse model via IVIS®. Figure 33b shows the results obtained by confirming the in vivo

distribution 4 hours after administration of each multispecific fusion protein in a HER2-expressing JIMT-1 human breast cancer CDX mouse model via IVIS®.

Figure 34 shows the results obtained by analyzing the in vivo tissue distribution of a multispecific fusion protein (anti-ANXA1-anti-EGFR; TD-0109-003-CW) comprising a ReleaDome, which is one embodiment of the present invention, in an EGFR-expressing JIMT-1 cell (human breast cancer cell) CDX mouse model via IVIS®. Figure 34a shows the results obtained by confirming the in vivo distribution of mice at each time point after administration of TD-0109-003-CW via imaging, and Figure 34b shows the results obtained by measuring the fluorescence intensity of major organs extracted from mice 72 hours after administration of TD-0109-003-CW.

Figure 35 shows the results obtained by analyzing the in vivo toxicity (safety evaluation) of a multispecific fusion protein (anti-ANXA1-anti-CD47; BA-0107-005) comprising a ReleaDome, which is one embodiment of the present invention.

Figure 36 shows the results obtained by confirming the anticancer activity of each multispecific fusion protein [anti-ANXA1-anti-HER2]-drug conjugate comprising a ReleaDome, which is one embodiment of the present invention, in an HER2-expressing NCI-N87 cell CDX mouse model. Figure 36a shows the results obtained by measuring the tumor size on a daily basis after administration of the test substance, and Figure 36b shows the results obtained by measuring the tumor weight extracted from mice on day 62 after administration of the test substance.

Figure 37 shows the results obtained by evaluating the anticancer activity of each multispecific fusion protein [anti-ANXA1-anti-EGFR]-drug conjugate comprising a ReleaDome, which is one embodiment of the present invention, in an EGFR-expressing MDA-MB-231 cell (human triple negative breast cancer) CDX mouse model. Figure 37a shows the results obtained by measuring the tumor size on a daily basis after administration of the test substance, and Figure 37b shows the results obtained by measuring the mouse body weight on a daily basis after administration of the test substance.

Figure 38 shows the results obtained by measuring the tumor size on a daily basis (Figure 38a) after administering each of the multispecific fusion protein [anti-ANXA1-anti-HER2]-drug conjugate (0.0175 umol/kg) or single antibody-drug conjugate (0.0338 umol/kg) comprising a ReleaDome, which is one embodiment of the present invention, in a HER2-expressing JIMT-1 cell CDX mouse model, and the results obtained by measuring the body weight of the mouse on a daily basis after administration of each test substance (Figure 38b).

Best Mode for Carrying out the Invention

<Definitions of Terms>

As used herein, the term "antibody" refers to an immunoglobulin (Ig) molecule that

reacts immunologically with a specific antigen, meaning a protein molecule that acts as a receptor specifically recognizing the antigen, and is a concept that encompasses both whole antibodies and antibody fragments. In addition, an antibody is also referred to as immunoglobulin. An antibody may refer to any one selected from IgG, IgE, IgM, IgD, and IgA, and may be a subclass of IgG such as IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2. In addition, an antibody may be an agonist antibody or an antagonist antibody.

Specifically, the antibody or fragment thereof may include, but is not limited to, monoclonal antibodies, polyclonal antibodies, single domain antibodies, single chain antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, intrabodies, Fv, scFv, disulfide-linked Fv (di-scFv), Fab fragments, $F(ab')_2$ fragments, domain antibodies, minibodies, nanobodies, VHH (heavy chain variable domain of heavy chain antibody), IgD antibodies, IgE antibodies, IgM antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies, antibody constant domain derivatives and any epitope binding fragment.

As used herein, the term "antigen" refers to a structure capable of selectively binding to an antibody. The target antigen may be a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. Specifically, the antigen may be a polypeptide and may be a protein present on or within a cell.

As used herein, the term "epitope" refers to an antigenic determinant and is a region on the antigen to which an antibody or polypeptide binds. Protein epitopes may include amino acid residues directly involved in binding as well as amino acid residues that are effectively blocked by specific antigen-binding antibodies or peptides. It is the simplest form or the smallest structural region of a complex antigen molecule capable of binding to an antibody or receptor. Epitopes may be linear or structural/structural morphological.

As used herein, the term "Fv," "Fv fragment," or "Fv region" refer to a polypeptide comprising a variable region of heavy chain (VH) and a variable region of light chain (VL) of a single antibody.

As used herein, the term "single chain Fv (scFv)" refers to an antibody fragment comprising the variable region of heavy chain and the variable region of light chain of an antibody within a single polypeptide chain.

As used herein, the term "Fab" or "Fab region" refer to an antibody region that binds to an antigen. Conventional IgG generally comprises two Fab regions. Each Fab region typically consists of one variable region and one constant region of each heavy and light chain, respectively. Specifically, in the Fab region, the variable and constant regions of the heavy chain are the VH and CH1 (constant region of heavy chain 1) regions, and in the Fab region, the variable and constant regions of the light chain are the VL and CL (constant region of light chain) regions. The VH, CH1, VL, and CL of the Fab region may be arranged in various ways in

order to confer antigen-binding ability according to the present disclosure, including a CrossMab Fab arrangement having an arrangement in which VH and VL are substituted for each other.

As used herein, the term "single domain antibody (sdAb)" refers to an antibody fragment composed of a single monomeric variable domain, also called a nanobody (VHH, heavy chain variable domain of heavy chain antibody). In general, it refers to an antibody having binding activity to an antigen that comprises only a single heavy chain variable domain. While sdAbs derived from the heavy chain are mainly used, it has been reported that single variable domain fragments derived from the light chain also specifically bind to antigens.

As used herein, the term "heavy chain" refers to a polypeptide chain of about 50 kDa to about 70 kDa. Here, the N-terminal portion comprises a variable region of about 120 to 130 or more amino acids, and the C-terminal portion comprises a constant region. The constant region may be one of five types: alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ). In this case, α, δ, and γ comprise about 450 amino acids, and μ and ε comprise about 550 amino acids. The constant domains (CH domains) of the heavy chain are numbered from the N-terminus to the C-terminus (e.g., CH1, CH2, CH3, etc.).

As used herein, the term "light chain" refers to a polypeptide chain of about 25 kDa. Here, the N-terminal portion comprises a variable region of about 100 to about 110 or more amino acids, and the C-terminal portion comprises a constant region. The light chain constant region (CL) is of two types: kappa (κ) or lambda (λ). Any CL and CH1 region of these antibody classes or a variant thereof may be used in the present disclosure.

In an exemplary embodiment of the present invention, CH1 and CL may each include the amino acid sequences of Table 1 below. The following amino acid sequences are described sequentially from the N-terminus to the C-terminus.

[Table 1]

Constant region of heavy chain 1(CH1)		
Isotype	Variant	Amino acid sequence
IgG1	WT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKV(SEQ ID NO:241)
IgG1	Variant-LALAPG-knob	ASTKGPSVFPLAPSSKSTSGGTAALGCLVEDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDEKV(SEQ ID NO:242)
IgG2	WT	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYT CNVDHKPSNTKVDKTV(SEQ ID NO:243)
IgG1	variant	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSC(SEQ ID NO:244)
IgG4	WT	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRV(SEQ ID NO:245)

Light chain(LC)			
Name	Isotype	Variant	Amino acid sequence
DL1	Kappa	WT	RSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:246)
DL2	Kappa	K149C	RSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW CVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:247)
DL5	Lambda	WT	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS(SEQ ID NO:248)

The structural formulas included in the fusion protein structure described as one embodiment of the present invention are listed in Table 2 below.

[Table 2]

Structural formula	**Structure**
structural formula (I)	first structure
structural formula (II)	second structure
structural formula (IV)	fourth structure
structural formula (V)	fifth structure
structural formula (I')	sixth structure
structural formula (IV')	seventh structure
structural formula (I")	eighth structure
structural formula (IV")	ninth structure
structural formula (I"')	eleventh structure
structural formula (I"")	twelfth structure
structural formula (IV"')	thirteenth structure
structural formula (IV"")	fourteenth structure
structural formula (VI)	fifteenth structure
structural formula (VII)	sixteenth structure
structural formula (VIII)	third structure

The terms listed in Tables 1 and 2 above are described in more detail below.

<Fusion protein>

In one aspect of the present invention, there is provided a fusion protein comprising: a first domain comprising a site that specifically binds to a first target; and a second domain comprising a site that specifically binds to an immune modulator or a second target. In this case, the first target may be a protein that is overexpressed in vascular cells or basal cells at a disease site, and the second target may be a protein that is overexpressed or secreted on the surface of

cancer cells or immune cells.

The first domain and the second domain may be linked via a linker, and the linker may be a cleavable linker or a non-cleavable linker. The fusion protein comprising the first domain and the second domain may further comprise an anticancer agent, and the anticancer agent and the fusion protein may be linked via a linker.

In addition, the fusion protein may further comprise an Fc region or a variant thereof and/or an antigen binding site. In this case, the fusion protein and the Fc region or a variant thereof or the antigen binding site may be linked via a linker. In addition, when the fusion protein and the antigen binding site are linked via a linker, the antigen binding site may comprise only the heavy chain variable region or the light chain variable region of the antibody.

In such a novel structure, the first domain may inhibit the activity of the second domain at a non-disease site by masking the second domain at a non-disease site. In addition, the first domain may be cleaved by a disease site-specific cleavage enzyme at a disease site, and as a result, the second domain may be exposed and specifically activated at the disease site, thereby efficiently exerting a therapeutic effect.

The specific structure of the fusion protein is described in more detail below.

ReleaDome

In one aspect of the present invention, there is provided a fusion protein comprising: a first domain comprising a site that specifically binds to a first target; and a second domain comprising a site that specifically binds to an immune modulator or a second target.

As used herein, the term "ReleaDome" refers to a dual functional domain structure comprising the first domain and the second domain. The first domain and the second domain may be linked via a linker. Therefore, in the present invention, "ReleaDome" refers to a structure comprising the first domain, the second domain, and the linker. In the present invention, the ReleaDome may be the minimum unit of the fusion protein according to the present invention.

First domain

In the present invention, the first domain may comprise a site that specifically binds to a first target. The first domain may be described interchangeably with "first component," "A," or "outer domain" in the present specification. The first domain may mask the second domain at a non-disease site and may be cleaved at the disease site to expose the second domain to the disease site, thereby activating the second domain specifically at the disease site.

The first target may be a protein that is overexpressed or overexposed in vascular cells or basal cells surrounding the disease site. In addition, the first target may be a protein that is overexpressed or overexposed in immune cells or disease cells within the microenvironment of the disease site. Through the first domain, the fusion protein according to the present invention allows the ReleaDome to be located at the disease site in a location-specific and expression-specific manner.

Specifically, the first target may be Annexin A1 (ANXA1), albumin, App2, B7H3, Cav-1, CD36, EphA2, EphA3, EphB1, FAPα (Fibroblast activation protein alpha), ICAM1, Integrins, KDR (VEGF2), TEM8, TSP-1, ED-B, Endothelin-1, Endoglin (CD105), VEGFR1 (FLT1), PDGFR, PSMA, VCAM-1, Myct1, etc. More specifically, it may be ANXA1, TEM8, albumin, KDR (VEGFR2), PSMA, ICAM1, FAPα, B7H3, or Myct1, but is not limited thereto.

The first domain may be any one selected from the group consisting of an antibody or a fragment thereof, a ligand or a fragment thereof, and a receptor or a fragment thereof, for a first target, but is not limited thereto. The form of the first domain may be, for example, an antibody or a fragment thereof (e.g., scFv, Fv, VHH, Fab), a peptide, an aptamer, etc., and may be a form comprising part or all of the naturally occurring counterpart/ligand of the target that can be the antigen of the first domain, but is not limited thereto. Preferably, it may be an antibody or a fragment thereof, or a peptide. The antibody and the fragment thereof are the same as described above. In one embodiment of the present invention, the antibody fragment may be a scFv or a single domain antibody.

Specifically, the first domain may be an antibody, a fragment thereof, or a peptide that binds to any one selected from the group consisting of ANXA1, TEM8, albumin, KDR (VEGFR2), PSMA, ICAM1, FAPα, B7H3, and Myct1. Table 3 below shows the variable region polypeptide sequences or peptide sequences of the antibodies or fragments thereof described as the first domains of the various fusion proteins described herein. The fusion proteins according to exemplary embodiments may include these variable region polypeptide or peptide sequences. The following amino acid sequences are described sequentially from the N-terminus to the C-terminus.

[Table 3]

First component: Transporting and Masking				
Part number	First target	Clone name; UNIT1	Outer domain in HC	Outer domain in LC
A1	ANXA1	Y004	QMQLVQSGGGLVQPGRSLRLSCA VSGFTFDDYAMHWVRQAPGKGL EWVSGINWDSSNIGYADSVKGRF TISRDNAKNSLYLQMNNLRSEDT AVYYCVKLASDSGGYFESWGQG TLVTVSS(SEQ ID NO:1)	QLVLTQPHSVSESPGKTVTISCA RSSGSIASKYVQWYQQRPGSAP TAVIYEDNQRPSGVPDRFSGSID TSSNSASLTISGLKTEDEADYYC QSYDSSSVVFGGGTKLTVL(SEQ ID NO:2)
A2	ANXA1	Y025	QVQLVESGGGLVESGGSLRLSCA ASGFTFSNAWMTWVRQAPGKGL EWVGVIRSKTYGGTTEYAAPLRG RFSISRDDSKNTLYLQMNSLRAE DTAVYYCAKGAAYGPFDYWGQ GTLITVSS(SEQ ID NO:3)	NFMLTQPHSVSESPGKTVTISCT RSSGSIASKYVQWYQQRPGSVP ITVIYEDDQRPSGVPDRFSGSIDS FSNSASLTITGLKTEDEAEYYCQ SYDDNTVVFGGGTKLTVL(SEQ ID NO:4)
A3	ANXA1	Y026	QVQLVESGGGLVKPGRSLRLSCT ASGFTFGDYAMSWFRQAPGKGL EWVGFIRSKAYGGTTEYASVKGR	DIVMTQTPLSLHVTPGEPASISC RSSQSLLHSNGYNYLEWYLQKP GQSPQLLIYLGSNRASGVPDRFS

			FTISRDDSKSIAYLQMNSLRAEDT AVYYCARDGNYYDSRGYYYDTF DLWGQGTMVTVSS(SEQ ID NO:5)	GSGSGTDFTLKISRVEAEDVGV YYCTQSIQVPYTFGQGTKLEIK(SEQ ID NO:6)
A4	ANXA1	Y031	QVQLVQSGGGVVQPGRSLKLSCE TSGFTFNMHPMHWVRQAPGKGL EWVASIKYDGSKRYYTDSVKGRF TVSRDHVDTVYLQMNSLRAEDT AVYYCSCNGLGQDDEAFDIWGQ GTMVTVSS(SEQ ID NO:7)	QLVLTQPHSVSESPGKTVTISCT RSSGSIASKYVQWYQQRPGSAP TTVIYEDNQRPSGVPDRFSGSIDI SSNSASLTISGLKTEDEADYYCQ SYDSSSVVFGGGTKLTVL(SEQ ID NO:8)
A5	ANXA1	Y041	QVQLVESGGGLVQPGRSLRLSCA ASGFTFDDYGMHWVRQAPGKGL EWVSGISWNSGSIGYADSVKGRF TISRDNAKNSLYLQMNSLRSEDT AVYYCTRYLHRLPFDVWGKGTT VTVSS(SEQ ID NO:9)	NFMLTQPHSVSESPGKMVTISC TRSSGSIASKYVQWYQQRPGSA PITVIYEDNKRPSGVPDRFSGSID SFSNSASLTITGLKTEDEADYYC QSYDDNTVVFGGGTKLTVL(SE Q ID NO:10)
A6	ANXA1	Y060	QVQLVESGGDWVEPGRSLRLSCR TSGFTFADYALNWVRQAPGKGL EWVGFIRSKTYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARRGGWTLGYAFDIWG QGTMITVSS(SEQ ID NO:11)	SYELTQPLSVSVSPGQTATITCS GHQLGNRYLSWYQKKPGQSPV LLISQDTNRPSGIPERFSGSDSGT TATLTIRETQAMDEADYYCQA WDSTTAVFGGGTKLTVL(SEQ ID NO:12)
A7	ANXA1	Y062	QMQLVESGGGLVKPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRNDSKSIAYLQMNSLRAED TAVYYCARIVAYGPFDYWGQGA LVTVSS(SEQ ID NO:13)	DIQMTQSPSTLSASVGDRVTITC RASQSISSWLAWYQQKPGIAPK LLIYQASTLETGVPLRFSGRGSG TEFTLTINSLQPDDFATYYCQQY DDYSPLTFGGGTKVEIK(SEQ ID NO:14)
A8	ANXA1	Y063	QVQLVESGGGLVQPGGSLRLSCA ASGFTFSDHYMDWVRQAPGKGL EWVGRSRNKANSHTTEYAASVK GRFTISRDDSKKSLYLQMNSLRA EDTAVYYCARGGAWLDYWGQG TLVTVSS(SEQ ID NO:15)	DIQMTQSPSSLSASVGDRLTITC RASQSILTYLNWYQQKPGKAPK LLVYAASSLQRGVPSRFSGRGS GTDFTLTISGLQPDDFALYYCQ QSYSSPYSFGPGTKVDIK(SEQ ID NO:16)
A9	ANXA1	Y065	QMQLVESGGGLVQPGGSLRLSCA ASGFTFSDFAMTWVRQAPGKGLE WVSSISGTSGRTYYADSVKGRST VSTDNSKNTVYLRMNSLRAEDTA VYYCARGSPSGSADYWGQGTLV TVSS(SEQ ID NO:17)	QLVLTQPHSVSESPGKTVTISCT RSSGSIASKYVQWYQQRPGSAP TTVIYEDNQRPSGVPDRFSGSIDI SSNSASLTISGLKTEDEADYYCQ SYDSSTVVFGGGTKLTVL(SEQ ID NO:18)
A10	ANXA1	Y090	QVQLVESGGGLVQPGRSLRLSCT GSGFTFGDYVMNWVRQVPGKGL EWVGFIRSKGYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:19)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPRLLIYSGSSRASGVPDRF SGSGSGTDFTLKISSVEAEDVGT YYCMQTLETPLTFGGGTKVEIK(SEQ ID NO:20)
A11	ANXA1	Y091	QVQLVQSGGGLVQPGRSLRLSCT ASGITFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT	DIQMTQSPSSVFASVGDRVTITC RASQAISSWLAWYQQKPGKAP KLLIYATSYLQTGVPSRFSGSGS GTDFTLSINNLQPEDSATYFCEQ AHSFPLTFGPGTKVDIK(SEQ ID

			FDLWGQGTMVTVSS(SEQ ID NO:21)	NO:22)
A12	ANXA1	Y092	QMQLVQSGAEVKKPGASVKVSC KVSGYTLTELSMHWVRQAPGKG LEWMGGFDLRNGETIYAQRFQG RVTMSGDTATDTAYMELSSLRSE DTAVYYCARSYYDILTGYYRDAF DIWGQGTMVTVSS(SEQ ID NO:23)	DIQMTQSPDSLAVSLGERATINC NSSRSVLHSSSNQNYLAWYQQ KPGQPPKLLISWASGRQSGVPD RFSGSGSGTDFTLTISSLQAEDV AVYYCQQCYSTPYTFGQGTKL DIK(SEQ ID NO:24)
A13	ANXA1	Y097	QMQLVQSGAEVQKPGASVKVSC KASGNTFNGYYIHWVRQAPGQG LEWMGIINPSGSSTFYAQKFRGRV TMTKDTSTSTVYMKLSSLRSEDT AVYYCAQEGWTEQHPYAEYLQN WGQGTLVTVSS(SEQ ID NO:25)	DIQMTQSPSFLSASVGDRVTITC RASQYIGTYLAWYQQQPGKAP KLLIYDASTLQPGVPSRFSGGGS GTDFTLTIRSVQPEDYATYFCQ QSYITPFAFGQGTKLEIK(SEQ ID NO:26)
A14	ANXA1	Y098	QVQLVESGGGLVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWIGFIRSKSFGGTTEYAASVKGR FTISRDDSRDIAYLQMNSLRAEDT AVYYCARDGNYYDSRDYYYDTF DLWGQGTMVTVSS(SEQ ID NO:27)	DIQMTQSPSSVSASVGDRVTITC RASQDISRWLAWYQQKPGKAP KLLIYAASILQTGVPSRFSGSGS GTDFTLSINNLQPEDSATYFCEQ AHSFPLTFGPGTKVDIK(SEQ ID NO:28)
A15	ANXA1	Y099	QVQLVESGGGAVKPGGSLRLSCE ASGFTFSDYYMSWIRQAPGKGLE WVADISGVNSFTNYAASVEGRFT ISRDNARNSLYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD MWGQGTLVTVSS(SEQ ID NO:29)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVEAEDVG VYYCMQALQTPRTFGQGTKVEI K(SEQ ID NO:30)
A16	ANXA1	Y100	QMQLVESGGGLVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGDYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:31)	DIQMTQSPSSVSASVGDSVTITC RASQDISTWLAWYQQKPGRAP KVLIYAASRLQDGVSSRFSGSGS GTDFNLSISSLQPEDFATYYCQQ ANSFPLTFGGGTKVEIK(SEQ ID NO:32)
A17	ANXA1	Y102	QVQLVESGGGLVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCAKDADFYDNSGYYDDA FDIWGQGTMVTVSS(SEQ ID NO:33)	DIQMTQSPATLSLSPGERATLSC RASQSVSSYLAWYQQKPGQAP RLLIYGASTRATGTPDRFSGSGS GTDFTLTISSLEPEDFAVYYCQQ RAKWPATFGQGTKLDIK(SEQ ID NO:34)
A18	ANXA1	Y105	QVQLVESGGGLVQPGRSLRLSCA TSGFTFGDYAMSWVRQAPGRGL EWVGFIRSKPHGGTTDFAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:35)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQPPQLLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVEAEDVG VYYCMQTLQTPRTFGQGTKVEI K(SEQ ID NO:36)
A19	ANXA1	Y107	QVQLVQSGGGLVKPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLDSNRASGVPDRF

			RFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTTVTVSS(SEQ ID NO:37)	SGSGSGTDFTLKISRVEAEDVGVYYCMQTLHTLYTFGQGTKLDIK(SEQ ID NO:38)
A20	ANXA1	Y112	QVQLVESGGGLIQPGGSLRLSCAASGLTSSTYAMNWVRQAPGKGLEWVAGVSASGGSAYYAESVKGRFTISRDNSNNTVFLQMNSLRAEDTAVYYCARHLAWGGMDVWGQGTTITVSS(SEQ ID NO:39)	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYGASILQNGVPSRFSGSGSGTEFTLTITNLQPEDFASYYCQQLSSYPYTFGQGTKLDIK(SEQ ID NO:40)
A21	ANXA1	Y122	QMQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:41)	DIVMTQSPLSLPVIPGEPASISCRSSKSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLTISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK(SEQ ID NO:42)
A22	ANXA1	Y123	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARATYYDILTGYYNDGYFDYWGQGTLVTVSS(SEQ ID NO:43)	DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYGASNLKSGVPSRFSGSGSGTHFTLTISSLHPEDFATYYCQQSYITQTWTFGQGTKVEIK(SEQ ID NO:44)
A23	ANXA1	Y124	QMQLVESGGGLVQPGRSLRLSCAASGFNFNTYAMHWVRQAPGRGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:45)	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVDIK(SEQ ID NO:46)
A24	ANXA1	Y125	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKTYGGTTEYAASVTGRFTISRDDSRGIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:47)	DIQMTQSPSSVSASVGDRVTITCRASQGIGNWLAWYQQKPGEAPNLLIYGASNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:48)
A25	ANXA1	Y126	QVQLVESGGGLIQPGRSLRLSCTTSGFTFGDYAMSWVRQAPGKGLEWVGFIRTKTYGGTPEYAASLKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCVRDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:49)	DIQMTQSPSSVSASVGDRVTITCRASQGISNWVAWYQQKPGKAPKLLIYAASTLHSGVPSRFSGSASGTDFTLTISSLQPEDFAIYYCQQGHSFPYTFGQGTKLEIK(SEQ ID NO:50)
A26	ANXA1	Y127	QVQLVESGGGLIQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:51)	DIVMTQTPLSLPVTPGEPAFISCRSSQNLLHSNGYNYLDWYLQKPGQSPQLLIYMGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQPLQIPFTFGGGTKVEIK(SEQ ID NO:52)
A27	ANXA1	Y096	QVQLVESGGDLVKPGRSLRLSCT	DIVMTQTPLSLPVTPGEPASISC

			ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:53)	RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPDRF SGSGSGTEFTLKISRVEAEDVGV YYCMHTLQLPFTFGPGTKVEIK(SEQ ID NO:54)
A28	ANXA1	Y108	QVQLVESGGGLVPPGGSLRLSCA ASGFSFSDHYMDWVRQAPGKGL EWVGFIRSAAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:55)	DIQMTQSPSSLSASVGDKVTITC RASQGISSYLAWYQQKPGKAPK LLIYVASSLQTGVPSRFSGSRSG TDFTLTISSLQSEDFGTYYCQQS YRTPYTFGQGTKLEIK(SEQ ID NO:56)
A29	ANXA1	Y132	QVQLVQSGGGLVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:57)	DIQMTQSPSSVSASLGDRVTITC RASQDIGHWLAWYQQKPGKAP KHLIYAASSLHSGVPSRFSGSGS GTEFTLTISNLQPEDFATYYCQQ ANSFPYTFGQGTKVDIK(SEQ ID NO:58)
A30	ANXA1	Y133	QVQLVESGGGLVKPGRSLRLSCT ASGFTFGDYAMSWFRQAPGKGL EWVGFIRSKAYGGTTEHAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:59)	DIVMTQTPLSLPVTPGEPASISC RSSQNLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVEAEDVG VYYCMQTLQTLYTFGQGTKVEI K(SEQ ID NO:60)
A31	ANXA1	Y140	QMQLVESGGGLVQPGRSLRLSCT ASGFTFRDYAMSWVRQAPGKGL EWIGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:61)	DIQMTQSPSSVSASVGDSVTITC RASQGISSWLAWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGS GTDFTLTIDSLQPEDFATYYCQQ ADSFPYTFGQGTKVEIK(SEQ ID NO:62)
A32	ANXA1	Y145	QVQLVESGGGVVQPGGSLRLSCD VSGLTFSIYGMHWVRQAPGKGLE WVAVIGYDGGNSFYAESVKGRFT ISRDNSKNTLYLQMNSLRAEDTA VYYCARGSLGTFDIWGQGTVVT VSS(SEQ ID NO:63)	DIQMTQSPSSVSASVGDRVTITC RASQGISSWLAWYQQKPGKAP KRLMYAASVLDAGVPSRFSGSG SGTDFTLTVSSLQPEDFATYYC QQGDSFPRTFGPGTKVDIK(SEQ ID NO:64)
A33	ANXA1	Y559	QVQLVESGGGVVQPGRSLRLSCA ASGFTFSSYAMHWVRQAPGKGL EWVAVISYDGSNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAED TAVYYCARDQTRLGPTTFDYWG QGSLVTVSS(SEQ ID NO:65)	DIQMTQSPSTLSASVGDRVTITC RASQNVDKWLAWYQQKPGKA PKLLIYKASGLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYDSYPLTFGGGTKVEIK(SEQ ID NO:66)
A34	ANXA1	Y569	QVQLVESGAEVKKPGESLKISCK GSGYSFTSFWISWVRQMPGKGLE WMGRIDPSDGYTSYSPSFQGHVTI SVDKSINTAYLQWNSLKASDTAM YYCARHNRKTLGRVDVWGQGTT	QSALTQPPSASGSPGQSVTISCS GGSRDVGAYNYVSWYQQHPG KAPKLMIYEVNKRPSGVPDRFS GSKSGNTASLTISGLQAEDEAD YYCTSFAGENNFGVFGGGTKLT

			VTVSS(SEQ ID NO:67)	VL(SEQ ID NO:68)
A35	ANXA1	Y683	QVQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLTWVRQAPGKGLE WIGFIRSKSFGGTTEYAASVKGRF TISRDDSRDIAYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD LWGQGTMITVSS(SEQ ID NO:69)	DIQMTQSPSSVSASVGDRVTITC RASQGISNWLAWYQQKPGKAP KLLIYAASALESGVPSRFSASGY GTDFTLTISSLQPEDFATYFCQQ GKSFPYTFGQGTKVEIK(SEQ ID NO:70)
A36	ANXA1	Y705	QVQLVESGGGVVQPGGSLRLSCA ASGFNFENYAMHWVRQVPGKGL EWVSLISGDGSSTHYTDSLRGRFT ISRDNSKNSLYLQMNSLRAEDTA VYYCARGGGKLDYWGQGTLVTV SS(SEQ ID NO:71)	QAVVTQEPSFSVSPGGTVTLTC GLTSGSVSTSHFPSWYQQTPGQ APRTLIYFTDTHSSGVPDRFSGSI LGNKAALTITGAQADDESDYYC VLYMGSGIYAFGTGTKVTVL((S EQ ID NO:72)
A37	ANXA1	Y711	QVQLVQSGGGLVQPGGSLRLSCA ASGFTFSDHYMDWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:73)	DIQMTQSPSSLSASVGDRVTITC RASQSISNYLNWYQQKPGKAPK LLMSAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQS YNTPRTFGQGTKVDIK(SEQ ID NO:74)
A38	ANXA1	Y712	QVQLVESGGGLIQPGRSLRLSCRT SGFSFGDYAMTWVRQAPGKGLE WVGFIRSKRFGGTTEYAASVKGR FTISRDDSTSIAYLQMNSLRAEDT AVYYCARDGNYYDSRGYYYDTF DLWGQGTMVTVSS(SEQ ID NO:75)	DIQMTQSPSSVSASVGDRVTITC RASQPISTWLVWYQHKPEKAPK LLIYAASNLQSGVPSRFSGSGSG TDFTLTINSLQPDDFATYYCQQ ANSFPYTFGQGTKLDIK(SEQ ID NO:76)
A39	ANXA1	Y715	QVQLVESGGGLVQPGHSLRLSCT SSGFNFGDHAVSWVRQAPGKGL EWVGFIRSKTYGGTPEYAASVKD RFSISRDDSKSSAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDMWGQGTLVTVSS(SEQ ID NO:77)	DIVMTQTPLSLPVIPGEPASISCR SSQSLLHSNGYNYLDWYLQKP GQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGV YYCMQTLQTLYTFGQGTKLEIK (SEQ ID NO:78)
A40	ANXA1	Y716	QVQLVESGGGLVQPGRSLRLSCT ASGFIFGDYAMSWVRQAPGKGLE WVGFIRSKAYGGTTDYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:79)	DIQMTQSPSSLSASVGDRITISCQ ASQDIKNYLNWYQKKPGKAPK LLIYGASNLAAGVPSRFSGSGY GTDFTFIISGLQPEDVATYYCQQ YEELAALTFGGGTKVEIK(SEQ ID NO:80)
A41	ANXA1	Y719	QVQLVESGGGLVQPGRSLRISCK ASGFNFGDYPLTWVRQAPGKGLE WIGFIRSKSFGGTTEYAASVKGRF TISRDDSRDIAYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD LWGQGTMVTVSS(SEQ ID NO:81)	DIQMTQSPSSLSASVGDRVTITC RASQSISSWLAWYQQKPGKAP KLLIYTSSTLQSEVPSRFSGSGSG TDFTLTISGLQPEDFATYYCQQS YSLPRTFGPGTKVDIK(SEQ ID NO:82)
A42	ANXA1	Y722	QMQLVQSGGGLVKPGRSLRLSCT ASGFTFGDYAMSWFRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED	DIQMTQSPSSVSASIGDRITITCR ASQGISTWLAWYQQKPGKAPK LLIYAASSLHSGVPSRFSGSGSG TDFTLTISSLQPDDFATYYCQQS

			TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:83)	YSIPRTFGQGTKVEIK(SEQ ID NO:84)
A43	ANXA1	Y723	QMQLVESGGGLVQPGGSLRLSCA ASGFTFSDHYMDWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:85)	DIQMTQSPSSLSASVGDRVTITC RASQGIRNYLGWYQQKPGRAP KLLIYAASSLQSGVPSRFRGSGS GTDFTLTISSLQPEDFATYYCLQ DHDYPYTFGQGTKVEIK(SEQ ID NO:86)
A44	ANXA1	Y727	QVQLVESGGGLVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:87)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLEWYLQKP GQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGV YYCMQSLQTPPYTFGQGTKVEI K(SEQ ID NO:88)
A45	ANXA1	Y728	QMQLVESGGDLVQPGRSLRLSCR TSGFTFGEYAMSWVRQAPGKGL EWVGFIRSKAFGGTPEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:89)	DIQMTQSPSSVSASVGDRVTITC RASHDISSWLAWYQQKPGKAP KLLIYATSSLQNGVPSRFSGSGS GTDFTLTISSLQPEDFATYFCQQ GKSFPYTFGQGTKVEIK(SEQ ID NO:90)
A46	ANXA1	Y735	QVQLVESGGGLIHPGESLRLSCAA SGFSFSSHAMSWVRQAPGKGLE WVATISETGGIAFYADSVKGLFTI SRDNSKNTLSLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDM WGQGTVVTVSS(SEQ ID NO:91)	DIVMTQTPLSLPVTLGEPASISC RSSQSLLHTNGYNYLDWYLQK PGQSPQLLVYSASTRASGVPDR FSGSGSGTDFTLKISRVEAEDVG IYYCMQALQTPWTFGQGTKVEI K(SEQ ID NO:92)
A47	ANXA1	Y738	QVQLVQSGGGVVQPGTSLRLSCA ASGFTFSSSTMHWVRQAPGKGLE WVAGFSYDGDTQWYADSVKGRF TISRDNSRNTLYLQMNSLRSEDTA VYYCARENVAADWFDAWGQGA LITVSS(SEQ ID NO:93)	QSALTQPASVSGSPGQSITFSCT GTSSDFGGYNYVSWYQQHPGK APKLMIYDVSKRPSGVSNHFSG SKSGNTASLTISGLQAEDEADY YCSSFTGDSVIFGGGTKLTVL(S EQ ID NO:94)
A48	ANXA1	Y741	QVQLVESGGGWVQPGGSLRLSC AGSGFTTNSYTMAWVRQAPGKG LEWVSSISSSTNYMYYADSVKGR FTISRDNAKNSVYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDMWGQGTLVTVSS(SEQ ID NO:95)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVQAEDVG TYYCMQTLQTLPYTFGQGTKLE IK(SEQ ID NO:96)
A49	ANXA1	Y748	QVQLVESGGGLVKPGGSLRLSCA ASGFTFGDYYMNWIRQAPGKGL EWVAYISSSSAYTRYADSVKGRF TISRDNTKNSLYLQMNSLRAEDT AVYYCARDGNYYDSRGYYYDTF DLWGQGTMITVSS(SEQ ID NO:97)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYYYLDWYLQK PGQSPQVLIYLGSNRAPGVPDRF SGSGSGTDFTLKISRVEADDVGI YYCMQGLMTPFTFGPGTKLDIK (SEQ ID NO:98)
A50	ANXA1	Y758	QVQLVESGGVAVQPGGSLRLSCT ASGFTLDDYSMHWVRQRPGKGL	DIVMTQTPLSLPVTPGGPASISC RSSQSLLHSNGYNYLDWYLQK

			EWVSVIYTGGNTYYSESVKGRFN IARDNSKNSLYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD LWGQGTMVTVSS(SEQ ID NO:99)	PGQSPQLLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVEAEDVG VYYCMQALRTPYTFGQGTKVD IK(SEQ ID NO:100)
A51	ANXA1	Y765	QVQLVQSGAEVKKPGASVKVSC KVSGYTLSELSIHWVRQAPGKGL EWMGRFDPEDGETSYAQKFQGR VTMTEDTSTDTAYMELSSLRSED TAVYYCARDGNYYDSRGYYYDT FDMWGQGTLVTVSS(SEQ ID NO:101)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYMGSNRASGVPDR FSGSGSGTDFTLKISRVEAEDVG VYYCMQGLQTPYTFGQGTKVEI K(SEQ ID NO:102)
A52	ANXA1	Y769	QVQLVESGGGLIQPGRSLRLSCV GSGFKFGDYAMSWVRQAPGKGL EWVGFIRSKAYGGTTEYAASVKG RFDISRDDSESIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:103)	DIQMTQSPSSVSASVGDRVTITC RASQEITTWLAWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQ ADSFPYTFGQGTKVEIK(SEQ ID NO:104)
A53	ANXA1	Y781	QVQLVQSGAEVKKPGASVKLSC KASGYTFSSYWMHWVRQAPGQR LEWMGEINPGNGHTNYNEKFKSR VTITVDKSASTAYMELSSLRSEDT AVYYCARDGNYYDSRGYYYDTF DMWGQGTLVTVSS(SEQ ID NO:105)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLGWYRQK PGQSPQLLIYLGSNRAFGVPDRF SGSGSGTDYTLKISRVEAEDVG VYYCMQALRTPYTFGQGAKLD IK((SEQ ID NO:106)
A54	ANXA1	Y813	QMQLVESGGGFVQPGRSLRLSCT ASGFTFGDYAMSWVRQAPGRGL EWLGFIRSKAYGGTTEYAASVKG RFTISRDDSKSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:107)	DIQMTQSPSSVSASVGDKVTIAC RASQGIVSWLAWYQQKPGKAP RLLIYAASNLQDGVPSRFSGSGS GTVFTLTISSLQPEDFATYYCQQ ANSFPYTFGQGTKLEIK(SEQ ID NO:108)
A55	ANXA1	Y829	QVQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLSWVRQAPGKGLE WIGFIRSKSFGGTTEYAASVKGRF TISRDDSRDIAYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD LWGQGTMITVSS(SEQ ID NO:109)	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFATYYCQ QANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A56	ANXA1	Y842	QMQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLTWVRQAPGKGLE WIGFIRSKSFGGTTEYAASVKGRF TISRDDSRDIAYLQMNSLRAEDTA VYYCARDGNYYDSRGYYYDTFD MWGQGTLITVSS(SEQ ID NO:111)	DIQMTQSPSSVSASIGDRVTITC RASEDISRQLAWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQA NSFPYTFGQGTKLDIK(SEQ ID NO:112)
A57	ANXA1	Y843	QVQLVESGGGLVQPGRSLRLSCT ASGFTFGDYALNWVRQAPGKGL EWVGFIRSQTYGGTTEYAASVKG RFTISRDDSRSIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMVTVSS(SEQ ID NO:113)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHTNGYNYLDWYLQK PGQSPQLLVYSASTRASGVPDR FSGSGSGTDFTLKISRLEAEDVG VYYCMQALQTPWTFGQGTKVE IK(SEQ ID NO:114)

A58	ANXA1	S001	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSGYYMSWVRQAPGKGL EWVSSISPSGSSIYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAKGSPGFDYWGQGTLVTVS S(SEQ ID NO:115)	QSVLTQPPSASGAPGQRVTISCS GSSFNIGSNDVSWYQQLPGTAP KLLIYSDSHRPSGVPDRFSGSKS GTSASLAISGLQSEDEADYYCG SWDYSLSAYVFGGGTKLTVL(S EQ ID NO:116)
A59	ANXA1	Y1471	QVQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRSKSFGGTTEYAASVKGR FTISRDDSRDIAYLQMNSLRAEDT AVYYCARDGNYYDSRGYYYDTF DLWGQGTMITVSS(SEQ ID NO:109)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYMGSNRASGVPDR FSGSGSGTDFTLKISRVEAEDVG VYYCMQALQTQLTFGGGTKVE IK(SEQ ID NO:117)
A60	ANXA1	Y1471.1	QVQLVQSGGGLVQPGRSLRLSCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRSKSFGGTTEYAASVKGR FTISRDDSRDIAYLQMNSLRAEDT AVYYCARDGNYYDSRGYYYDTF DLWGQGTMITVSS(SEQ ID NO:118)	DIVMTQTPLSLPVTPGEPASISC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYMGSNRASGVPDR FSGSGSGTDFTLKISRVEAEDVG VYYCMQALQTQLTFGGGTKVE IK(SEQ ID NO:117)
A61	ANXA1	Y1494	QVQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRDKRIGGTTEYAASVKG RFTISRDDSRDIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:119)	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFATYYCQ QANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A62	ANXA1	Y1494.1	QVQLVQSGGGLVQPGRSLRLSCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRDKRIGGTTEYAASVKG RFTISRDDSRDIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:120)	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFATYYCQ QANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A63	ANXA1	Y1494.2	QVQLVQSGGGLVQPGRSLRLSCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRDKRYGGTTEYAASVKG RFTISRDDSRDIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:121)	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFATYYCQ QANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A64	ANXA1	Y1501	QVQLVQSGGGLVQPGRSLRISCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRDKTVGGTTEYAASVKG RFTISRDDSRDIAYLQMNSLRAED TAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSS(SEQ ID NO:122)	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFATYYCQ QANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A65	ANXA1	Y1501.1	QVQLVQSGGGLVQPGRSLRLSCK ASGFNFGDYPLSWVRQAPGKGL EWIGFIRDKTVGGTTEYAASVKG	DIQMTQSPSSVSASVGDRVTLT CRASQGIRSWLAWYQQKPGKA PKLLIYAASNLQSGVPSRFSGSG

			RFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:123)	SGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A66	ANXA1	Y1501.2	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKTYGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:124)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A67	ANXA1	Y1502	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRPKWLGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:125)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A68	ANXA1	Y1502.1	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRPKWLGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:126)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A69	ANXA1	Y829.2	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:118)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)
A70	TEM8	m825	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSS(SEQ ID NO:127)	SSELTQDPVVSVALGETVSITCQGDNLRDFYASWYQQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVL(SEQ ID NO:128)
A71	Albumin	anti-Albumin	EVQLLESGGGLVQPGGSLRLSCAVSGIDLSNYAINWVRQAPGKGLEWIGIIWASGTTFYATWAKGRFTISRDNSKNTVYLQMNSLRAEDTAVYYCARTVPGYSTAPYFDLWGQGTLVTVSS(SEQ ID NO:129)	DIQMTQSPSSVSASVGDRVTITCQSSPSVWSNFLSWYQQKPGKAPKLLIYEASKLTSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCGGGYSSISDTTFGGGTKVEIK(SEQ ID NO:130)
A72	KDR(VEGFR2)	Ramucirumab	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVTDAFDIWGQGTMVTVSS(SEQ ID NO:131)	DIQMTQSPSSVSASIGDRVTITCRASQGIDNWLGWYQQKPGKAPKLLIYDASNLDTGVPSRFSGSGSGTYFTLTISSLQAEDFAVYFCQQAKAFPPTFGGGTKVDIK(SEQ ID NO:132)
A73	PSMA	MEDI3	EVQLVQSGPEVKKPGATVKISCK	DIQMTQSPSSLSTSVGDRVTLTC

		726	TSGYTFTEYTIHWVKQAPGKGLEWIGNINPNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNFDYWGQGTLLTVSS(SEQ ID NO:133)	KASQDVGTAVDWYQQKPGPSPKLLIYWASTRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKVDIK(SEQ ID NO:134)
A74	ICAM1	Icmo0191fgi	QVQLQESGPGLVKPSETLSLTCAVSGYPISSGYFWGWIRQPPGKGLEWIGSIYQSGSTYYNPSLKRRVTMSLDTSKNQFSLKLSSVTAADTAVYYCARDGYCSGGSCYPFDYWGQGTLVTVSS(SEQ ID NO:135)	QSVLTQPPSVSGTPGQRVTISCSGSSSNIGGSTVNWYQQLPGTAPKLLIYNNDQRPSGVPDRFSGSKSGTSGSLAISGLQSEDEADYYCESWDDSLSGRVFGGGTKLTVL(SEQ ID NO:136)
A75	FAPα	humanized MFP5	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNNGINWLRQAPGQGLEWMGEIYPRSTNTLYAQKFQGRVTITADRSSNTAYMELSSLRSEDTAVYFCARTLTAPFAFWGQGTLVTVSS(SEQ ID NO:137)	QIVLTQSPATLSLSPGERATLSCSASSGVNFMHWYQQKPGQAPRRLIFDTSKLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQWSFNPPTFGQGTKVEIK(SEQ ID NO:138)
A76	B7H3	m8524	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS(SEQ ID NO:139)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK(SEQ ID NO:140)
A77	ANXA1	Y829.2 scFv in HC	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:141)	N/A
A77-1	ANXA1	Y829.2 scFv in LC	N/A	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:141)
A78	ANXA1	Y829.2 VHH	QVQLVQSGGGSVKAGRSLRLSCTASGFTFGDYAMSWVRQAPGKEREFVAFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAED	N/A

			TAVYYCARDGNYYDSRGYYYDTFDLWGQGTTVTVSS(SEQ ID NO:142)	
A78-1	ANXA1	Y829.2 VHH in LC	N/A	QVQLVQSGGGSVKAGRSLRLSCTASGFTFGDYAMSWVRQAPGKEREFVAFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTTVTVSS(SEQ ID NO:142)
A79	ANXA1	Y829.2 Fab	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:143)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:144)
A80	ANXA1	IF7 in HC	IFLLWQR(SEQ ID NO:145)	N/A
A80-1	ANXA1	IF7 in LC	N/A	IFLLWQR(SEQ ID NO:145)
A81	TEM8	m825 Fab	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:146)	SSELTQDPVVSVALGETVSITCQGDNLRDFYASWYOQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVLRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:147)
A82	ANXA1	Y829 VH-VL cross	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:109)
N/D, Not determined; N/A, Not associated				

- ANXA1

More specifically, the first domain may be a peptide or an antibody that binds to ANXA1 or a fragment thereof.

As used herein, the term "Annexin A1 (ANXA1)" is also known as Lipocortin 1, Calpactin II, Chromobindin-9, Phospholipase A2 inhibitory protein, or p35. In general, ANXA1 is known to be involved in intercellular signaling and its function is regulated by calcium (Ca) concentration. In addition, ANXA1 is considered a factor that influences the growth and metastasis of cancer cells, and overexpression of ANXA1 in various cancers has been reported.

In the present invention, ANXA1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the ANXA1 protein may include both natural type and variant ANXA1 proteins, but is not limited thereto. The term "natural type" includes all proteins found in nature or nucleic acids encoding them, and may be described interchangeably with "wild type." The term "natural type ANXA1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type ANXA1 protein. The amino acid sequence and polynucleotide sequence for the ANXA1 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 1616. In addition, as long as it has the same activity as the protein or the same gene location encoding ANXA1 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, ANXA1 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 1616.

In the present invention, the ANXA1 protein variant refers to a fragment of ANXA1 in which a portion of the N-terminus is deleted. Specifically, the ANXA1 protein variant may be a form comprising amino acids in which the 1st to 26th amino acids from the N-terminus of a protein having the amino acid sequence of SEQ ID NO: 1616 are consecutively deleted. Specifically, it may comprise the amino acid sequence of SEQ ID NO: 1617. In addition, as long as it has the same activity as the variant or the same gene location encoding ANXA1 on the chromosome, it may consist of a sequence in which one or several amino acids are added, deleted, or substituted. Specifically, it may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 1617.

In one embodiment of the present invention, the first domain may be a peptide fragment comprising the amino acid sequence of SEQ ID NO: 145.

In one embodiment of the present invention, the first domain may be an antibody or a fragment thereof. The antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 277, 284, 291, 298, 304, 310, 320, 326, 332, 336, 338, 344, 355, 370, 382, 392,

396, 398, 405, 411, 417, 420, 427, 432, 436, 441, 444, 449, 456, 460, 465, 470, 475, 478 and 489, HCDR2 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 279, 286, 293, 300, 305, 322, 328, 334, 340, 346, 351, 357, 365, 372, 378, 386, 394, 400, 406, 413, 422, 429, 434, 442, 446, 451, 458, 462, 467, 472, 480, 486, 491, 494, 495, 496, 497 and 498, and HCDR3 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 281, 288, 295, 302, 307, 312, 317, 324, 330, 342, 348, 353, 359, 361, 362, 374, 380, 388, 402, 408, 415, 424, 453 and 492; and a light chain variable region comprising LCDR1 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 500, 512, 525, 531, 538, 551, 557, 564, 570, 575, 580, 592, 595, 599, 603, 608, 616, 621, 625, 631, 636, 645, 651, 654, 659, 667, 670, 675, 678, 684, 690, 698, 704, 708, 711 and 714, LCDR2 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 502, 508, 514, 523, 527, 533, 540, 547, 553, 559, 566, 582, 587, 609, 617, 632, 639, 647, 663, 680, 685 and 716, and LCDR3 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 504, 510, 516, 529, 535, 542, 544, 549, 555, 561, 568, 572, 578, 584, 586, 588, 590, 597, 602, 606, 611, 613, 619, 624, 627, 630, 634, 641, 643, 649, 653, 662, 665, 669, 673, 674, 682, 687, 689, 693, 696, 697, 718 and 719.

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 277, HCDR2 comprising the amino acid sequence of SEQ ID NO: 279, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 281; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 504. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 1, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 2 (A1).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 284, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 288; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 508, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 510. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 3, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 4 (A2).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the

amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 516. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 5, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 6 (A3).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 298, HCDR2 comprising the amino acid sequence of SEQ ID NO: 300, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 302; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 504. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 7, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 8 (A4).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 304, HCDR2 comprising the amino acid sequence of SEQ ID NO: 305, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 307; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 523, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 510. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 9, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 10 (A5).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 310, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 312; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 525, LCDR2 comprising the amino acid sequence of SEQ ID NO: 527, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 529. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 11, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 12 (A6).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 317; and a light chain variable region comprising LCDR1

comprising the amino acid sequence of SEQ ID NO: 531, LCDR2 comprising the amino acid sequence of SEQ ID NO: 533, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 535. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 13, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 14 (A7).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 322, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 324; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 538, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 542. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 15, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 16 (A8).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 326, HCDR2 comprising the amino acid sequence of SEQ ID NO: 328, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 330; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 544. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 17, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 18 (A9).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 332, HCDR2 comprising the amino acid sequence of SEQ ID NO: 334, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 547, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 549. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 19, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 20 (A10).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 336, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 551, LCDR2 comprising the amino acid

sequence of SEQ ID NO: 553, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 555. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 21, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 22 (A11).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 338, HCDR2 comprising the amino acid sequence of SEQ ID NO: 340, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 342; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 557, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 561. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 23, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 24 (A12).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 344, HCDR2 comprising the amino acid sequence of SEQ ID NO: 346, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 348; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 564, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 568. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 25, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 26 (A13).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 353; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 570, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 555. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 27, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 28 (A14).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 355, HCDR2 comprising the amino acid sequence of SEQ ID NO: 357, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO:

572. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 29, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 30 (A15).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 361; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 575, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 578. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 31, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 32 (A16).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 362; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 584. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 33, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 34 (A17).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 365, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 586. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 35, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 36 (A18).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 587, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 588. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ

ID NO: 37, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 38 (A19).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 370, HCDR2 comprising the amino acid sequence of SEQ ID NO: 372, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 374; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 564, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 590. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 39, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 40 (A20).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 592, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 572. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 41, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 42 (A21).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 355, HCDR2 comprising the amino acid sequence of SEQ ID NO: 378, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 380; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 595, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 597. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 43, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 44 (A22).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 382, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 572. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 45, and the light chain variable region may comprise the amino acid sequence of SEQ ID

NO: 46 (A23).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 599, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 47, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 48 (A24).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 386, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 388; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 603, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 606. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 49, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 50 (A25).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 608, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 611. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 51, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 52 (A26).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 613. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 53, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 54 (A27).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 392, HCDR2 comprising the amino acid sequence of SEQ ID NO: 394, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 616, LCDR2 comprising the amino acid sequence of SEQ ID NO: 617, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 619. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 55, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 56 (A28).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 621, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 57, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 58 (A29).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 608, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 624. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 59, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 60 (A30).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 396, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 625, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 627. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 61, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 62 (A31).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain

variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 398, HCDR2 comprising the amino acid sequence of SEQ ID NO: 400, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 402; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 625, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 630. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 63, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 64 (A32).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 405, HCDR2 comprising the amino acid sequence of SEQ ID NO: 406, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 408; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 631, LCDR2 comprising the amino acid sequence of SEQ ID NO: 632, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 634. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 65, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 66 (A33).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 411, HCDR2 comprising the amino acid sequence of SEQ ID NO: 413, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 415; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 636, LCDR2 comprising the amino acid sequence of SEQ ID NO: 639, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 641. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 67, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 68 (A34).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 603, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 643. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 69, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 70 (A35).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 420,

HCDR2 comprising the amino acid sequence of SEQ ID NO: 422, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 424; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 645, LCDR2 comprising the amino acid sequence of SEQ ID NO: 647, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 649. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 71, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 72 (A36).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 651, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 653. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 73, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 74 (A37).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 427, HCDR2 comprising the amino acid sequence of SEQ ID NO: 429, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 654, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 75, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 76 (A38).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 432, HCDR2 comprising the amino acid sequence of SEQ ID NO: 434, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 624. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 77, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 78 (A39).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 436, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the

amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 659, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 662. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 79, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 80 (A40).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 531, LCDR2 comprising the amino acid sequence of SEQ ID NO: 663, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 665. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 81, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 82 (A41).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 667, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 669. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 83, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 84 (A42).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 670, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 673. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 85, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 86 (A43).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1

comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 674. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 87, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 88 (A44).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 441, HCDR2 comprising the amino acid sequence of SEQ ID NO: 442, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 675, LCDR2 comprising the amino acid sequence of SEQ ID NO: 553, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 643. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 89, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 90 (A45).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 444, HCDR2 comprising the amino acid sequence of SEQ ID NO: 446, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 678, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 682. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 91, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 92 (A46).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 449, HCDR2 comprising the amino acid sequence of SEQ ID NO: 451, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 453; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 684, LCDR2 comprising the amino acid sequence of SEQ ID NO: 685, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 687. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 93, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 94 (A47).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 456, HCDR2 comprising the amino acid sequence of SEQ ID NO: 458, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid

sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 689. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 95, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 96 (A48).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 460, HCDR2 comprising the amino acid sequence of SEQ ID NO: 462, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 690, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 693. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 97, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 98 (A49).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 465, HCDR2 comprising the amino acid sequence of SEQ ID NO: 467, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 696. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 99, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 100 (A50).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 470, HCDR2 comprising the amino acid sequence of SEQ ID NO: 472, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 697. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 101, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 102 (A51).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 475, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 698, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO:

627. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 103, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 104 (A52).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 478, HCDR2 comprising the amino acid sequence of SEQ ID NO: 480, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 696. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 105, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 106 (A53).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 704, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 107, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 108 (A54).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 109, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A55/A82). In addition, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 118, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A69/A77/A77-1).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 711, LCDR2 comprising the amino acid

sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 111, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 112 (A56).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 486, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 678, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 682. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 113, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 114 (A57).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 489, HCDR2 comprising the amino acid sequence of SEQ ID NO: 491, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 492; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 714, LCDR2 comprising the amino acid sequence of SEQ ID NO: 716, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 718. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 115, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 116 (A58).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 719. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 109, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 117 (A59).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO:

719. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 118, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 117 (A60).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 494, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 119, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A61). In addition, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 120, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A62).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 495, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 121, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A63).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 496, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 122, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A64). In addition, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 123, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A65).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 497, and HCDR3 comprising the

amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 124, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A66).

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 498, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 125, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A67). In addition, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 126, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (A68).

In the present invention, the antibody fragment may be a single domain antibody. In this case, the antibody fragment may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295. The heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 142 (A78).

- TEM8

More specifically, the first domain may be an antibody that binds to TEM8 or a fragment thereof.

As used herein, the term "TEM8" is also known as Anthrax toxin receptor 1 (ANTXR1) and is a type 1 transmembrane protein. TEM8 is known to be overexpressed in endothelial cells or tumor cells surrounding various tumors, including large intestine cancer.

In the present invention, TEM8 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the TEM8 protein may include both natural type and variant TEM8 proteins, but is not limited thereto. The term "natural type TEM8 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type TEM8 protein. The amino acid sequence and polynucleotide sequence for the TEM8 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 177.

In addition, as long as it has the same activity as the protein or the same gene location encoding TEM8 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, TEM8 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 177.

In one embodiment, the antibody or fragment thereof may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 721, HCDR2 comprising the amino acid sequence of SEQ ID NO: 723, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 725; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 763, LCDR2 comprising the amino acid sequence of SEQ ID NO: 765, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 767. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 127, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 128 (A70/A81).

- Albumin

More specifically, the first domain may be an antibody that binds to albumin or a fragment thereof.

As used herein, the term "albumin" refers to a simple protein that exists in nature and is one of the proteins constituting the basic material of a cell, with a molecular weight of 65-70 kDa.

In the present invention, albumin may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the albumin protein may include both natural type and variant albumin proteins, but is not limited thereto. The term "natural type albumin protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type albumin protein. The amino acid sequence and polynucleotide sequence for the albumin protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 178.

In addition, as long as it has the same activity as the protein or the same gene location encoding albumin on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, albumin may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 178.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO:

727, HCDR2 comprising the amino acid sequence of SEQ ID NO: 729, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 731; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 770, LCDR2 comprising the amino acid sequence of SEQ ID NO: 772, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 774. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 129, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 130 (A71).

- KDR (VEGFR2)

More specifically, the first domain may be an antibody that binds to KDR (VEGFR2, vascular endothelial growth factor receptor 2) or a fragment thereof.

As used herein, the term "KDR" is also known as vascular endothelial growth factor receptor 2 (VEGFR2; KDR/Flk-1). Vascular endothelial growth factor (VEGF) is a glycoprotein that binds to heparin with a molecular weight of 34 to 42 kDa and is a representative growth factor that promotes the migration of endothelial cells. VEGF exists in five subtypes (VEGF-A, -B, -C, -D, and F) and is known to react with each receptor. The known receptors include VEGFR1 (Flt-1; Fms-like-tyrosine kinase-1), VEGFR2 (flk-1/KDR), VEGFR3, the PDGF (platelet derived growth factor) receptor, and NP-1 (neuropilin-1). VEGFR1 binds to VEGF-A, VEGF-B, or PDGF; VEGFR2 binds to VEGF-A, VEGF-C, VEGF-D, or VEGF-E; and VEGFR3 binds to VEGF-C or VEGF-D. Each of these VEGF receptors is activated through autophosphorylation along with the receptor dimer when VEGF binds. Recent reports indicate that VEGF-induced angiogenesis is mediated through the activation of Flt-1 and KDR expressed in endothelial cells. In particular, KDR has been shown to play an important role in cell growth, survival, and migration.

In the present invention, KDR may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the KDR protein may include both natural type and variant KDR proteins, but is not limited thereto. The term "natural type KDR protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type KDR protein. The amino acid sequence and polynucleotide sequence for the KDR protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 179.

In addition, as long as it has the same activity as the protein or the same gene location encoding KDR on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the KDR protein may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 179.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 733, HCDR2 comprising the amino acid sequence of SEQ ID NO: 735, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 736; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 775, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 778. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 131, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 132 (A72).

- PSMA

More specifically, the first domain may be an antibody that binds to PSMA (prostate specific membrane antigen) or a fragment thereof.

As used herein, the term "PSMA" refers to a glycoprotein enzyme synthesized in the epithelial cells of the prostate. Since it is rarely produced in tissues other than the prostate, it is used as a useful tumor marker for screening and monitoring prostate cancer.

In the present invention, PSMA may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the PSMA protein may include both natural type and variant PSMA proteins, but is not limited thereto. The term "natural type PSMA protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type PSMA protein. The amino acid sequence and polynucleotide sequence for the PSMA protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 180.

In addition, as long as it has the same activity as the protein or the same gene location encoding the PSMA protein on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the PSMA protein may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 180.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 738, HCDR2 comprising the amino acid sequence of SEQ ID NO: 740, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 742; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 781, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 784. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 133, and the light chain variable region may comprise the amino acid sequence of

SEQ ID NO: 134 (A73).

- ICAM1

More specifically, the first domain may be an antibody that binds to ICAM1 (intercellular adhesion molecule 1) or a fragment thereof.

As used herein, the term "ICAM1," also referred to as CD54, is a cell surface adhesion molecule belonging to the immunoglobulin superfamily. ICAM1 is a cell surface glycoprotein of about 90 kDa that is distributed in most nucleated cells, such as the HLA-DR antigen. It is known to be involved in cell-to-cell interaction by forming ligand bonds with LFA-1 (lymphocyte function associated antigen-1), a lymphocyte surface contact molecule.

In the present invention, ICAM1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the ICAM1 protein may include both natural type and variant ICAM1 proteins, but is not limited thereto. The term "natural type ICAM1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type ICAM1 protein. The amino acid sequence and polynucleotide sequence for the ICAM1 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 181.

In addition, as long as it has the same activity as the protein or the same gene location encoding the ICAM1 protein on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the ICAM1 protein may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 181.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 745, HCDR2 comprising the amino acid sequence of SEQ ID NO: 747, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 749; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 786, LCDR2 comprising the amino acid sequence of SEQ ID NO: 788, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 790. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 135, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 136 (A74).

- FAPα

More specifically, the first domain may be an antibody that binds to FAPα (fibroblast activation protein α) or a fragment thereof.

As used herein, the term "FAPα" refers to a transmembrane protein of about 170 kDa, existing in a water-soluble form without an intracellular domain and a transmembrane domain.

Although generally absent in normal adult tissues, it is known to be overexpressed in more than 90% of reactive stromal fibroblasts in all primary and metastatic epithelial tumors, including lung cancer, large intestine cancer, bladder cancer, ovary cancer, and breast cancer. In addition, it is expressed not only in stromal fibroblasts but also in some types of malignant cells derived from epithelium, and it is known that FAP expression is correlated with a malignant phenotype.

In the present invention, FAPα may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the FAPα protein may include both natural type and variant FAPα proteins, but is not limited thereto. The term "natural type FAPα protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type FAPα protein. The amino acid sequence and polynucleotide sequence for the FAPα protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 182.

In addition, as long as it has the same activity as the protein or the same gene location encoding the FAPα protein on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the FAPα protein may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 182.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 751, HCDR2 comprising the amino acid sequence of SEQ ID NO: 753, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 755; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 792, LCDR2 comprising the amino acid sequence of SEQ ID NO: 794, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 796. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 137, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 138 (A75).

- B7H3

More specifically, the first domain may be an antibody that binds to B7H3 (B7 homologue 3) or a fragment thereof.

As used herein, the term "B7H3" is also referred to as CD276 (cluster of differentiation 276) and refers to an immune checkpoint inhibitor molecule. It is very limited in normal cells but significantly increased in primary and metastatic tumors as well as in tumor vasculature. In addition, it is expressed in a number of cell types, including differentiated tumor cells, tumor initiating cells, or cancer stem cells, and such expression is known to be deeply correlated with poor prognosis in some tumor types.

In the present invention, B7H3 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the B7H3 protein may include both natural type and variant B7H3 proteins, but is not limited thereto. The term "natural type B7H3 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type B7H3 protein. The amino acid sequence and polynucleotide sequence for the B7H3 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 183.

In addition, as long as it has the same activity as the protein or the same gene location encoding the B7H3 protein on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the B7H3 protein may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 183.

In one embodiment of the present invention, the first domain may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 757, HCDR2 comprising the amino acid sequence of SEQ ID NO: 759, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 761; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 799. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 139, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 140 (A76).

- Myct1

More specifically, the first domain may be an antibody that binds to Myct1 (myc target 1) or a fragment thereof.

As used herein, the term "Myct1" is known as MTLC and refers to the target gene of c-Myc. c-Myc is a tumor protein that is most frequently activated during the carcinogenesis process and regulates the expression of genes involved in the cell cycle, apoptosis, and cellular transformation. The transcription of Myct1 is promoted by the c-Myc protein, and abnormal expression is reported to be associated with cancer development, progression, metastasis, and prognosis. In particular, it is known as a key protein that regulates angiogenesis and immunity within the tumor microenvironment (TME). In addition, in blood-related diseases, it is known to play an important role in the self-renewal and differentiation of hematopoietic stem cells (HSCs), as well as in the proliferation and apoptosis of acute myeloid leukemia (AML) cells.

In the present invention, Myct1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and

mice. In addition, the Myct1 protein may include both natural type and variant Myct1 proteins, but is not limited thereto. The term "natural type Myct1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type Myct1 protein. The amino acid sequence and polynucleotide sequence for the Myct1 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI).

In addition, as long as it has the same activity as the protein or the same gene location encoding the Myct1 protein on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted.

In the present invention, the antibody or fragment thereof, peptide, or protein binding site constituting the first domain is referred to as "UNIT1."

Second domain

In the present invention, the second domain may comprise a site that specifically binds to an immune modulator or a second target. The second domain may be described interchangeably with "third component," "C," or "inner domain" in the present specification.

In the present invention, the binding ability of the second domain of the ReleaDome to the target protein may be masked through the first domain at the non-disease site and transported to the target site of the first domain in an inactivated state.

In the present specification, the term "immune modulator" refers to a regulatory substance that plays a major role in regulating the immune system of a disease site. Specifically, the immune modulator may be a cytokine, a chemokine, or a fragment thereof. In addition, the immune modulator may be a molecule that binds to the cytokine, chemokine, or a fragment thereof.

In the present invention, the second target may be a protein that is overexpressed or specifically expressed or activated in target cells at a disease site. In this case, the target cells may be tumor cells, disease-related stromal cells, or immune cells.

In the present invention, the fusion protein may exhibit pharmacological activity against the disease by binding to a disease-specific target protein through the second domain.

Specifically, the second target may be 4-1-BB, 5T4, ACE, ADAM9, ADRB3, AKAP4, ALK, ANXA1, ANXA2, ANXA5, ASCT2, AXL, B7H3, B7H4, BCL2, BCMA, CA125, CA6, CA9, CCL11, CCR5, CEN106, CD2, CD4, CD5, CD15, CD16, CD19, CD20, CD22, CD23, CD24, CD25, CD27, CD30, CD33, CD37, CD38, CD40, CD41, CD44, CD44v6, CD46, CD48, CD51, CD52, CD54, CD56, CD62, CD70, CD71, CD72, CD73, CD74, CD79, CD80, CD90, CD97, CD99, CD105, CD117, CD123, CD133, CD135, CD138, CD142, CD163, CD171, CD, CD242, CD319, CD352, CDCP1, CEA, CLDN3, CLDN6, CLDN9, CLDN18.2, CXCR2, CXCR4, CXCR5, CFC1B, CEACAM5, CEACAM6, c-Met, c-Kit, CTLA4, DLL3, DLK-1, DR5, DPEP3, Dectin-2, ED-B, EGFR, Endothelin-1, Endoglin, ENPP3, EpCAM, EphA2, ETA, FAPα, FGFR1, FGFR2, FGFR3, FRα, GD2, GD3, GloboH, GPC3, GPR20, GPRC5D, HER2,

HER3, ICAM1, ICAM2, ICOS-L, IGF-1R, KAAG-1, L1CAM, LCK, LGR5, LIV-1, LRRC15, LY6E, MAGE, Mesothelin, MUC1, MUC16, MMP-14, NCAM1, Nectin-4, Notch3, NaPi2b, PDGFR, PD-L1, PD-L2, PSCA, PSMA, PTK7, RAGE-1, RANKL, RNF43, RON, ROR1, ROR2, SAP-1, SLAMF7, SLC44A4, Survivin, SAIL, STn, SSEA-4, SEZ6, SLC44A4, SLTRK6, TEM1, TEM8, TM4SF1, TNFLYPD3, TF, TIE2, TIM-1, TRAC, TROP-2, VEGFR1 (FLT1), VEGFR2 (KDR), VCAM-1, VSIG4, VISTA, or XAGE-1, but is not limited thereto.

The form of the second domain may be, for example, an antibody or a fragment thereof (e.g., Fv, scFv, VHH, Fab), a peptide, an aptamer, etc., or may be a form comprising part or all of a naturally occurring counterpart/ligand of a target that can be an antigen of the second domain, but is not limited thereto. Preferably, it may be an antibody or a fragment thereof. The antibody and the fragment thereof are the same as described above. In one embodiment of the present invention, the fragment of the antibody may be a scFv or a single domain antibody.

Specifically, the second domain may be an antibody or a fragment thereof that binds to any one selected from the group consisting of HER2, CD47, EGFR, CTLA4, B7H3, ANXA1, DLR1, CD3, CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, and amyloid-beta (Aβ) protofibrils. Table 4 below shows the variable region polypeptide sequences of the antibodies or fragments thereof described as the second domains of the various fusion proteins described herein. The fusion proteins according to exemplary embodiments may include these variable region polypeptides.

[Table 4]

Third component: Target binding				
Part Number	Second target	Clone Name; UNIT2	Inner domain in HC	Inner domain of LC
C1	HER2	Trastuzumab	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS(SEQ ID NO:184)	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK(SEQ ID NO:185)
C2	HER2	Trastuzumab (disulfide)	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS(SEQ ID NO:186)	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:187)
C3	CD47	Candidate14	QVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRGLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYYCARGG	DVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGAGTKLELK(SE

			YTMDYWGQGTSVTVSS(SEQ ID NO:188)	Q ID NO:189)
C4	CD47	Candidate14 (disulfide)	QVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRCLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARGGYTMDYWGQGTSVTVSS(SEQ ID NO:190)	DVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGCGTKLELK(SEQ ID NO:191)
C5	CD47	Magrolimab	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWVRQAPGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTSASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTLVTVSS(SEQ ID NO:192)	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIK(SEQ ID NO:193)
C6	CD47	Magrolimab (disulfide)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWVRQAPGQCLEWMGTIYPGNDDTSYNQKFKDRVTITADTSASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTLVTVSS(SEQ ID NO:194)	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGCGTKLEIK(SEQ ID NO:195)
C7	CD47	CC-90002	QMQLVQSGAEVKKTGSSVKVSCKASGFNIKDYYLHWVRQAPGQALEWMGWIDPDQGDTEYAQKFQDRVTITRDRSMSTAYMELSSLRSEDTAMYYCNAAYGSSSYPMDYWGQGTIVTVSS(SEQ ID NO:196)	NIQMTQSPSAMSASVGDRVTITCKASQDIHRYLSWFQQKPGKVPKHLIYRANRLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQYDEFPYTFGGGTKVEIK(SEQ ID NO:197)
C8	CD47	CC-90002 (disulfide)	QMQLVQSGAEVKKTGSSVKVSCKASGFNIKDYYLHWVRQAPGQCLEWMGWIDPDQGDTEYAQKFQDRVTITRDRSMSTAYMELSSLRSEDTAMYYCNAAYGSSSYPMDYWGQGTIVTVSS(SEQ ID NO:198)	NIQMTQSPSAMSASVGDRVTITCKASQDIHRYLSWFQQKPGKVPKHLIYRANRLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQYDEFPYTFGCGTKVEIK(SEQ ID NO:199)
C9	EGFR	Cetuximab	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA(SEQ ID NO:200)	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELK(SEQ ID NO:201)
C10	EGFR	Cetuximab (disulfide)	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKCLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA(SEQ ID NO:202)	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGCGTKLELK(SEQ ID NO:203)

C11	EGFR	Panitumumab	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS(SEQ ID NO:204)	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIK(SEQ ID NO:205)
C12	EGFR	Panitumumab (disulfide)	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKCLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS(SEQ ID NO:206)	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGCGTKVEIK(SEQ ID NO:207)
C13	EGFR	Necitumumab	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSS(SEQ ID NO:208)	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAEIK(SEQ ID NO:209)
C14	EGFR	Necitumumab (disulfide)	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKCLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVS(SEQ ID NO:210)	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGCGTKAEIK(SEQ ID NO:211)
C15	CTLA4	Ipilimumab (disulfide)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKCLEWVTFISYDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSS(SEQ ID NO:212)	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGCGTKVEIK(SEQ ID NO:213)
C16	CTLA4	Tremelimumab (disulfide)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKCLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPRGATLYYYYYGMDVWGQGTTVTVSS(SEQ ID NO:214)	DIQMTQSPSSLSASVGDRVTITCRASQSINSYLDWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPFTFGCGTKVEIK(SEQ ID NO:215)
C17	B7H3	m8524	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS(SEQ ID NO:139)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK(SEQ ID NO:140)
C18	B7H3	m8524 (disulfide)	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRL

			GQCLEWMGGIIPILGIANYAQ KFQGRVTITADESTSTAYMEL SSLRSEDTAVYYCARGGSGSY HMDVWGKGTTVTVSS(SEQ ID NO:216)	LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQRSN WPPRITFGCGTRLEIK(SEQ ID NO:217)
C19	ANXA1	Y829	QVQLVQSGGGLVQPGRSLRIS CKASGFNFGDYPLSWVRQAP GKGLEWIGFIRSKSFGGTTEY AASVKGRFTISRDDSRDIAYL QMNSLRAEDTAVYYCARDG NYYDSRGYYYDTFDLWGQG TMITVSS(SEQ ID NO:109)	DIQMTQSPSSVSASVGDRVTLTC RASQGIRSWLAWYQQKPGKAPK LLIYAASNLQSGVPSRFSGSGSGT DFILTINSLQPDDFATYYCQQAN SFPYTFGQGTKVEIK(SEQ ID NO:110)
C20	DLK1	18A5	QVQLVQSGGAVVQPGHSLRL SCEASGFKFKDYGMHWVRQ APGKGLEWLAVISHDGRNKN YADSVKGRLTISRDNSKNTLS FQMNSLRAEDTAVYYCVRD WSYAFDIWGQGTLVTVSS(SE Q ID NO:218)	DIQMTQSPSFLSASVGDRVNITC RASQDISRRLAWYQQKPGKAPK LLIYGAASLQSAVASRFSGSGSG TEFTLTISSLQPEDFANYYCQQIY TTPLTFGGGTKVEIK(SEQ ID NO:219)
C21	CD3	SP34#8	EVQLVESGGGLVQPGGSLRLS CAASGFTFSTYAMNWVRQAP GKGLEWVGRIRSKYNNYATY YADSVKDRFTISRDDSKNSLY LQMNSLKTEDTAVYYCARHG NFGNSYVSYFAYWGQGTLVT VSS(SEQ ID NO:220)	DIQMTQSPSSLSASVGDRVTITCR SSTGAVTTSNYANWVQQKPGKA PKALIGGTNKRAPGVPSRFSGSLI GDKATLTISSLQPEDFATYYCAL WYSNLWVFGQGTKVEIK(SEQ ID NO:221)
C22	CLDN18.2	Zolbetuximab	QVQLQQPGAELVRPGASVKL SCKASGYTFTSYWINWVKQR PGQGLEWIGNIYPSDSYTNYN QKFKDKATLTVDKSSSTAYM QLSSPTSEDSAVYYCTRSWRG NSFDYWGQGTTLTVSS(SEQ ID NO:222)	DIVMTQSPSSLTVTAGEKVTMSC KSSQSLLNSGNQKNYLTWYQQK PGQPPKLLIYWASTRESGVPDRF TGSGSGTDFTLTISSVQAEDLAV YYCQNDYSYPFTFGSGTKLEIK(S EQ ID NO:223)
C23	CLDN18.2	PR002726	EVQLLESGGGLVQPGGSLRLS CAASGFTFSSFVMSWVRQAP GKGLEWVSTISGSGRSTYYAD SVKGRFTISRDNSKNTLHLQM NSLRAEDTAVYYCAKDAAAA GTKFDYWGQGTLVTVSS(SEQ ID NO:224)	EIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQRSN WPLTFGGGTKVEIK(SEQ ID NO:225)
C24	TEM8	m825	QVQLVQSGAEVKKPGTSVKV SCKVPGYTFSSYAISWVRQAP GQGLEWMGGIIPIFGTTNYAQ KFQGRVTITGEESTSTVYMEL SSLRSEDTAVYYCARDTDYM FDYWGQGTLVTVSS (SEQ ID NO:127)	SSELTQDPVVSVALGETVSITCQ GDNLRDFYASWYQQKPGQAPLL VMYGKNRRPSGIPDRFSGSTSGN TLSLTITGAQAEDEADYYCSSRD NSKHVVFGGGTKVTVL(SEQ ID NO:128)
C25	FAPα	humanized MFP5	QVQLVQSGAEVKKPGASVKV SCKASGYTFTNNGINWLRQAP GQGLEWMGEIYPRSTNTLYA QKFQGRVTITADRSSNTAYME	QIVLTQSPATLSLSPGERATLSCS ASSGVNFMHWYQQKPGQAPRR LIFDTSKLASGIPARFSGSGSGTD YTLTISSLEPEDFAVYYCQQWSF

			LSSLRSEDTAVYFCARTLTAP FAFWGQGTLVTVSS(SEQ ID NO:137)	NPPTFGQGTKVEIK(SEQ ID NO:138)
C26	EpCAM	ING-1	QIQLVQSGPEVKKPGESVKISC KASGYTFTKYGMNWVKQAP GQGLKWMGWINTYTEEPTYG DDFKGRFTFTLDTSTSTAYLEI SSLRSEDTATYFCARFGSAVD YWGQGTLVTVSS(SEQ ID NO:226)	DIVMTQSALSNPVTLGESGSISCR SSKSLLHSNGITYLYWYLQKPGQ SPQLLIYQMSNRASGVPDRFSSS GSGTDFTLKISRVEAEDVGVYYC AQNLELPRTFGQGTKLEMK(SEQ ID NO:227)
C27	PD-1	Nivolumab	QVQLVESGGGVVQPGRSLRL DCKASGITFSNSGMHWVRQA PGKGLEWVAVIWYDGSKRYY ADSVKGRFTISRDNSKNTLFL QMNSLRAEDTAVYYCATNDD YWGQGTLVTVSS(SEQ ID NO:228)	EIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQSSN WPRTFGQGTKVEIK(SEQ ID NO:229)
C28	PD-L1	Atezolizumab	EVQLVESGGGLVQPGGSLRLS CAASGFTFSDSWIHWVRQAP GKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCARRHW PGGFDYWGQGTLVTVSS(SEQ ID NO:230)	DIQMTQSPSSLSASVGDRVTITCR ASQDVSTAVAWYQQKPGKAPK LLIYSASFLYSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQYL YHPATFGQGTKVEIK(SEQ ID NO:231)
C29	CD3	SP34#8(disdulfide)	EVQLVESGGGLVQPGGSLRLS CAASGFTFSTYAMNWVRQAP GKCLEWVGRIRSKYNNYATY YADSVKDRFTISRDDSKNSLY LQMNSLKTEDTAVYYCARHG NFGNSYVSYFAYWGQGTLVT VSS(SEQ ID NO:232)	DIQMTQSPSSLSASVGDRVTITCR SSTGAVTTSNYANWVQQKPGKA PKALIGGTNKRAPGVPSRFSGSLI GDKATLTISSLQPEDFATYYCAL WYSNLWVFGCGTKVEIK(SEQ ID NO:233)
C30	EGFR	Panitumumab (cross)	DIQMTQSPSSLSASVGDRVTIT CQASQDISNYLNWYQQKPGK APKLLIYDASNLETGVPSRFSG SGSGTDFTFTISSLQPEDIATYF CQHFDHLPLAFGGGTKVEIK(SEQ ID NO:205)	QVQLQESGPGLVKPSETLSLTCT VSGGSVSSGDYYWTWIRQSPGK GLEWIGHIYYSGNTNYNPSLKSR LTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTM VTVSS(SEQ ID NO:204)
C31	PD-L1	Atezolizumab(disulfide,cross)	DIQMTQSPSSLSASVGDRVTIT CRASQDVSTAVAWYQQKPG KAPKLLIYSASFLYSGVPSRFS GSGSGTDFTLTISSLQPEDFAT YYCQQYLYHPATFGCGTKVEI K(SEQ ID NO:236)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDSWIHWVRQAPGKCL EWVAWISPYGGSTYYADSVKGR FTISADTSKNTAYLQMNSLRAED TAVYYCARRHWPGGFDYWGQG TLVTVSS(SEQ ID NO:237)
C32	PD-L1	Atezolizumab scFv	EVQLVESGGGLVQPGGSLRLS CAASGFTFSDSWIHWVRQAP GKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCARRHW PGGFDYWGQGTLVTVSSGGG GSGGGGSGGGGSDIQMTQSPS SLSASVGDRVTITCRASQDVS	N/A

			TAVAWYQQKPGKAPKLLIYS ASFLYSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQYLY HPATFGQGTKVEIK(SEQ ID NO:238)	
C33	Amyloid-beta(Aβ-protofibrils)	Lecanemab	EVQLVESGGGLVQPGGSLRLS CSASGFTFSSFGMHWVRQAP GKGLEWVAYISSGSSTIYYGD TVKGRFTISRDNAKNSLFLQM SSLRAEDTAVYYCAREGGYY YGRSYYTMDYWGQGTTVTV SS(SEQ ID NO:239)	DVVMTQSPLSLPVTPGAPASISC RSSQSIVHSNGNTYLEWYLQKPG QSPKLLIYKVSNRFSGVPDRFSGS GSGTDFTLRISRVEAEDVGIYYCF QGSHVPPTFGPGTKLEIK(SEQ ID NO:240)
N/D, Not determined; N/A or '-', Not associated				

- HER2

More specifically, the second domain may be an antibody that binds to HER2 or a fragment thereof.

As used herein, the term "HER2" is also known as ErbB-2 or CD340 and is a protein belonging to the ErbB (HER/EGFR/ERBB) family. The ErbB family consists of four types of binding receptor tyrosine kinase subfamilies: ErbB-1 (HER1, EGFR), ErbB-2 (HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4). All four types of receptors include an extracellular ligand binding domain, a transmembrane domain, and an intracellular domain. In this case, the intracellular domain interacts with multiple signaling molecules either ligand-dependently or independently. In particular, the ligand of HER2 is not yet known. HER2 is known to function by forming a heterodimer with one of three other types of receptors. The receptors of the ErbB family are known to be involved in regulating cell adhesion, migration, and differentiation, in addition to cell proliferation and survival. In particular, HER2 is known as the most potent oncoprotein in breast cancer. When HER2 is at normal levels, it is involved in the growth and development of normal mammary gland tissue; however, if HER2 is abnormally overexpressed or amplified, normal cell regulation is disrupted, leading to the formation of aggressive cancer cells in the mammary gland tissue. HER2 overexpression occurs in about 20-30% of invasive breast cancers, and overexpression is known to be associated with a poor prognosis for breast cancer, as it is a more aggressive cancer with higher malignancy.

In the present invention, HER2 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the HER2 protein may include both natural type and variant HER2 proteins, but is not limited thereto. The term "natural type HER2 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type HER2 protein. The amino acid sequence and polynucleotide sequence for the HER2 protein can be obtained from known databases, such

as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 148.

In addition, as long as it has the same activity as the protein or the same gene location encoding HER2 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, HER2 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 148.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Trastuzumab, which is an anti-HER2 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 802, HCDR2 comprising the amino acid sequence of SEQ ID NO: 804, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 806; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 913, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 915. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 184, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 185 (C1). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 186, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 187 (C2).

- CD47

More specifically, the second domain may be an antibody that binds to CD47 or a fragment thereof.

As used herein, the term "CD47" refers to a member of the immunoglobulin superfamily, also known as integrin-associated protein (IAP). CD47 is a cell surface immunoglobulin, and its ligand interacts with SIRPα, which is primarily expressed in macrophages and dendritic cells, thereby inhibiting the phagocytosis of macrophages and dendritic cells. While CD47 is known to be overexpressed in various tumors, it has also been reported to be overexpressed in normal tissues.

In the present invention, CD47 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the CD47 protein may include both natural type and variant CD47 proteins, but is not limited thereto. The term "natural type CD47 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type CD47 protein. The amino acid sequence and polynucleotide sequence for the CD47 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 149.

In addition, as long as it has the same activity as the protein or the same gene location encoding CD47 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, CD47 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 149.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Candidate 14, which is an anti-CD47 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 809, HCDR2 comprising the amino acid sequence of SEQ ID NO: 811, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 813; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 918, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 922. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 188, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 189 (C3). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 190, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 191 (C4).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of Magrolimab, which is an anti-CD47 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 815, HCDR2 comprising the amino acid sequence of SEQ ID NO: 817, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 819; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 926, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 929. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 192, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 193 (C5). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 194, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 195 (C6).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of CC-90002, which is an anti-CD47 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 821, HCDR2 comprising the amino acid sequence of SEQ ID NO: 823, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 825; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 932, LCDR2 comprising the amino acid sequence of SEQ ID NO: 934, and LCDR3 comprising the amino

acid sequence of SEQ ID NO: 936. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 196, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 197 (C7). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 198, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 199 (C8).

- EGFR

More specifically, the second domain may be an antibody that binds to the epidermal growth factor receptor (EGFR) or a fragment thereof.

As used herein, the term "EGFR" is also known as HER1 or ErbB-1 as described above and is a protein belonging to the ErbB (HER/EGFR/ERBB) family. EGFR regulates cell growth, division, survival, and death. Overexpression of EGFR in tumor tissues has been reported in various cancers, and tumor tissues with increased EGFR are known to have high invasiveness, metastasis, and resistance to anticancer drugs.

In the present invention, EGFR may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the EGFR protein may include both natural type and variant EGFR proteins, but is not limited thereto. The term "natural type EGFR protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type EGFR protein. The amino acid sequence and polynucleotide sequence for the EGFR protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 150.

In addition, as long as it has the same activity as the protein or the same gene location encoding EGFR on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, EGFR may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 150.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Cetuximab, which is an anti-EGFR antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 829, HCDR2 comprising the amino acid sequence of SEQ ID NO: 832, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 834; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 939, LCDR2 comprising the amino acid sequence of SEQ ID NO: 941, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 943. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 200, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 201 (C9). Alternatively,

the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 202, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 203 (C10).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of Panitumumab, which is an anti-EGFR antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 838, HCDR2 comprising the amino acid sequence of SEQ ID NO: 840, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 842; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 903, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 906. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 204, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 205 (C11). In this case, the heavy chain variable region may be located in the light chain, and the light chain variable region may be located in the heavy chain (C30). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 206, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 207 (C12).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of Necitumumab, which is an anti-EGFR antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 844, HCDR2 comprising the amino acid sequence of SEQ ID NO: 846, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 848; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 937. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 208, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 209 (C13). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 210, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 211 (C14).

- CTLA4

More specifically, the second domain may be an antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or a fragment thereof.

As used herein, the term "CTLA4" refers to an immune checkpoint protein, also known as CD152. CTLA4 has homology with CD28 and competitively binds to B7-1 (CD80) or B7-2 (CD86) on the surface of antigen-presenting cells (APCs). In this case, when CD28 binds to CD80 or CD86, the immune response is activated, but when CTLA4 binds, the immune response is inhibited. It is known to inhibit the immune response by binding. In particular, CTLA4 is

known to exhibit greater affinity and binding avidity for CD80 or CD86 compared to CD28.

In the present invention, CTLA4 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the CTLA4 protein may include both natural type and variant CTLA4 proteins, but is not limited thereto. The term "natural type CTLA4 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type CTLA4 protein. The amino acid sequence and polynucleotide sequence for the CTLA4 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 151.

In addition, as long as it has the same activity as the protein or the same gene location encoding CTLA4 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, CTLA4 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 151.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Ipilimumab, which is an anti-CTLA4 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 850, HCDR2 comprising the amino acid sequence of SEQ ID NO: 852, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 854; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 948, LCDR2 comprising the amino acid sequence of SEQ ID NO: 949, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 951. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 212, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 213 (C15).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of Tremelimumab, which is an anti-CTLA4 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 855, HCDR2 comprising the amino acid sequence of SEQ ID NO: 857, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 858; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 952, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 954. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 214, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 215 (C16).

- B7H3

More specifically, the second domain may be an antibody that binds to B7H3 or a

fragment thereof. The B7H3 is the same as described above.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of the anti-B7H3 antibody (m8524). Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 757, HCDR2 comprising the amino acid sequence of SEQ ID NO: 759, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 761; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 799. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 139, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 140 (C17). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 216, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 217 (C18).

- ANXA1

More specifically, the second domain may be an antibody that binds to ANXA1 or a fragment thereof. The ANXA1 is the same as described above.

In the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of A55 of UNIT1. The heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 109, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 110 (C19). The A55 of UNIT1 is the same as described above.

- DLK1

More specifically, the second domain may be an antibody that binds to DLK1 (delta-like 1 homolog) or a fragment thereof.

As used herein, the term "DLK1" refers to a transmembrane protein that is a member of the Notch/delta/serrate family.

DLK1 comprises an extracellular domain, a transmembrane domain, and an intracellular domain. The extracellular domain has six EGF-like repeat domains. In addition, DLK1 is known to function independently when its extracellular domain is shed from the cell membrane by tumor necrosis factor alpha converting enzyme (TACE). Overexpression has been reported in brain cancer and liver cancer in relation to cancer.

In the present invention, DLK1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the DLK1 protein may include both natural type and variant DLK1 proteins, but is not limited thereto. The term "natural type DLK1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type DLK1 protein. The amino acid sequence and polynucleotide sequence for the DLK1 protein can be obtained from known databases, such

as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 152.

In addition, as long as it has the same activity as the protein or the same gene location encoding DLK1 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, DLK1 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 152.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of the anti-DLK1 antibody (18A5). Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 861, HCDR2 comprising the amino acid sequence of SEQ ID NO: 863, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 865; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 957, LCDR2 comprising the amino acid sequence of SEQ ID NO: 958, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 960. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 218, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 219 (C20).

- CD3

More specifically, the second domain may be an antibody that binds to CD3 or a fragment thereof.

As used herein, the term "CD3" refers to a homodimeric or heterodimeric protein expressed on T cells in relation to the T cell receptor complex, which is an essential element for T cell activation. The functional CD3 is formed by the dimeric association of two or more of four different chains, such as ε, ζ, δ, and γ, and CD3 dimeric arrangements include γ/ε, δ/ε, and ζ/ζ. Antibodies against CD3 are known to bind to CD3 present on T cells and induce T cell activation.

In the present invention, CD3 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the CD3 protein may include both natural type and variant CD3 proteins, but is not limited thereto. The term "natural type CD3 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type CD3 protein. The amino acid sequence and polynucleotide sequence for the CD3 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 153.

In addition, as long as it has the same activity as the protein or the same gene location encoding CD3 on the chromosome, it may consist of a sequence in which one or several amino

acids of the protein are added, deleted, or substituted. Specifically, CD3 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 153.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of the anti-CD3 antibody (SP34#8). Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 866, HCDR2 comprising the amino acid sequence of SEQ ID NO: 868, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 870; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 962, LCDR2 comprising the amino acid sequence of SEQ ID NO: 964, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 966. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 220, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 221 (C21). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 232, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 233 (C29).

- CLDN18.2

More specifically, the second domain may be an antibody that binds to CLDN18.2 (Claudin 18.2) or a fragment thereof.

As used herein, the term "CLDN18.2" refers to one of the isoforms of Claudin 18, a transmembrane protein that is a major component of epithelial cells and epithelial tight junctions in which cells regulate material flow. CLDN18.2 is known to be expressed restrictively in the stomach and to maintain the barrier function of the gastric mucosa and prevent the leakage of hydrogen ions from gastric acid. Overexpression has been reported in various types of tumors, including pancreatic cancer, esophageal cancer, ovarian adenocarcinoma, and lung cancer.

In the present invention, CLDN18.2 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the CLDN18.2 protein may include both natural type and variant CLDN18.2 proteins, but is not limited thereto. The term "natural type CLDN18.2 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type CLDN18.2 protein. The amino acid sequence and polynucleotide sequence for the CLDN18.2 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 154.

In addition, as long as it has the same activity as the protein or the same gene location encoding CLDN18.2 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, CLDN18.2 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about

93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 154.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Zolbetuximab, which is an anti-CLDN18.2 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 872, HCDR2 comprising the amino acid sequence of SEQ ID NO: 874, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 876; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 968, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 971. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 222, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 223 (C22).

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of PR002726, which is an anti-CLDN18.2 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 878, HCDR2 comprising the amino acid sequence of SEQ ID NO: 880, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 882; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 973. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 224, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 225 (C23).

- TEM8

More specifically, the second domain may be an antibody that binds to TEM8 or a fragment thereof. The TEM8 is the same as described above.

In the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of A70 of UNIT1. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 127, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 128 (C24). The A70 of UNIT1 is the same as described above.

- FAPα

More specifically, the second domain may be an antibody that binds to FAPα or a fragment thereof. The FAPα is the same as described above.

In the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of A75 of UNIT1. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 137, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 138 (C25). The A75 of UNIT1 is the

same as described above.

- EpCAM

More specifically, the second domain may be an antibody that binds to an epithelial cell adhesion molecule (EpCAM) or a fragment thereof.

As used herein, the term "EpCAM" refers to a type of cell adhesion molecule that exists in epithelial tissue and exhibits specific adhesion to homologous receptors.

The cell adhesion molecule (CAM) refers to a collective term for molecules such as fibronectin, collagen, and laminin that constitute the extracellular matrix, and receptors present on the cell surface that receive these molecules. Among these, cadherin and NCAM (neural cell adhesion molecule) exhibit specific adhesion to homologous receptors, but most cell adhesion molecules excluding the above molecules are known to exhibit adhesion activity to heterologous adhesion molecules as well.

In the present invention, EpCAM may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the EpCAM protein may include both natural type and variant EpCAM proteins, but is not limited thereto. The term "natural type EpCAM protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type EpCAM protein. The amino acid sequence and polynucleotide sequence for the EpCAM protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 155.

In addition, as long as it has the same activity as the protein or the same gene location encoding EpCAM on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, EpCAM may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 155.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of ING-1, which is an anti-EpCAM antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 884, HCDR2 comprising the amino acid sequence of SEQ ID NO: 886, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 888; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 975, LCDR2 comprising the amino acid sequence of SEQ ID NO: 977, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 979. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 226, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 227 (C26).

- PD-1

More specifically, the second domain may be an antibody that binds to PD-1 (programmed cell death-1) or a fragment thereof.

As used herein, the term "PD-1," also known as CD279, refers to an immune checkpoint protein that is expressed on the surface of activated T cells (immune cells). Under normal circumstances, PD-1 plays a positive role in preventing the development of autoimmune diseases by mediating and maintaining autoimmune tolerance in body tissues and preventing the immune system from becoming overly activated and damaging self-tissues during inflammatory responses. However, under pathological conditions, PD-1 is known to be involved in tumor immunity and the development and progression of various autoimmune diseases. PD-1 is also expressed in B cells, natural killer cells, mononuclear cells, and dendritic cells, and weakens the cellular immune response by binding to PD-L1 or PD-L2 and inducing apoptosis of T cells.

In the present invention, PD-1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the PD-1 protein may include both natural type and variant PD-1 proteins, but is not limited thereto. The term "natural type PD-1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type PD-1 protein. The amino acid sequence and polynucleotide sequence for the PD-1 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 156.

In addition, as long as it has the same activity as the protein or the same gene location encoding PD-1 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, PD-1 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 156.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Nivolumab, which is an anti-PD-1 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 890, HCDR2 comprising the amino acid sequence of SEQ ID NO: 892, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 894; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 981. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 228, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 229 (C27).

- PD-L1

More specifically, the second domain may be an antibody that binds to PD-L1

(programed cell death ligand 1) or a fragment thereof.

As used herein, the term "PD-L1" refers to a protein expressed on the surface of tumor cells or hematopoietic cells. It is known as CD274 or B7H1. PD-L1 is a ligand of PD-1. When PD-L1 and PD-1 bind, they induce apoptosis of T cells, thereby weakening the immune activity of the cells.

In the present invention, PD-L1 may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice. In addition, the PD-L1 protein may include both natural type and variant PD-L1 proteins, but is not limited thereto. The term "natural type PD-L1 protein" generally refers to a polypeptide comprising the amino acid sequence of the natural type PD-L1 protein. The amino acid sequence and polynucleotide sequence for the PD-L1 protein can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 157.

In addition, as long as it has the same activity as the protein or the same gene location encoding PD-L1 on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, PD-L1 may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 157.

In one embodiment, the second domain may comprise a heavy chain variable region and a light chain variable region of Atezolizumab, which is an anti-PD-L1 antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 895, HCDR2 comprising the amino acid sequence of SEQ ID NO: 898, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 900; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 982, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 984. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 230, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 231 (C28). Alternatively, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 237, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 236. In this case, the second domain may be an antibody or a fragment thereof in which the heavy chain variable region is located on the light chain and the light chain variable region is located on the heavy chain (C31).

- Amyloid beta protofibrils

More specifically, the second domain may be an antibody that binds to amyloid beta protofibrils (Aβ protofibrils) or a fragment thereof.

As used herein, the term "Amyloid beta (Aβ) protofibrils" refers to an intermediate form of Aβ aggregate generated in a cascade of aggregate forms from Aβ monomers to the formation of Aβ plaques. Although amyloid plaques composed of Aβ fibril deposits are a characteristic of Alzheimer's disease, soluble Aβ, particularly oligomers and protofibrils, measured in the brain tissue and cerebrospinal fluid of post-mortem Alzheimer's patients, are reported to be more associated with disease progression and harmful to synapses and neurons.

In the present invention, Aβ protofibril may be included without limitation as long as it is of mammalian origin, including humans, primates such as monkeys, and rodents such as rats and mice.

The amino acid sequence and polynucleotide sequence for the Aβ protofibril can be obtained from known databases, such as the GenBank of the National Center for Biotechnology Information (NCBI), and preferably may comprise the amino acid sequence of SEQ ID NO: 158.

In addition, as long as it has the same activity as the protein or the same gene location encoding the amyloid beta on the chromosome, it may consist of a sequence in which one or several amino acids of the protein are added, deleted, or substituted. Specifically, the amyloid beta may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity, or 100% identity with the amino acid sequence of SEQ ID NO: 158.

In one embodiment of the present invention, the second domain may comprise a heavy chain variable region and a light chain variable region of Lecanemab, which is an anti-Aβ protofibril antibody. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 908, HCDR2 comprising the amino acid sequence of SEQ ID NO: 910, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 912; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 986, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 989. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 239, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 240 (C33).

In the present invention, the immune modulator, the antibody or fragment thereof, or the antigen binding site constituting the second domain is referred to as "UNIT2".

Linker

In the present invention, the first domain and the second domain of the fusion protein may be linked via a linker. In this case, the linker may be a first linker. Preferably, it may be a first cleavable linker.

In the ReleaDome of the present invention, the first domain and the second domain are linked via the first cleavable linker, so that at a non-disease site, the binding avidity of the second domain is masked by the first domain, allowing it to exist in an inactivated state. In addition,

when the ReleaDome is located at a disease site to which the first domain specifically binds, the cleavable linker is cleaved by a proteolytic enzyme specifically expressed at the disease site, thereby dissociating the first domain and allowing the second domain to bind to a target, which can exhibit a pharmacological effect.

First linker

The first linker may be a peptide linker. In addition, the first linker may be a cleavable linker or a non-cleavable linker. Hereinafter, the cleavable linker of the first linker is described as 'first cleavable linker', and the non-cleavable linker is described as 'first non-cleavable linker'. In addition, in the present specification, the first linker is described interchangeably with "second component" or "B".

As used herein, the term "peptide linker" refers to a peptide composed of one or more amino acids. Typically, it may consist of 1 to 100 consecutive amino acids, 1 to 50 consecutive amino acids, 3 to 30 consecutive amino acids, or 5 to 15 amino acids. The peptide linker is known in the art or described herein.

- First cleavable linker

As used herein, the term "first cleavable linker" refers to a polypeptide linker comprising a cleavable peptide. The cleavable peptide is a polypeptide comprising a proteolytic enzyme cleavage site and can be specifically cleaved by a proteolytic enzyme (protease). In the present specification, the term "cleavable peptide" may be described interchangeably with "substrate peptide." The proteolytic enzyme is an enzyme that hydrolyzes the peptide bond between two specific amino acid residues within a target substrate protein (substrate). Therefore, the term "cleavage site" refers to an amino acid sequence within the target substrate protein that is recognized and cleaved by the proteolytic enzyme, and the cleavable peptide may comprise the amino acid sequence (substrate sequence) of such a proteolytic enzyme cleavage site. The cleavable peptide is generally cleaved by enzymes, typically peptidases, proteases, nucleases, lipases, etc. In addition, the cleavable peptide may be cleaved by environmental signals, e.g., changes in temperature, pH, salt concentration, etc.

In the present invention, the cleavable peptide may comprise an amino acid sequence of a cleavage site that is cleaved by a proteolytic enzyme that is specifically overexpressed or overactivated at a disease site compared to a non-disease site.

In one embodiment, the cleavable peptide may comprise an amino acid sequence of a tumor-associated proteolytic enzyme cleavage site. Here, the tumor-associated proteolytic enzyme may be a proteolytic enzyme that is overexpressed in tumor cells or in the tumor environment.

In one embodiment, the cleavable peptide may comprise an amino acid sequence of a proteolytic enzyme cleavage site associated with a degenerative brain disease (e.g., Alzheimer's disease). Here, the degenerative brain disease-related proteolytic enzyme may be a proteolytic

enzyme that is overexpressed in an environment where degenerative brain disease has developed.

In the present invention, the masking effect of the first domain (first component) masking the second domain (third component) may vary depending on the length, amino acid composition, and arrangement of the cleavable peptide.

The cleavable peptide may exhibit different cleavage efficiencies, and may not be cleaved or may exhibit very weak cleavage efficiency at a non-disease site.

Specifically, the proteolytic enzymes that are specifically expressed at the disease site may be any one selected from the group consisting of human matrix metalloprotease (MMP)-1, MMP-2, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20, MMP-21, MMP-22, MMP-23, MMP-24, MMP-25, MMP-26, MMP-27, MMP-28, human Cathepsin A, Cathepsin B, Cathepsin C, Cathepsin D, Cathepsin E, Cathepsin F, Cathepsin G, Cathepsin H, Cathepsin K, Cathepsin L1, Cathepsin V, Cathepsin O, Cathepsin S, Cathepsin W, Cathepsin Z, human Enterokinase (EK), human Thrombin (Thr), human tPA (tissue plasminogen activator), human Granzyme BGrB, human uPA (Urokinase-type plasminogen activator), human ADAMTs-5 (A disintegrin-like and metalloproteinase with thrombospondin type1 motif 5, A5), Kallikreins, human K1, human K10, human Plasmin, Collagenase, Type IV collagenase, Sromelysin, Factor Xa, Cymotrypsin-like protease, Typsin-like protease, Elastase-like protease, Sbtilisin-like protease, Atinidain, Bomelain, Calpain, Caspases, Caspase-3, Mirl CP, Papain, HIV-1 protease, HSV protease, CMV protease, Chymosin, Renin, Pepsin, Matriptase, Legumain, Plasmepsin, Nepenthesin, Metalloexopeptidases, Metalloendopeptidases, Prostate specific antigen (PSA/hK3), Interleukin-1β converting enzyme, Thrombin, FAPα, Dipeptidyl peptidase, Type II transmembrane serine proteases (TTSP), Neutrophil serine protease, Proteinase 3, Neutrophil serine protease 4, Mast cell chymase, Mast cell tryptases, and combinations thereof, but are not limited thereto.

The cleavable peptide may consist of 2 to 20 consecutive amino acids. Specifically, the cleavable peptide may consist of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 consecutive amino acids.

In addition, in the present invention, the cleavable peptide may comprise a variant. In this case, the variant (or PRS variant) refers to a cleavable peptide comprising a substrate sequence for one or more proteolytic enzymes. In this case, the composition and arrangement of the substrate sequences of each included proteolytic enzyme may be combined differently. Therefore, the proteolytic enzymes that recognize the cleavable peptide variant may be one type or more than one types, and the cleavage efficiency of the substrate peptide may vary depending on the substrate sequence and the proteolytic enzyme.

More specifically, the cleavable peptide may be cleaved by any one proteolytic enzyme selected from the group consisting of MMP-2, MMP-9, uPA, MT-SP1, MMP-3, MMP-7, and

combinations thereof. In one embodiment of the present invention, the cleavable peptide may comprise any one amino acid selected from the group consisting of SEQ ID NO: 159 to SEQ ID NO: 176.

In one embodiment, the cleavable peptide may be cleaved by MMP-2. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-9. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 163 to SEQ ID NO: 166, SEQ ID NO: 169, or SEQ ID NO: 170. In one embodiment, the cleavable peptide may be cleaved by uPA. In one embodiment, the cleavable peptide may be cleaved by MT-SP1. In one embodiment, the cleavable peptide may be cleaved by MMP-3. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 163 to SEQ ID NO: 166. In one embodiment, the cleavable peptide may be cleaved by MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 166, or SEQ ID NO: 174.

In one embodiment, the cleavable peptide may be cleaved by MMP-2 and MMP-9. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2 and uPA. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2 and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-9 and uPA. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 163 to SEQ ID NO: 166, SEQ ID NO: 169, or SEQ ID NO: 170. In one embodiment, the cleavable peptide may be cleaved by MMP-9 and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 163 to SEQ ID NO: 166, SEQ ID NO: 169, or SEQ ID NO: 170. In one embodiment, the cleavable peptide may be cleaved by uPA and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 161 to SEQ ID NO: 168. In one embodiment, the cleavable peptide may be cleaved by MMP-2, MMP-9, and uPA. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2, uPA, and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable

peptide may be cleaved by MMP-9, uPA, and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 161 to SEQ ID NO: 170. In one embodiment, the cleavable peptide may be cleaved by MMP-2, MMP-9, uPA, and MT-SP1. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-3 and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 166, or SEQ ID NO: 174.

In one embodiment, the cleavable peptide may be cleaved by MMP-2, MMP-9, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2, uPA, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-9, uPA, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160 to SEQ ID NO: 170, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-9, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 166, SEQ ID NO: 169, SEQ ID NO: 170, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by uPA, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160 to SEQ ID NO: 168 or SEQ ID NO: 174.

In one embodiment, the cleavable peptide may be cleaved by MMP-2, MMP-9, uPA, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 161, SEQ ID NO: 163 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-2, uPA, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 159 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174. In one embodiment, the cleavable peptide may be cleaved by MMP-9, uPA, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid sequence of SEQ ID NO: 160 to SEQ ID NO: 170 or SEQ ID NO: 174.

In one embodiment, the cleavable peptide may be cleaved by MMP-2, MMP-9, uPA, MT-SP1, MMP-3, and MMP-7. Specifically, the cleavable peptide may comprise the amino acid

sequence of SEQ ID NO: 159 to SEQ ID NO: 170, SEQ ID NO: 173, or SEQ ID NO: 174.

Table 5 below shows exemplary sequences of cleavable peptides that may be included in the cleavable linkers provided herein. The following amino acid sequences are described sequentially from the N-terminus to the C-terminus. The fusion proteins according to the present invention according to exemplary embodiments may comprise these cleavable peptides.

Hereinafter, the first cleavable linker comprising the cleavable peptide is described in the present invention interchangeably with "PRS (protein recognition site)" or "first cleavable linker."

[Table 5]

Second component: Protease recognition site(PRS)			
Part Number	PRS	PRS attached to VH1	PRS attached to VL1
B1	PRS0	PLSAAAGSDN((SEQ ID NO:159)	PLSAAAGSDNH(SEQ ID NO:160)
B2	PRS1	LSGRSDN(SEQ ID NO:161)	LSGRSDNH(SEQ ID NO:162)
B3	PRS2	PLGLSGRSDN(SEQ ID NO:163)	PLGLSGRSDNH(SEQ ID NO:164)
B4	PRS3	LSGRSANPAGL(SEQ ID NO:165)	LSGRSANPAGLY(SEQ ID NO:166)
B5	PRS4	PLSGRSDN(SEQ ID NO:167)	PLSGRSDNH(SEQ ID NO:168)
B6	PRS5	PLGL(SEQ ID NO:169)	PLGLY(SEQ ID NO:170)
B7	PRS6	ASTKG(SEQ ID NO:171)	ASTKGP(SEQ ID NO:172)
B8	PRS7	PLSAAA(SEQ ID NO:173)	PLSAAAH(SEQ ID NO:174)
B9	PRS8	EAD(SEQ ID NO:175)	EADH(SEQ ID NO:176)

In the present invention, the first cleavable linker may comprise a space domain at the N-terminus and/or C-terminus of the cleavable peptide. The space domain is a peptide that is located at the N-terminus and/or C-terminus of a cleavable peptide that does not comprise a proteolytic enzyme cleavage site, and can serve to position the proteolytic enzyme so that it is more accessible to the cleavage site of the cleavable peptide. The length of the space domain may be optimized to suit accessibility for enzymatic cleavage. Each of the space domains may comprise about 1 to 100 amino acids. Specifically, it may consist of 1 to 100, 1 to 80, 1 to 60, 1 to 50, or 1 to 30 amino acids.

- First non-cleavable linker

As used herein, the term "first non-cleavable linker" refers to a peptide linker that does not comprise a cleavage site that is cleaved by a protease. The non-cleavable linker is known in the art or described herein. The first non-cleavable linker may consist of 1 to 50 consecutive amino acids, 3 to 30 consecutive amino acids, or 5 to 20 amino acids. The non-cleavable linker may be (G4S)n and may further comprise (G)n. The non-cleavable linker may be (G)n or (GS3)n. In this case, n may be each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In one embodiment of the present invention, the non-cleavable linker may comprise the amino acid

sequence of SEQ ID NO: 261 to SEQ ID NO: 266. Table 6 below shows exemplary sequences that may be included in the non-cleavable linker provided herein. The following amino acid sequences are described sequentially from the N-terminus to the C-terminus. The fusion proteins according to the present invention according to exemplary embodiments may include, but are not limited to, the sequences thereof.

Hereinafter, the first non-cleavable linker in the present invention is described interchangeably with "fifth component" or "E".

[Table 6]

Fifth component	Part Number	Variant	Amino acid sequnece
G4S linker	E1	$(G4S)_1$	GGGGS(SEQ ID NO: 261)
	E2	$(G4S)_2$	GGGGSGGGGS(SEQ ID NO: 262)
	E3	$(G4S)_3$	GGGGSGGGGSGGGGS(SEQ ID NO: 263)
	E4	PCPAPELLGGP$(G4S)_1$	PCPAPELLGGPGGGGS(SEQ ID NO: 264)
linker	E5	-	PCPAPELLGGP(SEQ ID NO: 265)
(G)n linker	E6	$(G)_7$	GGGGGGG (SEQ ID NO: 266)

Second linker

In the present specification, the second linker refers to a linker that connects the fusion protein of the present invention and the payload. The second linker may be a cleavable linker and a non-cleavable linker. The non-cleavable linker refers to a form in which, after the fusion protein-drug conjugate is internalized into a target cell, the drug is released in a form bound to the linker through catabolism in the cytoplasm or lysosome. On the other hand, the cleavable linker refers to a form in which, after the fusion protein-drug conjugate is internalized into a target cell, the drug is released by being cleaved by a specific environment or enzyme in a lysosome or endosome. Hereinafter, the cleavable linker may be referred to as a "second cleavable linker," and the non-cleavable linker may be referred to as a "second non-cleavable linker."

The second cleavable linker may be classified according to the principle by which cleavage occurs.

The second cleavable linker may be chemically cleavable or enzymatically cleavable.

In one embodiment, the chemically cleavable linker may be an acid-labile linker or a reducible linker.

As used herein, the term "acid-labile linker" refers to a linker that is stable at a neutral

pH, such as blood, but undergoes cleavage by acid hydrolysis in an acidic environment (pH 5 to pH 6), such as the cancer cell microenvironment, lysosomes, or endosomes. The acid-labile linker includes a hydrazone linker or an ester linker.

As used herein, the term "reducible linker" refers to a linker that undergoes cleavage by reduction by a reducing agent. In one embodiment, the reducible linker may be a disulfide linker.

As used herein, the term "enzyme cleavable linker" refers to a linker that is cleaved by a reducing agent within a cell. The enzyme cleavable linker may be a peptide-based linker or a specific enzyme-based linker.

As used herein, the term "peptide-based linker" refers to a linker that is cleaved by an enzyme that is relatively abundant within a cell and is a linker that comprises a specific peptide bond cleavage site. The peptide-based linker may be a linker that comprises one or more binding sites selected from the group consisting of valine-citrulline, valine-alanine, and phenylalanine-glycine. In one embodiment, it may be a valine-citrulline linker, a valine-alanine linker, an alanine-alanine-alanine linker, or a phenylalanine-glycine linker, but is not limited thereto.

As used herein, the term "specific enzyme-based linker" refers to a linker designed to be cleaved by a specific enzyme. The specific enzyme-based linker may be cleaved by one or more enzymes selected from the group consisting of β-galactoside, β-glucuronide, and phosphodiester. In one embodiment, the specific enzyme-based linker may be one or more selected from the group consisting of a β-galactoside linker, a β-glucuronide linker, a phosphodiester linker, and combinations thereof.

In one embodiment, the second non-cleavable linker may be a maleimidocaproyl (MC) linker or a succimidyl 4-(N-aleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker, but is not limited thereto.

In one embodiment, the cleavable linker may be any one selected from the group consisting of a hydrazone linker, an ester linker, a disulfide linker, a valine-citrulline linker, a valine-alanine linker, an alanine-alanine-alanine linker, a phenylalanine-glycine linker, a β-galactoside linker, a β-glucuronide linker, a phosphodiester linker, and combinations thereof.

In one embodiment, the linker may comprise a structural modification. In one embodiment, the linker may have polyethylene glycol (PGE) substituted in some of its structure or may comprise a self-immolative chemical structure (SIG).

Third linker

In the present invention, the third linker may be a peptide linker consisting of 5 to 80 consecutive amino acids, 7 to 70 consecutive amino acids, 10 to 60 consecutive amino acids, or 12 to 50 amino acids. The third linker may comprise at least one cysteine. Specifically, it may comprise one, two, or three cysteines. In addition, the third linker may be derived from the hinge of an immunoglobulin.

The third linker may comprise the hinge of an immunoglobulin or a variant thereof. In

this case, the hinge may be modified to delete disulfide bonds or to introduce additional disulfide bonds.

In one embodiment of the present invention, the third linker may comprise any one amino acid sequence selected from the group consisting of SEQ ID NO: 270 to SEQ ID NO: 275. Table 7 below lists exemplary IgG subtypes and fragments thereof having a core hinge sequence that may be included in the third linker provided herein. In this case, the amino acid sequences are described sequentially from the N-terminus to the C-terminus.

Hereinafter, the third linker is described interchangeably with "hinge" or "core hinge" in the present invention.

[Table 7]

Third linker	Part Number	IgG subtype	Amino acid sequence
Core hinge (hinge/hinge variant)	DHH1	IgG1	EPKSCDKTHTCPPCP(SEQ ID NO: 270)
	DHH2	IgG2	ERKCCVECPPCP(SEQ ID NO: 271)
	DHH3	IgG3	ELKTPLDTTHTCPRCP(EPKSCDTPPPCPRCP)$_3$(SEQ ID NO: 272)
	DHH4	IgG4	ESKYGPPCPSCP(SEQ ID NO: 273)
	DHH5	IgG1-RB	DKTHTCPPCP(SEQ ID NO: 274)
	DHH6	IgG4-Variant	ESKYGPPCPPCP(SEQ ID NO: 275)

Structure of fusion protein

Specifically, the fusion protein of the present invention may comprise the following structural formulas (I) and (II).

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-C' (I);

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I) and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L1, L2', L2", and L3 are each independently peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, and d are each independently 0 or 1.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, and the light chain constant region are the same as described above.

L1 and L3 may be each independently a first non-cleavable linker, and L2' and L2" may be a first non-cleavable linker or a first cleavable linker. The first linker, the first cleavable linker, and the first non-cleavable linker are the same as described above.

Specifically, the first structure of the structural formula (I) comprises a heavy chain variable region (VH1) or a light chain variable region (VL) of an antibody or a fragment thereof that specifically binds to the first target, and a heavy chain variable region (VH2) or a light chain variable region (VL2) that specifically binds to the second target; and the second structure of the structural formula (II) comprises a light chain variable region (VL1) or a heavy chain variable region (VH1) that specifically binds to the first target, and a light chain variable region (VL2) or a heavy chain variable region (VH2) that specifically binds to the second target, wherein the first structure and the second structure may be linked to each other to form a binding site that specifically binds to the first target and the second target.

In this case, the bond between the first structure and the second structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4, or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4 and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1".

Specifically, the bond between the first structure and the second structure may be formed by a disulfide bond existing between the cysteine at the 103rd position of CH1 and the cysteine at the 107th position of CL according to Kabat numbering. In addition, the first structure and the

second structure may further comprise cysteine (Cys) through amino acid substitution. Examples of such variants may include variations in the variable region of the second domain. Specifically, a disulfide bond may be formed by substituting cysteine at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering.

Specifically, the fusion protein may comprise the following structural formulas (IV) and (V).

N'-T2-(L7)-I2'-((L8)f-CR1)g-C' (IV);

N'-I2''-((L8)f-CR2)h-C' (V)

in the structural formulas (IV) and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2'' are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L7 and L8 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, and h are each independently 0 or 1, wherein g and h are identical.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, and the light chain constant region are the same as described above.

L7 may be a first linker, and L8 may be a first non-cleavable linker. The first linker, the first linker, and the first non-cleavable linker are the same as described above.

Specifically, the fourth structure of the structural formula (IV) comprises a heavy chain variable region (VH1) of a peptide or an antibody fragment that specifically binds to the first target and a heavy chain variable region (VH2) or a light chain variable region (VL2) of an antibody that specifically binds to the second target; and the fifth structure of the structural formula (V) comprises a light chain variable region (VL2) or a heavy chain variable region (VH2) of an antibody that specifically binds to the second target, and the fourth structure and the fifth structure may be linked to each other to form a binding site that specifically binds to the

first target and the second target.

In this case, the bond between the fourth structure and the fifth structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL), or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I2' and I2", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I2' and I2".

Specifically, the bond between the fourth structure and the fifth structure may be formed by a disulfide bond existing between the cysteine at the 103rd position of CH1 and the cysteine at the 107th position of CL according to Kabat numbering. In addition, the fourth structure and the fifth structure may further comprise cysteine (Cys) through amino acid substitution. Examples of such variants may include variations in the variable region of the second domain. Specifically, a disulfide bond may be formed by substituting cysteine at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering.

ReleaDome comprising a seventh component

In the present invention, the fusion protein may further comprise a payload. In this case, the fusion protein and the payload may be linked via a linker. Specifically, the payload may be linked to the fusion protein via a linker at the C-terminus of the light chain constant region of the second domain of the fusion protein. The payload may be an anticancer agent, and the linker may be a second linker.

In the present specification, the second linker and the payload are referred to as "the seventh component" and are described interchangeably with "UNIT3". In addition, the fusion protein comprising the seventh component is described interchangeably with "fusion protein-drug conjugate".

In addition, the fusion protein may further comprise a peptide motif in order to enhance binding with the seventh component. In this case, the fusion protein and the peptide motif may be linked via a first non-cleavable linker, and the peptide motif may be bound to the seventh component via an enzymatic reaction.

In one embodiment, a first non-cleavable linker and a peptide motif may be included at the C-terminus of the light chain constant region (CL) of the second domain of the fusion protein, and the peptide motif may be bound to the seventh component via an enzymatic reaction.

- Peptide motif

As used herein, the term "peptide motif" refers to an amino acid motif that can be recognized by an enzyme. In this case, the enzyme may be, but is not limited to, sortase, FGE

(formylglycine generating enzyme), transglutaminase (TG), or isoprenoid transferase.

The term "sortase" refers to an enzyme derived from Gram-positive bacteria that recognizes the amino acid sequence 'LPXTG' and catalyzes the replacement of terminal glycine (Gly) with a conjugation partner comprising an N-terminal glycine residue. Therefore, a fusion protein comprising the amino acid motif at the C-terminus can conjugate with a glycine-functionalized payload to form various fusion protein-drug conjugates. The amino acid motif may be LPXTG, LPXAG, LPXSG, LAXTG, LPXTG, LPXTA, or NPQTG (where X is any amino acid, preferably X is E or Q).

The "FGE" recognizes the amino acid sequence of the amino acid motif "LCXPXR" (where X is serine (Ser), threonine (Thr), alanine (Ala), or glycine (Gly)) and converts the cysteine (Cys) within the sequence into formyl-glycine having an aldehyde group by oxidizing it. Therefore, the fusion protein comprising the amino acid motif can form a Hydrazino-iso-Pictet-Spengler (HIPS) ligation to selectively form fusion protein-drug conjugates at various locations.

The "transglutaminase" generally catalyzes the formation of an amide bond between a glutamine (Gln) side chain and a primary amine in a finite number of small molecules. Among the enzymes mentioned above, the transglutaminase of Streptoverticillium mobaraense recognizes glutamine (Gln) within the "LLQG" amino acid sequence. Therefore, a fusion protein comprising the amino acid motif can selectively form fusion protein-drug conjugates at various locations.

The term "isoprenoid transferase" refers to an enzyme capable of recognizing a specific amino acid motif at or near the C-terminus of a protein and performing selective alkylation at the thiol position of the cysteine (Cys) residue(s) of the specific amino acid motif by adding isoprenoid unit(s) to a protein having the specific amino acid motif. Examples of the isoprenoid transferase may include farnesyl transferase (FTase) and geranylgeranyl transferase (GGTase). Each of the above enzymes involves the transfer of a farnesyl or geranyl-geranyl residue to the C-terminal cysteine(s) of the target protein. In this case, the protein to which the C-terminal cysteine of the target protein has been transferred as described above is referred to as a functionalized protein. GGTase can be classified into GGTase I and GGTase II. FTase and GGTase I can recognize the CAAX motif, and GGTase II can recognize the XXCC, XCXC, or CXX motif (where C is cysteine, A is an aliphatic amino acid, and X is an amino acid that determines the substrate specificity of isoprenoid transferase). In addition, isoprenoid transferase can recognize not only substrates but also isosubstrates. An isosubstrate refers to a substrate analog that has a modification of the substrate. A fusion protein comprising the amino acid motif at the C-terminus can be conjugated with a payload to form various fusion protein-drug conjugates.

In one embodiment, the peptide motif may comprise a CAAX motif, and more specifically, may comprise the amino acid sequence CVIM (SEQ ID NO: 267). In this case, the

first non-cleavable linker may be GGGGGGG (SEQ ID NO: 266).

- Payload

In the present specification, the term "payload" refers to a substance that is bound to the fusion protein and transported together with the fusion protein. The payload may be a substance such as a drug, toxin, phosphor, affinity ligand, diagnostic substance, and detection probe, but is not limited thereto.

In one embodiment, the payload may be a phosphor. The phosphor may include FITC, GFP, YFP, CFP, IRDye® 800CW, etc., but is not limited thereto.

In one embodiment, the payload may be a drug.

More specifically, the drug may be an anticancer agent.

As used herein, the term "anticancer agent" refers collectively to all drugs effective in treating cancer. In the present invention, the anticancer agent may include any anticancer agent that can be used as the drug (payload) of the fusion protein-drug conjugate according to the present invention.

More specifically, it may be Camptothecin including MMAF (Monomethyl auristatin F), Auristatin F, MMAE (Monomethyl auristatin E), SN-38, Synthetic analogue topotecan, Exatecan, Belotecan, etc., Cryptophycins, Duocarmycin (synthetic analogues including KW-2189 and CB1-TM1), Calicheamycin, Adrlimycin, Doxorubicin, Maytansinoids, Taxoids, Taxotrer, Doxetaxel, Chloranbucil, Gemcitabine, Platinum analog auristatin, Geldanamycin, Vindesine, Dolastatin, Dolastatin analog's auristatin, PBD (Pyrrolobenzodiazepine) derivatives, α-amanitin, β-amanitin, etc. In addition, it may include compounds that exhibit cell growth inhibition and toxicity by binding to tubulin, DNA, polymerase, topoisomerase, or kinase, immunomodulatory drugs (e.g., TLR (Toll-like receptor) 7, TLR 8 antagonists, STING antagonists, etc.), and target protein degraders (e.g., PROTAC (Proteolysis-targeting chimera)), but is not limited thereto.

In one embodiment, the anticancer agent may be MMAF or MMAE.

Table 8 below shows an example of a linker and a drug that may be included in the drug conjugate provided herein. The fusion protein-drug conjugates according to the present invention according to exemplary embodiments may include these seventh components. In addition, the fusion protein-drug conjugates of the present invention are shown in Tables 44 and 45 as embodiments of the present invention.

[Table 8]

Seventh component: linker-payload			
Part Number	Linker-payload; UNIT3	Variant	Description
G1	IRDye-800CW	LI-COR, IRDye® 800CW	IRDye-800CW

		Maleimide	
G2	LT-336	mal-FITC	mal-FITC
G3	LT-017	mal-VC-MMAF	mal-VC-MMAF
G4	LT-303	mal-TROSIG^{TM}-MMAF	mal-bGal-Thiophene2-MMAF
G5	LT-304	mal-TROSIG^{TM}-MMAF	mal-bGal-Thiophene2'-MMAF
G6	LT-317	mal-TROSIG^{TM}-$MMAF_2$	mal-bGal-Se2'-$MMAF_2$
G7	LT-327	mal-TROSIG^{TM}-$MMAE_2$	mal-bG-Se2'-$MMAE_2$
G8	LT-348	mal-TROSIG^{TM}-$MMAE_2$	mal-bG-Se1"-$MMAE_2$

Multispecific fusion protein

In the present invention, the fusion protein may further comprise a component selected from the group consisting of an Fc region or a variant thereof (fourth component), an antigen binding site (sixth component), a linker-payload (seventh component), and combinations thereof.

Specifically, the fusion protein according to the present invention may further comprise an Fc region or a variant thereof (fourth component) and/or an antigen binding site (seventh component), or an Fc region or a variant thereof (fourth component) and a linker-payload (seventh component) in the ReleaDome, which is the minimum unit of the fusion protein of the present invention. In the present invention, the ReleaDome with each of the above components added is referred to as "multispecific fusion protein." The ReleaDome and each of the above components may be linked via a linker. The linker used in this case is the third linker, which is the same as described above.

The multispecific fusion protein may bind to at least one or more targets or antigens.

Multispecific fusion protein comprising a fourth component

In one embodiment, the fusion protein may further comprise an Fc region or a variant thereof (fourth component). In this case, the fusion protein may be a ReleaDome. The ReleaDome is the same as described above.

In the present invention, the increase or decrease in the multi-antibody assembly rate, drug half-life (Pk), and effector functions of the multispecific fusion proteins according to the present invention can be controlled through the Fc region or a variant thereof, and multispecific fusion proteins of various modality structures can be produced.

Hereinafter, the Fc region or a variant thereof is described interchangeably with "fourth component" or "D".

- Fc region and variant thereof

As used herein, the term "Fc region" refers to an Fc region of an immunoglobulin. The Fc region refers to a protein that comprises a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3) of the immunoglobulin, but does not comprise a heavy chain

variable region, a light chain variable region, a heavy chain constant region 1 (CH1), and a light chain constant region (CL) of the immunoglobulin.

The Fc region of the immunoglobulin may be a wild type Fc domain as well as an Fc domain fragment. For example, the fragment of the Fc region may have lysine (K) deleted at the C-terminus. Alternatively, the fragment of the Fc region may comprise only CH3. The immunoglobulin may be IgG, IgA, IgE, IgD, or IgM. In addition, it may be IgG1, IgG2, IgG3, IgG4, which are subclasses of IgG, or IgA1 or IgA2, which are subclasses of IgA.

As used herein, the term "Fc region variant" may be a form that has a glycosylation pattern different from that of the wild type Fc region, an increased glycosylation pattern compared to the wild type Fc region, or a decreased glycosylation pattern compared to the wild type Fc region, or a form in which the glycosylation pattern is removed (deglycosylated). In addition, it may also include an aglycosylated Fc region. The Fc region or variant may have a number of sialic acid, fucosylation, or glycosylation adjusted through culture conditions or genetic manipulation of the host.

In addition, the glycosylation of the Fc region of the immunoglobulin can be modified by conventional methods, such as chemical methods, enzymatic methods, and genetic engineering methods using microorganisms. In addition, the Fc domain variant may be a form in which the Fc region of the immunoglobulin IgG, IgA, IgE, IgD, or IgM is mixed. In addition, the Fc region variant may be a form in which some amino acids of the Fc region are substituted.

The "amino acid" introduced by the substitution and/or addition may be any one selected from the group consisting of lysine (K), alanine (A), arginine (R), asparagine (N), aspartic acid (D), cysteine (C), glutamine (Q), glutamic acid (E), glycine (G), histidine (H), isoleucine (I), leucine (L), methionine (M), phenylalanine (F), proline (P), serine (S), threonine (T), tryptophan (W), tyrosine (Y), and valine (V).

In addition, the Fc region variant may have a new linker introduced or be substituted with a new domain.

In addition, the Fc region variant may comprise a knob structure or a hole structure.

"Knob-into-hole" is a design strategy for producing antibodies that specifically bind to different regions, such as bispecific antibodies, multispecific antibodies, or heterodimers. In general, this technique involves introducing a knob at the interface of a first polypeptide (e.g., the first CH3 region of the first antibody heavy chain) and a corresponding hole at the interface of a second polypeptide (e.g., the second CH3 region of the second antibody heavy chain), thereby positioning the knob within the hole to promote heterodimer formation and inhibit homodimer formation.

A "knob" is constructed by replacing small amino acid side chains from the interface of the first polypeptide (e.g., the first CH3 region of the first antibody heavy chain) with larger side chains (e.g., arginine, phenylalanine, tyrosine, or tryptophan). A complementary "hole" of the

same or similar size as the knob is created by replacing large amino acid side chains from the interface of the second polypeptide (e.g., the second CH3 region of the second antibody heavy chain) with smaller side chains (e.g., alanine, serine, valine, or threonine). The knob and hole may be created, for example, by inducing site-specific mutations in the nucleic acid encoding the polypeptide or by making changes during the peptide synthesis step.

Examples of the knob-into-hole technology in the Fc region may include the variations described in WO2014084607A1 and WO2018059502A1, etc. The disclosures of WO2014084607A1 and WO2018059502A1 are incorporated by reference into the present specification. WO2014084607A1 describes, for example, a variation of the CH3 domain that comprises, in a CH3 domain, (a-1) a combination of tryptophan (W) substituted at Lys409 of one CH3 domain, valine (V) substituted at Asp399 of another CH3 domain, and threonine (T) substituted at Phe405; and (a-2) a combination of serine (S) substituted at Tyr349 of one CH3 domain and tryptophan (W) substituted at Glu357 of another CH3 domain; and may further comprise (b-1) a combination of glutamic acid (E) substituted at Lys360 of one CH3 domain and arginine (R) substituted at Gln347 of another CH3 domain; and (b-2) a combination of glutamic acid (E) substituted at Gln347 and glutamic acid substituted at Lys360 of one CH3 domain and arginine (R) substituted at Gln347 of another CH3 domain. Here, the positions of the amino acid residues are numbered according to the EU index. WO2018059502A1 describes, for example, variations of the Fc domain comprising one or more variations selected from each of a) to e) below: a) L351G, L351Y, L351V, L351P, L351D, L351E, L351K, or L351W; b) T366L, T366P, T366W, or T366V; c) D399C, D399N, D399I, D399G, D399R, D399T, or D399A; d) Y407L, Y407A, Y407P, Y407F, Y407T, or Y407H; and e) K409C, K409P, K409S, K409F, K409V, K409Q, or K409R. Here, the positions of the amino acid residues are numbered according to the EU index.

Table 9 below shows the amino acid sequences of the Fc regions or variants thereof of the various fusion proteins described herein. The fusion proteins according to exemplary embodiments may comprise an Fc region or a variant thereof comprising or consisting of the same. The following amino acid sequences are described sequentially from the N-terminus to the C-terminus.

[Table 9]

Fourth component			
Part Number	Type	Variant	Heavy chain
DDH1	IgG1 (CH2/CH3)	WT	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:249)

DDH2	IgG1 (CH2/CH3)	Variant-LALA	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:250)
DDH3	IgG1 (CH2/CH3)	Variant-LALAPG	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:251)
DDH4	IgG1 (CH2/CH3)	Variant-LALAPG-knob	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:252)
DDH5	IgG1 (CH2/CH3)	Variant-LALAPG-hole	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:253)
DDH6	IgG1(CH3)	WT	GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:254)
DDH7	IgG1 (CH3)	variant	APEAAGGPGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:255)
DDH8	IgG1 (CH3)	Variant-knob	APEAAGGPGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:256)
DDH9	IgG1 (CH3)	Variant-hole	APEAAGGPGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:257)
DDH10	IgG2 (CH2/CH3)	WT	APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:258)
DDH11	IgG4 (CH2/CH3)	WT	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK(SEQ ID NO:259)
DDH12	IgG4(CH3)	IgG1-Variant	APELLGGPGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:260)

The fusion protein and the Fc region or variant thereof may be linked via a linker. In this case, the fusion protein may be a ReleaDome. The ReleaDome is the same as described above.

Specifically, the Fc region or variant thereof may be linked via a linker to the C-terminus of the first structure.

More specifically, it may comprise the following structural formulas (I') and (II).

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-Fc region or variant thereof-C' (I'); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I') and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L1, L2', L2", L3, and L5 are peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, and d are each independently 0 or 1.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, the light chain constant region, and the Fc region and variant thereof are the same as described above.

L1 and L3 may be first non-cleavable linkers, and L2' and L2" may be first linkers. The first non-cleavable linker, the first linker, the second linker, and the third linker are the same as

described above.

The bond between the sixth structure of the structural formula (I') and the second structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4, or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4 and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1".

Specifically, the Fc region or variant thereof may be linked via a linker to the C-terminus of the fourth structure.

More specifically, it may comprise the following structural formulas (IV') and (V).

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-Fc region or variant thereof-C' (IV');

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV') and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L7, L8, and L9 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, and h are each independently 0 or 1, wherein g and h are identical.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, the light chain constant region, and the Fc region and variant thereof are the same as described above.

L7 may be a first linker, L8 may be a first non-cleavable linker, and L9 may be a third linker. The first non-cleavable linker, the first linker, and the third linker are the same as described above.

The bond between the seventh structure and the fifth structure of the structural formula (IV') may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL), or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I2' and I2", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I2' and I2".

In the present invention, the multispecific fusion protein comprising the sixth structure or the seventh structure may further comprise a payload. The payload may be linked to a specified or unspecified location of the Fc region, which is the fourth component in one embodiment of the multispecific fusion protein of the present invention, or a variant thereof, to form a modality structure of the fusion protein-drug conjugate. In this case, the Fc region or a variant thereof and the payload may be linked via a linker. The linker may be a second linker.

The multispecific fusion protein and the payload may be conjugated using known techniques. Examples include, but are not limited to, the lysine (K) and AcBut-calicheamicin linkage technology used in Mylotarg® and Besponsa®, the lysine (K) and SMCC-DM1 linkage technology used in Kadcyla®, and the Thiol-maleimide technique used in Adcetris®, Polivy®, Padcev®, Enhertu®, Trodelvy®, and Blenrep®. In addition, the following technologies may be used, but are not limited to: THIOMAB™ technology using modified cysteine, C-Lock™ using a dibromomethylquinoxaline functional group, SMARTag™ using a Pictet-Spengler reaction, GlycoConnect™ using azidosugar, ConjuAll™ using prenyltransferase, SMAC-Technology™ using Sortase, and glutamine binding technology using transglutaminase.

In addition, the multispecific fusion protein comprising the sixth structure or the seventh structure may further comprise a peptide motif. In this case, the peptide motif may be linked via a linker to the C-terminus of the Fc region or variant thereof of the sixth structure or the seventh structure. If the multispecific fusion protein comprising the sixth structure or the seventh structure comprises a peptide motif, the seventh component may be bound to the peptide motif via an enzymatic reaction. In one embodiment, the peptide motif may comprise a CAAX motif, and more specifically, may comprise the amino acid sequence CVIM (SEQ ID NO: 267). In this case, the first non-cleavable linker may be GGGGGGG (SEQ ID NO: 266). The payload, the linker, the peptide motif, and the seventh component are the same as described above.

Multispecific fusion protein comprising a fourth component and a sixth component

In the present invention, the fusion protein may further comprise an Fc region or a variant thereof (fourth component), and an antigen binding site (sixth component).

Specifically, the antigen binding site may be linked to the C-terminus of the sixth structure via a linker.

More specifically, it may comprise the following structural formulas (I") and (II).

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-Fc region or variant thereof-(L6)e-O-C' (I"); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I") and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

O is an antigen binding site,

L1, L2', L2", L3, L5, and L6 are each independently peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, d, and e are each independently 0 or 1.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, the light chain constant region, and the Fc region and variant thereof are the same as described above.

L1, L3, and L6 may be first linkers, specifically first non-cleavable linkers, and L2' and L2" may be first linkers. L5 may be a third linker. The first non-cleavable linker, the first linker, the second linker, and the third linker are the same as described above.

In this case, the bond between the eighth structure of the structural formula (I") and the second structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4, or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2)

and the light chain variable region (VL2) within I1' and I1", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4 and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1".

Specifically, the fusion protein may have an antigen binding site linked to the C-terminus of the seventh structure via a linker.

More specifically, it may comprise the following structural formulas (IV") and (V).

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-Fc region or variant thereof-(L10)i-P-C' (IV");

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV") and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

P is an antigen binding site,

L7, L8, L9, and L10 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and i are each independently 0 or 1.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, the light chain constant region, and the Fc region and variant thereof are the same as described above.

L7 may be a first linker, L8 and L10 may be first non-cleavable linkers, and L9 may be a third linker. The first non-cleavable linker, the first linker, and the third linker are the same as described above.

In this case, the bond between the ninth structure and the fifth structure of the structural formula (IV") may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL), or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain

variable region (VL2) within I2' and I2", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH) and the light chain variable region (VL) within I2' and I2".

- Antigen binding site

The antigen binding site may be an antigen binding site that specifically binds to a protein that is overexpressed or specifically expressed or activated in target cells at a disease site. The protein that is overexpressed or specifically expressed or activated in target cells at a disease site is the same as described above. The antigen may be the same as or different from the first target and/or the second target.

As an example of the antigen binding site, it may be an antibody or a fragment thereof (e.g., Fv, scFv, VHH, Fab), a peptide, an aptamer, etc., and may be in a form comprising part or all of a naturally occurring counterpart/ligand of a target that can be an antigen of the second domain, but is not limited thereto. More specifically, it may be an antibody or a fragment thereof. The antibody and fragment thereof are the same as described above. More preferably, it may be a scFv.

In addition, the antigen may be CLDN18.2 or PD-L1 as an example, but is not limited thereto.

In one embodiment, the antigen binding site may comprise a heavy chain variable region and a light chain variable region of Zolbetuximab, which is an antibody that binds to CLDN18.2. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 872, HCDR2 comprising the amino acid sequence of SEQ ID NO: 874, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 876; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 968, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 971. In this case, the heavy chain variable region may comprise the amino acid sequence of SEQ ID NO: 222, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 223. The antigen binding site may comprise the amino acid sequence of SEQ ID NO: 268.

In one embodiment, the antigen binding site may comprise a heavy chain variable region and a light chain variable region of Atezolizumab, which is an antibody that binds to PD-L1. Specifically, it may comprise a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 895, HCDR2 comprising the amino acid sequence of SEQ ID NO: 898, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 900; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 982, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 984. In this case, the heavy chain variable region may

comprise the amino acid sequence of SEQ ID NO: 230, and the light chain variable region may comprise the amino acid sequence of SEQ ID NO: 231. The antigen binding site may comprise the amino acid sequence of SEQ ID NO: 238.

Table 10 below shows the polypeptide sequences of antibody fragments described as antigen binding sites (sixth component) of various multispecific fusion proteins described herein. The fusion proteins according to exemplary embodiments may comprise these polypeptides. The polypeptide sequences are described sequentially from the N-terminus to the C-terminus.

In the present specification, the antigen binding site of the sixth component is referred to as "UNIT2'", and hereinafter the antigen binding site is described interchangeably with "sixth component" or "F".

[Table 10]

Sixth component: Antigen binding site(scFv)			
Part Number	Target of part F	Clone Name; UNIT2'	Amino acid sequence
F1	Claudin18.2	Zolbetuximab	QVQLQQPGAELVRPGASVKLSCKASGYTFTSYW INWVKQRPGQGLEWIGNIYPSDSYTNYNQKFKD KATLTVDKSSSTAYMQLSSPTSEDSAVYYCTRS WRGNSFDYWGQGTTLTVSSGGGGSGGGGSGGG GSDIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNS GNQKNYLTWYQQKPGQPPKLLIYWASTRESGV PDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDY SYPFTFGSGTKLEIK(SEQ ID NO:268)
F2	PD-L1	Atezolizumab	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWI HWVRQAPGKGLEWVAWISPYGGSTYYADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR RHWPGGFDYWGQGTLVTVSSGGGGSGGGGSG GGGSDIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQYLYHPAT FGQGTKVEIK(SEQ ID NO:238)

Multispecific fusion protein comprising a sixth component

In the present invention, the fusion protein may further comprise an antigen binding site (sixth component). In this case, the fusion protein may be a ReleaDome. The fusion protein and the antigen binding site may be linked via a linker, and the linker may be a third linker. In addition, the antigen binding site may be a variable region of an antibody, specifically a heavy chain variable region or a light chain variable region of an antibody. The third linker, the antibody, the variable region, the heavy chain variable region, and the light chain variable region are the same as described above.

Specifically, the antigen binding site may be linked to the variable region of an antibody via a third linker at the C-terminus of the first structure.

More specifically, it may comprise the following structural formulas (I'") and (II).

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-(L18)s-Q'-C' (I'"); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I'") and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

Q' is a heavy chain variable region (VH) of an antibody that specifically binds to a third target,

L1, L2', L2", L3, L5, and L18 are each independently peptide linkers, wherein L2 is a cleavable or non-cleavable linker, and

a, b, c, d, and s are each independently 0 or 1, wherein b and d are identical.

Alternatively, it may comprise the following structural formulas (I"") and (II).

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-(L18)s-Q"-C' (I""); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I"") and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

Q" is a light chain variable region (VL) of an antibody that specifically binds to a third target,

L1, L2', L2", L3, L5, and L18 are each independently peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, d, and s are each independently 0 or 1, wherein b and d are identical.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, and the light chain constant region are the same as described above.

Q' and Q", which are the heavy chain variable region and the light chain variable region of the antibody that specifically binds to the third target, may linked to each other to form an antigen binding site that binds to the same antigen (Q, third target). The antigen may be a protein that is overexpressed or specifically expressed or activated in target cells at a disease site. The protein that is overexpressed or specifically expressed or activated in target cells at a disease site is the same as described above. In addition, the third target may be the same as or different from the first target and/or the second target.

L1, L3, and L18 may be each independently a first non-cleavable linker, and L2' and L2" may be a first non-cleavable linker or a first cleavable linker. In addition, L5 may be a third linker.

The protein that is overexpressed or specifically expressed or activated in target cells at a disease site, the first linker, the first cleavable linker, and the first non-cleavable linker, and the third linker are the same as described above.

The bond between the eleventh structure of the structural formula (I"') or the twelfth structure of the structural formula (I"") and the second structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4, or ii) through a disulfide bond by cysteine (Cys)

present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I' and I", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) of CR3 and CR4 and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2) within I1' and I1".

The antigen binding site may be linked to the variable region of an antibody via a third linker at the C-terminus of the fourth structure.

Specifically, it may comprise the following structural formulas (IV"') and (V).

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-(L19)t-S'-C' (IV"');

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV"') and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

S' is a heavy chain variable region (VH) of an antibody that specifically binds to a fourth target,

L7, L8, L9, and L19 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and t are each independently 0 or 1, wherein g and h are identical.

Alternatively, it may comprise the following structural formulas (IV"") and (V).

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L10)-(L19)t-S"-C' (IV"");

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV"") and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that

specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

S" is a light chain variable region (VL) of an antibody that specifically binds to a fourth target,

L7, L8, L10, and L19 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and t are each independently 0 or 1, wherein g and h are identical.

The first target, the second target, the heavy chain variable region, the light chain variable region, the heavy chain constant region, and the light chain constant region are the same as described above.

S' and S", which are the heavy chain variable region and the light chain variable region of the antibody, may linked to each other to form an antigen binding site that binds to the same antigen (S, fourth target). The antigen may be a protein that is overexpressed or specifically expressed or activated in target cells at a disease site. The protein that is overexpressed or specifically expressed or activated in target cells at a disease site is the same as described above. In addition, the fourth target may be the same as or different from the first target and/or the second target.

L7 may be a first linker, L8 may be a first non-cleavable linker, and L10 may be a third linker.

The protein that is overexpressed or specifically expressed or activated in target cells at a disease site, the first linker, the first cleavable linker, the first non-cleavable linker, and the third linker are the same as described above.

The bond between the thirteenth structure of the structural formula (IV'") or the fourteenth structure of the structural formula (IV"") and the fifth structure may be formed i) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL), or ii) through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH) and the light chain variable region (VL) within I2' and I2", or iii) through a disulfide bond by cysteine (Cys) present in the heavy chain constant region (CH1) and the light chain constant region (CL) and through a disulfide bond by cysteine (Cys) present in the heavy chain variable region (VH2) and the light chain variable region (VL2)

within I2' and I2".

<Fusion protein dimer>

In another aspect of the present invention, there is provided a fusion protein dimer in which two of the fusion proteins are linked to each other.

In this case, the fusion protein may be a multispecific fusion protein. The multispecific fusion protein is the same as described above.

Multispecific fusion protein homodimer

In the present invention, the fusion protein dimer may be a homodimer.

In one embodiment, the fusion protein dimer may be a form in which two identical multispecific fusion proteins comprising a sixth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two identical multispecific fusion proteins comprising a seventh structure and a fifth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two identical multispecific fusion proteins comprising an eighth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two identical multispecific fusion proteins comprising a ninth structure and a fifth structure are linked to each other. The second structure, the fifth structure to the ninth structure are the same as described above.

Multispecific fusion protein heterodimer

The fusion protein dimer may be a heterodimer.

In one embodiment, the fusion protein dimer may be a form in which two different multispecific fusion proteins comprising a sixth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two different multispecific fusion proteins comprising a seventh structure and a fifth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two different multispecific fusion proteins comprising an eighth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which two different multispecific fusion proteins comprising a ninth structure and a fifth structure are linked to each other.

In addition, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a sixth structure and a second structure, or a multispecific fusion protein comprising an eighth structure and a second structure; and a multispecific fusion protein comprising a seventh structure and a fifth structure, or a multispecific fusion protein comprising a ninth structure and a fifth structure are linked to each other. In this case, the first targets of the structures may be the same or different, and the second targets may be the same or different. The second structure, the fifth structure to the ninth structure are the same as described above.

In one embodiment, the fusion protein dimer may be a form in which a multispecific

fusion protein comprising a sixth structure and a second structure; and a multispecific fusion protein comprising a seventh structure and a fifth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a sixth structure and a second structure; and a multispecific fusion protein comprising a ninth structure and a fifth structure are linked to each other. The fusion protein dimer may be a form in which a multispecific fusion protein comprising an eighth structure and a second structure; and a multispecific fusion protein comprising a seventh structure and a fifth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eighth structure and a second structure; and a multispecific fusion protein comprising a ninth structure and a fifth structure are linked to each other.

Specifically, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eleventh structure and a second structure, or a multispecific fusion protein comprising a thirteenth structure and a fifth structure; and a multispecific fusion protein comprising a twelfth structure and a second structure, or a multispecific fusion protein comprising a fourteenth structure and a fifth structure are linked to each other. In this case, the first targets of the structures may be the same or different, and the second targets may be the same or different. The heavy chain variable region and the light chain variable region of the antibody, which is the antigen binding site, may be linked to each other to form a binding site that binds to the same antigen. The second structure, the fifth structure, and the eleventh structure to the fourteenth structure are the same as described above.

In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eleventh structure and a second structure; and a multispecific fusion protein comprising a twelfth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eleventh structure and a second structure; and a multispecific fusion protein comprising a fourteenth polystructure and a fifth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a thirteenth structure and a fifth structure; and a multispecific fusion protein comprising a twelfth structure and a second structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a thirteenth structure and a fifth structure; and a multispecific fusion protein comprising a fourteenth structure and a fifth structure are linked to each other.

Specifically, the fusion protein dimer may be a form in which the multispecific fusion protein and a fusion protein comprising the following structural formulas (VI) and (VII) are linked to each other.

N'-I3'-(L11)k-CR1-(L12)-Fc region or variant thereof-((L13)l-V)m-C' (VI); and

N'-I3"-(L11)k-CR2-C' (VII)

in the structural formulas (VI) and (VII),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

I3' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I3" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I3' and I3" are linked to each other to form a binding site (I3) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

V is an antigen binding site,

L11, L12, and L13 are each independently peptide linkers, and

k, l, and m are each independently 0 or 1.

L11 and L13 may be first non-cleavable linkers, and L12 may be a third linker. In addition, in the structural formulas (VI) and (VII), the second target and the antigen binding site may be same as or different from the second target and the antigen binding site of the multispecific fusion protein. The second target, the antigen binding site, the antibody fragment, the first non-cleavable linker, and the third linker are the same as described above.

Hereinafter, in the present specification, the structure of structural formula (VI) is described as the fifteenth structure, and the structure of structural formula (VII) is described as the sixteenth structure. In this case, the fusion protein comprising the fifteenth structure may further comprise a payload. The payload may be linked via a linker, and the linker may be a second linker. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may further comprise a peptide motif. In this case, the peptide motif may be linked via a linker to the C-terminus of the Fc region or variant thereof of the fifteenth structure; or to the C-terminus of the light chain constant region (CL) of the sixteenth structure. If the fusion protein comprising the fifteenth structure or the sixteenth structure comprises a peptide motif, the seventh component may be bound to the peptide motif via an enzymatic reaction. In one embodiment, the peptide motif may comprise a CAAX motif, and more specifically, may comprise the amino acid sequence CVIM (SEQ ID NO: 267). In this case, the first non-cleavable linker may be GGGGGGG (SEQ ID NO: 266). The payload, the second linker, the linker, the peptide motif, and the seventh component are the same as described above.

More specifically, the fusion protein dimer may be a form in which any one of the

multispecific fusion proteins selected from the group consisting of a multispecific fusion protein comprising a sixth structure and a second structure, a multispecific fusion protein comprising an eighth structure and a second structure, a multispecific fusion protein comprising a seventh structure and a fifth structure, and a multispecific fusion protein comprising a ninth structure and a fifth structure; and a fusion protein comprising a fifteenth structure and a sixteenth structure are linked to each other.

In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a sixth structure and a second structure; and a fusion protein comprising a fifteenth structure and a sixteenth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eighth structure and a second structure; and a fusion protein comprising a fifteenth structure and a sixteenth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a seventh structure and a fifth structure; and a fusion protein comprising a fifteenth structure and a sixteenth structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a ninth structure and a fifth structure; and a fusion protein comprising a fifteenth structure and a sixteenth structure are linked to each other.

Specifically, the fusion protein dimer may be a form in which the multispecific fusion protein and the fusion protein comprising the following structural formula (VIII) are linked to each other.

N'-I3'''-(L14)-Fc region or variant thereof-((L15)n-W)o-C' (VIII)

in the structural formula (VIII),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

I3''' is an antibody fragment that specifically binds to the second target,

W is an antigen binding site,

L14 and L15 are each independently peptide linkers, and

n and o are each independently 0 or 1.

L14 may be a third linker, and L15 may be a first non-cleavable linker.

In addition, in the structural formula (VIII), the second target and the antigen binding site may be same as or different from the second target and the antigen binding site of the multispecific fusion protein. The second target, the antigen binding site, the antibody fragment, the first cleavable linker, and the third linker are the same as described above.

Hereinafter, in the present specification, the structure of structural formula (VIII) is described as the third structure. In this case, the fusion protein comprising the third structure may further comprise a payload. The payload may be linked via a linker, and the linker may be a third linker. In addition, the fusion protein comprising the third structure may further comprise a

peptide motif. In this case, the peptide motif may be linked via a linker to the C-terminus of the Fc region or variant thereof of the third structure. If the fusion protein comprising the third structure comprises a peptide motif, the seventh component may be bound to the peptide motif via an enzymatic reaction. In one embodiment, the peptide motif may comprise a CAAX motif, and more specifically, may comprise the amino acid sequence CVIM (SEQ ID NO: 267). In this case, the first non-cleavable linker may be GGGGGGG (SEQ ID NO: 266). The payload, the third linker, the linker, the peptide motif, and the seventh component are the same as described above.

More specifically, the fusion protein dimer may be a form in which any one of the multispecific fusion proteins selected from the group consisting of a multispecific fusion protein comprising a sixth structure and a second structure, a multispecific fusion protein comprising an eighth structure and a second structure, a multispecific fusion protein comprising a seventh structure and a fifth structure, and a multispecific fusion protein comprising a ninth structure and a fifth structure; and a fusion protein comprising a third structure are linked to each other.

In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a sixth structure and a second structure; and a fusion protein comprising a third structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising an eighth structure and a second structure; and a fusion protein comprising a third structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a seventh structure and a fifth structure; and a fusion protein comprising a third structure are linked to each other. In one embodiment, the fusion protein dimer may be a form in which a multispecific fusion protein comprising a ninth structure and a fifth structure; and a fusion protein comprising a third structure are linked to each other.

Specific example of a fusion protein dimer

- DVD-Ig type multispecific fusion protein dimer comprising a ReleaDome

As shown in Figure 3a, the DVD-Ig type multispecific fusion protein dimer comprising a ReleaDome may be a homodimer in which two multispecific fusion proteins, in which the sixth structure of structural formula (I') and the second structure of structural formula (II) are linked to each other, are linked to each other.

Specifically, the multispecific fusion protein of the sixth structure may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, CL may further

comprise a first non-cleavable protein and a peptide motif.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to HER2 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to HER2, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other.

In one embodiment, it may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 991 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 992. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 993 and a light chain comprising the amino acid sequence of SEQ ID NO: 994. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 995 and a light chain comprising the amino acid sequence of SEQ ID NO: 996. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 997 and a light chain comprising the amino acid sequence of SEQ ID NO: 998. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 999 and a light chain comprising the amino acid sequence of SEQ ID NO: 1000. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1001 and a light chain comprising the amino acid sequence of SEQ ID NO: 1002. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1003 and a light chain comprising the amino acid sequence of SEQ ID NO: 1004. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1005 and a light chain comprising the amino acid sequence of SEQ ID NO: 1006. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1007 and a light chain comprising the amino acid sequence of SEQ ID

NO: 1008. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1009 and a light chain comprising the amino acid sequence of SEQ ID NO: 1010. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1011 and a light chain comprising the amino acid sequence of SEQ ID NO: 1012. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1013 and a light chain comprising the amino acid sequence of SEQ ID NO: 1014. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1015 and a light chain comprising the amino acid sequence of SEQ ID NO: 1016. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1017 and a light chain comprising the amino acid sequence of SEQ ID NO: 1018. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1019 and a light chain comprising the amino acid sequence of SEQ ID NO: 1020. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1021 and a light chain comprising the amino acid sequence of SEQ ID NO: 1022. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1023 and a light chain comprising the amino acid sequence of SEQ ID NO: 1024. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1025 and a light chain comprising the amino acid sequence of SEQ ID NO: 1026. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1027 and a light chain comprising the amino acid sequence of SEQ ID NO: 1028. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1029 and a light chain comprising the amino acid sequence of SEQ ID NO: 1030. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1031 and a light chain comprising the amino acid sequence of SEQ ID NO: 1032. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1033 and a light chain comprising the amino acid sequence of SEQ ID NO: 1034. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1035 and a light chain comprising the amino acid sequence of SEQ ID NO: 1036. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1037 and a light chain comprising the amino acid sequence of SEQ ID NO: 1038. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1039 and a light chain comprising the amino acid sequence of SEQ ID NO: 1040. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1041 and a light chain comprising the amino acid sequence of SEQ ID NO: 1042. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1043 and a light chain comprising the amino acid sequence of SEQ ID NO: 1044. In one embodiment, it may comprise a heavy chain comprising the amino acid

sequence of SEQ ID NO: 1045 and a light chain comprising the amino acid sequence of SEQ ID NO: 1046. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1047 and a light chain comprising the amino acid sequence of SEQ ID NO: 1048. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1049 and a light chain comprising the amino acid sequence of SEQ ID NO: 1050. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1051 and a light chain comprising the amino acid sequence of SEQ ID NO: 1052. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1053 and a light chain comprising the amino acid sequence of SEQ ID NO: 1054. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1055 and a light chain comprising the amino acid sequence of SEQ ID NO: 1056. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1057 and a light chain comprising the amino acid sequence of SEQ ID NO: 1058. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1059 and a light chain comprising the amino acid sequence of SEQ ID NO: 1060. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1061 and a light chain comprising the amino acid sequence of SEQ ID NO: 1062. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1063 and a light chain comprising the amino acid sequence of SEQ ID NO: 1064. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1065 and a light chain comprising the amino acid sequence of SEQ ID NO: 1066. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1067 and a light chain comprising the amino acid sequence of SEQ ID NO: 1068. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1069 and a light chain comprising the amino acid sequence of SEQ ID NO: 1070. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1071 and a light chain comprising the amino acid sequence of SEQ ID NO: 1072. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1073 and a light chain comprising the amino acid sequence of SEQ ID NO: 1074. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1075 and a light chain comprising the amino acid sequence of SEQ ID NO: 1076. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1077 and a light chain comprising the amino acid sequence of SEQ ID NO: 1078. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1079 and a light chain comprising the amino acid sequence of SEQ ID NO: 1080. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1081 and a light chain comprising the amino acid sequence of SEQ ID

NO: 1082. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1083 and a light chain comprising the amino acid sequence of SEQ ID NO: 1084. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1085 and a light chain comprising the amino acid sequence of SEQ ID NO: 1086. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1087 and a light chain comprising the amino acid sequence of SEQ ID NO: 1088. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1089 and a light chain comprising the amino acid sequence of SEQ ID NO: 1090. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1091 and a light chain comprising the amino acid sequence of SEQ ID NO: 1092. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1093 and a light chain comprising the amino acid sequence of SEQ ID NO: 1094. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1095 and a light chain comprising the amino acid sequence of SEQ ID NO: 1096. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1097 and a light chain comprising the amino acid sequence of 1098. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1099 and a light chain comprising the amino acid sequence of SEQ ID NO: 1100. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1101 and a light chain comprising the amino acid sequence of SEQ ID NO: 1102. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1103 and a light chain comprising the amino acid sequence of SEQ ID NO: 1104. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1105 and a light chain comprising the amino acid sequence of SEQ ID NO: 1106. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1107 and a light chain comprising the amino acid sequence of SEQ ID NO: 1108.

- <u>DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CD47 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region

(VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD47, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD47, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other.

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1109 and a light chain comprising the amino acid sequence of SEQ ID NO: 1110. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1111 and a light chain comprising the amino acid sequence of SEQ ID NO: 1112. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1113 and a light chain comprising the amino acid sequence of SEQ ID NO: 1114. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1115 and a light chain comprising the amino acid sequence of SEQ ID NO: 1116. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1117 and a light chain comprising the amino acid sequence of SEQ ID NO: 1118. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1119 and a light chain comprising the amino acid sequence of SEQ ID NO: 1120. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1121 and a light chain comprising the amino acid sequence of SEQ ID NO: 1122. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1123 and a light chain comprising the amino acid sequence of SEQ ID NO: 1124. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1125 and a light chain comprising the amino acid sequence of SEQ ID NO: 1126. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1127 and a light chain comprising the amino acid sequence of SEQ ID NO: 1128. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1129 and a light chain comprising the amino acid sequence of SEQ ID NO: 1130. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1131 and a light chain comprising the amino acid sequence of SEQ ID NO: 1132. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1133 and a light chain comprising the amino acid sequence of SEQ ID NO: 1134. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1135 and a light chain comprising the amino acid sequence of SEQ ID NO: 1136.

- <u>DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprisinga light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. In addition, the multispecific fusion protein may sequentially comprise a first non-cleavable linker and a peptide motif at the C-terminus of the light chain constant region (CL).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1137 and a light chain comprising the amino acid sequence of SEQ ID NO: 1138. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1139 and a light chain comprising the amino acid sequence of SEQ ID NO: 1140. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1141 and a light chain comprising the amino acid sequence of SEQ ID NO: 1142. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1143 and a light chain comprising the amino acid sequence of SEQ ID NO: 1144. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1145 and a light chain comprising the amino acid sequence of SEQ ID NO: 1146. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1147 and a light chain comprising the amino acid sequence of SEQ ID NO: 1148. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1149 and a light chain comprising the amino acid sequence of SEQ ID NO: 1150. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1151 and a light chain comprising the amino acid sequence of SEQ ID NO: 1152. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1153 and a light chain comprising the amino acid sequence of SEQ ID NO: 1154. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO:

1155 and a light chain comprising the amino acid sequence of SEQ ID NO: 1156. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1157 and a light chain comprising the amino acid sequence of SEQ ID NO: 1158. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1159 and a light chain comprising the amino acid sequence of SEQ ID NO: 1160. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1161 and a light chain comprising the amino acid sequence of SEQ ID NO: 1162. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1163 and a light chain comprising the amino acid sequence of SEQ ID NO: 1164. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1165 and a light chain comprising the amino acid sequence of SEQ ID NO: 1166. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1167 and a light chain comprising the amino acid sequence of SEQ ID NO: 1168. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1169 and a light chain comprising the amino acid sequence of SEQ ID NO: 1170. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1171 and a light chain comprising the amino acid sequence of SEQ ID NO: 1172. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1173 and a light chain comprising the amino acid sequence of SEQ ID NO: 1174. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1175 and a light chain comprising the amino acid sequence of SEQ ID NO: 1176. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1177 and a light chain comprising the amino acid sequence of SEQ ID NO: 1178. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1179 and a light chain comprising the amino acid sequence of SEQ ID NO: 1180. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1181 and a light chain comprising the amino acid sequence of SEQ ID NO: 1182. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1183 and a light chain comprising the amino acid sequence of SEQ ID NO: 1184. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1185 and a light chain comprising the amino acid sequence of SEQ ID NO: 1186. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1187 and a light chain comprising the amino acid sequence of SEQ ID NO: 1188. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1159 and a light chain comprising the amino acid sequence of SEQ ID NO: 1189. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1167 and a light chain comprising the amino acid sequence of SEQ ID NO: 1190. In one

embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1191 and a light chain comprising the amino acid sequence of SEQ ID NO: 1192. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1193 and a light chain comprising the amino acid sequence of SEQ ID NO: 1194. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1195 and a light chain comprising the amino acid sequence of SEQ ID NO: 1196. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1197 and a light chain comprising the amino acid sequence of SEQ ID NO: 1198. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1199 and a light chain comprising the amino acid sequence of SEQ ID NO: 1200. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1201 and a light chain comprising the amino acid sequence of SEQ ID NO: 1202. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1203 and a light chain comprising the amino acid sequence of SEQ ID NO: 1204. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1205 and a light chain comprising the amino acid sequence of SEQ ID NO: 1206. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1207 and a light chain comprising the amino acid sequence of SEQ ID NO: 1208.

- <u>DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-DLK1]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to DLK1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to DLK1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to DLK1, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. In addition, the multispecific fusion protein may sequentially comprise a first non-cleavable linker and a peptide motif at the C-terminus of the light chain constant region

(CL).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1209 and a light chain comprising the amino acid sequence of SEQ ID NO: 1210. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1211 and a light chain comprising the amino acid sequence of SEQ ID NO: 1212. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1213 and a light chain comprising the amino acid sequence of SEQ ID NO: 1214. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1215 and a light chain comprising the amino acid sequence of SEQ ID NO: 1216. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1217 and a light chain comprising the amino acid sequence of SEQ ID NO: 1218. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1219 and a light chain comprising the amino acid sequence of SEQ ID NO: 1220. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1221 and a light chain comprising the amino acid sequence of SEQ ID NO: 1222. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1223 and a light chain comprising the amino acid sequence of SEQ ID NO: 1224. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1225 and a light chain comprising the amino acid sequence of SEQ ID NO: 1226. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1209 and a light chain comprising the amino acid sequence of SEQ ID NO: 1227. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1211 and a light chain comprising the amino acid sequence of SEQ ID NO: 1228. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1213 and a light chain comprising the amino acid sequence of SEQ ID NO: 1229. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1215 and a light chain comprising the amino acid sequence of 1230. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1217 and a light chain comprising the amino acid sequence of SEQ ID NO: 1231. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1219 and a light chain comprising the amino acid sequence of SEQ ID NO: 1232. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1221 and a light chain comprising the amino acid sequence of SEQ ID NO: 1233. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1223 and a light chain comprising the amino acid sequence of SEQ ID NO: 1234. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1225 and a light chain comprising the amino acid sequence of SEQ ID NO: 1235. In one embodiment, it may

comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1236 and a light chain comprising the amino acid sequence of SEQ ID NO: 1237. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1238 and a light chain comprising the amino acid sequence of SEQ ID NO: 1239.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CLDN18.2]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CLDN18.2 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CLDN18.2, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CLDN18.2, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1240 and a light chain comprising the amino acid sequence of SEQ ID NO: 1241. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1242 and a light chain comprising the amino acid sequence of SEQ ID NO: 1243.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-TEM8]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region, a heavy chain constant region, a light chain variable region, and a light chain constant region of an antibody that binds to TEM8 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In this case,

Specifically, the multispecific fusion protein dimer may be a form in which two

multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to TEM8, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to TEM8, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1244 and a light chain comprising the amino acid sequence of SEQ ID NO: 1245.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-FAPα]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to FAPα are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to FAPα, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to FAPα, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1246 and a light chain comprising the amino acid sequence of SEQ ID NO: 1247.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EpCAM]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first

domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EpCAM are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EpCAM, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EpCAM, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1248 and a light chain comprising the amino acid sequence of SEQ ID NO: 1249.

- <u>DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-PD-1]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to PD-1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to PD-1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to PD-1, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region

(human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1250 and a light chain comprising the amino acid sequence of SEQ ID NO: 1251.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-PD-L1]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to PD-L1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to PD-L1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1252 and a light chain comprising the amino acid sequence of SEQ ID NO: 1253.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-Aβ protofibrils]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to Aβ protofibrils are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region

(VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to Aβ protofibrils, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to Aβ protofibrils, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1254 and a light chain comprising the amino acid sequence of SEQ ID NO: 1255.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-TEM8-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to TEM8, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to TEM8, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to TEM8, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1256 and a light chain comprising the amino acid sequence of SEQ ID NO: 1257.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-TEM8-anti-ANXA1]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain

variable region (VL1) of an antibody that binds to TEM8, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to ANXA1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to TEM8, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to TEM8, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to ANXA1, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1258 and a light chain comprising the amino acid sequence of SEQ ID NO: 1259.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-albumin-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to albumin, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to albumin, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to albumin, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1260 and a light chain comprising the amino acid sequence of SEQ ID NO: 1261.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-KDR (VEGFR2)-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to KDR (VEGFR2), and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to KDR (VEGFR2), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to KDR, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1262 and a light chain comprising the amino acid sequence of SEQ ID NO: 1263.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-PSMA-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to PSMA, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to PSMA, a first cleavable linker, a heavy chain variable region

(VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to PSMA, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1264 and a light chain comprising the amino acid sequence of SEQ ID NO: 1265.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ICAM1-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ICAM1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ICAM1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ICAM1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1266 and a light chain comprising the amino acid sequence of SEQ ID NO: 1267.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-FAPα-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to FAPα, and a second domain (third

component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to FAPα, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to FAPα, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1268 and a light chain comprising the amino acid sequence of SEQ ID NO: 1269.

- DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-B7H3-anti-EGFR]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to B7H3, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to B7H3, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to B7H3, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other, are linked to each other. It may be a form in which the amino acid in CH2 within the Fc region (human IgG1) is substituted with L234A/L235A (LALA).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence

of SEQ ID NO: 1270 and a light chain comprising the amino acid sequence of SEQ ID NO: 1271.

- ReleaBody type multispecific fusion protein comprising a ReleaDome

As shown in Figure 3b, it may be a homodimer in which two multispecific fusion proteins, each comprising a polypeptide of the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. In addition, the fusion protein may further comprise a payload (seventh component).

A fusion protein dimer in which two of the multispecific fusion proteins of the above form are linked to each other is referred to as "ReleaBody" in the present specification. The ReleaBody is referred to as "ReleaBody-RB" (2 bonds) and "ReleaBody-RC" (3 bonds), respectively, depending on the number of disulfide bonds formed in the third linker.

- <u>ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to HER2 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to HER2 are linked to each other, are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The fusion protein may further comprise a payload (seventh component).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1272 and a light chain comprising the amino acid sequence of SEQ ID NO: 1273. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1274 and a light chain comprising the amino acid sequence of SEQ ID NO: 1275. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1276 and a light chain comprising the amino acid sequence of SEQ ID NO: 1277. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1278 and a light chain comprising the amino acid sequence of SEQ ID NO: 1279. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1280 and a light chain comprising the amino acid sequence of SEQ ID NO: 1281. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1282 and a light chain comprising the amino acid sequence of SEQ ID NO: 1277. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1283 and a light chain comprising the amino acid sequence of SEQ ID NO: 1284. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1285 and a light chain comprising the amino acid sequence of SEQ ID NO: 1286. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1287 and a light chain comprising the amino acid sequence of SEQ ID NO: 1279. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1288 and a light chain comprising the amino acid sequence of SEQ ID NO: 1281. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1289 and a light chain comprising the amino acid sequence of SEQ ID NO: 1284. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1290 and a light chain comprising the amino acid sequence of SEQ ID NO: 1286.

- <u>ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CTLA4]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CTLA4 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CTLA4, a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that

binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CTLA4 are linked to each other, are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering.

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1291 and a light chain comprising the amino acid sequence of SEQ ID NO: 1292. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1293 and a light chain comprising the amino acid sequence of SEQ ID NO: 1294. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1295 and a light chain comprising the amino acid sequence of SEQ ID NO: 1296. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1297 and a light chain comprising the amino acid sequence of SEQ ID NO: 1298. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1299 and a light chain comprising the amino acid sequence of SEQ ID NO: 1300. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1301 and a light chain comprising the amino acid sequence of SEQ ID NO: 1302. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1303 and a light chain comprising the amino acid sequence of SEQ ID NO: 1304. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1305 and a light chain comprising the amino acid sequence of SEQ ID NO: 1306.

- <u>ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD47 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD47, a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD47 are linked to each other, are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering.

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1307 and a light chain comprising the amino acid sequence of SEQ ID NO: 1308. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1309 and a light chain comprising the amino acid sequence of SEQ ID NO: 1310. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1311 and a light chain comprising the amino acid sequence of SEQ ID NO: 1312. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1313 and a light chain comprising the amino acid sequence of SEQ ID NO: 1314. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1315 and a light chain comprising the amino acid sequence of SEQ ID NO: 1316. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1317 and a light chain comprising the amino acid sequence of SEQ ID NO: 1318. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1319 and a light chain comprising the amino acid sequence of SEQ ID NO: 1320. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1321 and a light chain comprising the amino acid sequence of SEQ ID NO: 1322. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1323 and a light chain comprising the amino acid sequence of SEQ ID NO: 1324. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1325 and a light chain comprising the amino acid sequence of SEQ ID NO: 1326. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1327 and a light chain comprising the amino acid sequence of SEQ ID NO: 1328. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1329 and a light chain comprising the amino acid sequence of SEQ ID NO: 1330.

- <u>ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]</u>

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that

binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to EGFR are linked to each other, are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The fusion protein may further comprise a payload (seventh component).

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1331 and a light chain comprising the amino acid sequence of SEQ ID NO: 1332. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1333 and a light chain comprising the amino acid sequence of SEQ ID NO: 1334. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1335 and a light chain comprising the amino acid sequence of SEQ ID NO: 1336. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1337 and a light chain comprising the amino acid sequence of SEQ ID NO: 1338. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1339 and a light chain comprising the amino acid sequence of SEQ ID NO: 1340. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1341 and a light chain comprising the amino acid sequence of SEQ ID NO: 1342. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1343 and a light chain comprising the amino acid sequence of SEQ ID NO: 1344. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1345 and a light chain comprising the amino acid sequence of SEQ ID NO: 1346. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1347 and a light chain comprising the amino acid sequence of SEQ ID NO: 1348. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1349 and a light chain comprising the amino acid sequence of SEQ ID NO: 1350.

- ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-B7H3]

The multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to B7H3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

Specifically, the multispecific fusion protein dimer may be a form in which two multispecific fusion proteins, in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to B7H3, a third linker, and an Fc region or a variant

thereof, and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to B7H3 are linked to each other, are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering.

In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1351 and a light chain comprising the amino acid sequence of SEQ ID NO: 1352. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1353 and a light chain comprising the amino acid sequence of SEQ ID NO: 1354. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1355 and a light chain comprising the amino acid sequence of SEQ ID NO: 1356. In one embodiment, it may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1357 and a light chain comprising the amino acid sequence of SEQ ID NO: 1358.

- DVD-Ig variant type multispecific fusion protein comprising a ReleaDome

- [DVD-Ig CrossMab, KIH, single arm-cleavable] type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]

As shown in Figure 13a, the multispecific fusion protein dimer may be a heterodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, among the above multispecific fusion proteins, the first multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other.

In addition, among the above multispecific fusion proteins, the second multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH2) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain variable

region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a light chain constant region (CL), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL2) that binds to EGFR, a first non-cleavable linker, and a heavy chain constant region (CH1) are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution (LALAPG) in CH3. In addition, the CH3 may comprise a 'knob' structure or a 'hole' structure. Therefore, the first multispecific fusion protein and the second multispecific fusion protein may promote dimer formation through variations within the Fc region.

In one embodiment, the first multispecific fusion protein may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1359 and a light chain comprising the amino acid sequence of SEQ ID NO: 1360. In addition, the second multispecific fusion protein may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1361 and a light chain comprising the amino acid sequence of SEQ ID NO: 1362.

- [DVD-Ig asymmetric] type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]

As shown in Figure 14a, the multispecific fusion protein dimer may be a heterodimer in which a third multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), and a fusion protein comprising the fifteenth structure of structural formula (VI) and the sixteenth structure of structural formula (VII) are linked to each other.

Specifically, the third multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a fusion protein, in which a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the third multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a

first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region are linked to each other. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a fifteenth structure comprising a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a light chain constant region (CL), a third linker, and an Fc region or a variant thereof; and a sixteenth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a heavy chain constant region (CH1) are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution (LALAPG) in CH3. In addition, the CH3 may comprise a 'knob' structure or a 'hole' structure. Therefore, the third multispecific fusion protein and the fusion protein comprising the fifteenth structure and the sixteenth structure may promote dimer formation through variations within the Fc region.

In one embodiment, the third multispecific fusion protein may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1363 and a light chain comprising the amino acid sequence of SEQ ID NO: 1364. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 1365 and a light chain comprising the amino acid sequence of SEQ ID NO: 1366.

- Various forms of multispecific fusion protein variants comprising a ReleaDome

Exemplary embodiments of the multispecific fusion protein variant dimers of the present invention are described in Figures 3a to 3c and Table 42.

- <u>ST-017</u>

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a seventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first

non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1).

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1367 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1368.

- <u>ST-018</u>

As shown in Figure 3c, it may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a seventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1).

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1369 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1370.

- <u>ST-019</u>

As shown in Figure 3c, the multispecific fusion protein dimer may be a heterodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in

which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1).

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1371 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1372.

- <u>ST-020</u>

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a peptide that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a seventh structure comprising a peptide that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region are linked to each other. The variant may

comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1).

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1373 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1374.

- ST-021

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to TEM8, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to TEM8, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to TEM8, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1).

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1375 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1376.

- ST-022

As shown in Figure 3b, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to ANXA1, and a second domain (third component)

comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to HER2 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to HER2 are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1377 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1378.

- <u>ST-023</u>

As shown in Figure 3b, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to TEM8, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to HER2 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, it may be a multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to TEM8, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to TEM8, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to HER2 are linked to each other. In this case, it may be linked through a disulfide bond by introducing

cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1379 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1380.

- ST-024

As shown in Figure 3a, the multispecific fusion protein dimer may be a heterodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2, VH3), a heavy chain constant region (CH1), a light chain variable region (VL2, VL3), and a light chain constant region (CL) of an antibody that binds to CD3 or PD-L1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a fourth multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other.

In addition, the multispecific fusion protein may be a fifth multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL3) of an antibody that binds to PD-L1, and a light chain constant region (CL) are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. The fourth multispecific fusion protein and the fifth multispecific fusion protein may promote heterodimer formation.

In one embodiment, the fourth multispecific fusion protein may comprise a heavy chain

(HC) comprising the amino acid sequence of SEQ ID NO: 1381 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1382. The fifth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1383 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1384.

- ST-025

As shown in Figure 3b, the multispecific fusion protein dimer may be a heterodimer in which a multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), and a fusion protein of the third structure of structural formula (VIII) are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. The fusion protein of the third structure may be a form in which a heavy chain variable region (VH3) and a light chain variable region (VL3) that binds to PD-L1 are linked to an Fc region or a variant (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3 are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. In addition, the fusion protein of the third structure may comprise a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a heavy chain variable region (VL3), a third linker, and an Fc region or a variant thereof. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds. The multispecific fusion protein and the fusion protein comprising the third structure may promote heterodimer formation.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1385 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1386.

- ST-026

As shown in Figure 3b, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1387 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1388.

- <u>ST-027</u>

As shown in Figure 3b, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a second structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, and a

light chain variable region (VL2) of an antibody that binds to EGFR are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1389 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1390.

- ST-028

As shown in Figure 3b, the multispecific fusion protein dimer may be a heterodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2, VH3) and a light chain variable region (VL2, VL3) of an antibody that binds to CD3 or PD-L1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a sixth multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD3 are linked to each other. In addition, the multispecific fusion protein may be a seventh multispecific fusion protein in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL3) of an antibody that binds to PD-L1 are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH and the 100th position of VL according to Kabat numbering of VH2, VL2, VH3, and VL3, respectively. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the sixth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1391 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1386. The seventh multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1392 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1393.

- ST-029

As shown in Figure 3b, the multispecific fusion protein dimer may be a heterodimer in which a multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II) and a fusion protein comprising the third structure of structural formula (VIII) are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the third structure may be a form in which a heavy chain variable region (VH3) and a light chain variable region (VL3) of an antibody that binds to PD-L1 are linked to an Fc region or a variant thereof via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD3 are linked to each other. In addition, the fusion protein comprising the third structure may comprise a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain variable region (VL3), a third linker, and an Fc region or a variant thereof. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1391 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1386. The fusion protein comprising the third structure may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1394.

- ST-030

As shown in Figure 3a, the multispecific fusion protein dimer may be a heterodimer in which an eighth multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II) and a fusion protein comprising the fifteenth structure of structural formula (VI) and the sixteenth structure of structural formula (VII) are linked to each other.

Specifically, the eighth multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a heavy chain variable region (VH3), a heavy chain constant region (CH1), a light chain variable region (VL3), and a light chain constant region (CL) of an antibody that binds to PD-L1 are linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the eighth multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a fifteenth structure comprising a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain constant region (CL), a third linker, and an Fc region or a variant thereof; and a sixteenth structure comprising a light chain variable region (VL3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a heavy chain constant region (CH1) are linked to each other. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3.

In one embodiment, the eighth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1381 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1382. The fusion protein comprising the fifteenth structure and the sixteenth structure may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1395 and a light chain (LC) comprising the amino acid

sequence of SEQ ID NO: 1396.

- ST-031

As shown in Figure 3a, the multispecific fusion protein dimer may be a heterodimer in which a multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II) and a fusion protein comprising the third structure of structural formula (VIII) are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the third structure may be a form in which a heavy chain variable region (VH3) and a light chain variable region (VL3) of an antibody that binds to PD-L1 are linked to an Fc region or a variant thereof via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. In addition, the fusion protein comprising the third structure may comprise a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain variable region (VL3), a third linker, and an Fc region or a variant thereof. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1381 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1382. The fusion protein comprising the third structure may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1394.

- ST-032

As shown in Figure 3b, the multispecific fusion protein dimer may be a heterodimer in which a ninth multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II) and a fusion protein comprising the fifteenth structure of structural formula (VI) and the sixteenth structure of structural formula (VII) are

linked to each other.

Specifically, the ninth multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a heavy chain variable region (VH3), a heavy chain constant region (CH1), a light chain variable region (VL3), and a light chain constant region (CL) of an antibody that binds to PD-L1 are linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the ninth multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD3 are linked to each other. In addition, the fusion protein comprising the fifteenth structure and the sixteenth structure may be a form in which a fifteenth structure comprising a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a sixteenth structure comprising a light chain variable region (VL3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other.

In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the ninth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1397 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1398. The fusion protein comprising the fifteenth structure and the sixteenth structure may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1399 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1400.

- ST-033

As shown in Figure 3b, the multispecific fusion protein dimer may be a heterodimer in which a multispecific fusion protein comprising the sixth structure of structural formula (I') and the second structure of structural formula (II) and a fusion protein comprising the third structure of structural formula (VIII) are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker. In addition, the fusion protein comprising the third structure may be a form in which a heavy chain variable region (VH3) and a light chain variable region (VL3) of an antibody that binds to PD-L1 are linked to an Fc region or a variant thereof via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD3 are linked to each other. In addition, the fusion protein comprising the third structure may comprise a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a first non-cleavable linker, and a light chain variable region (VL3), a third linker, and an Fc region or a variant thereof. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1397 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1398. The fusion protein comprising the third structure may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1394.

- ST-034

As shown in Figure 3c, the multispecific fusion protein dimer may be a heterodimer in which a tenth multispecific fusion protein comprising the eleventh structure of structural formula

(I'") and the second structure of structural formula (II) and an eleventh multispecific fusion protein comprising the twelfth structure of structural formula (I"") and the second structure of structural formula (II) are linked to each other.

Specifically, the tenth multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an antigen binding site (sixth component) via a third linker. In addition, the eleventh multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to CD3 are serially linked via a first linker (second component), is linked to an antigen binding site (sixth component) via a third linker.

More specifically, the tenth multispecific fusion protein may comprise an eleventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and a heavy chain variable region (VH3) of an antibody that binds to PD-L1; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL). In addition, the eleventh multispecific fusion protein may comprise a twelfth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and a light chain variable region (VL3) of an antibody that binds to PD-L1; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL). In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the tenth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1401 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1382. The eleventh multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO:

1402 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1382.

- ST-035

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may comprise a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) that binds to EGFR. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. In addition, the Fc region may comprise only CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1403 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1404.

- ST-036

As shown in Figure 3c, the multispecific fusion protein dimer may be a heterodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2, VH3) of an antibody that binds to CD3 or PD-L1 are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a twelfth multispecific fusion protein comprising a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a

first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD3. In addition, the multispecific fusion protein may be a thirteenth multispecific fusion protein comprising a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH3) of an antibody that binds to PD-L1, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL3) of an antibody that binds to PD-L1. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH and the 100th position of VL according to Kabat numbering of VH2, VL2, VH3, and VL3, respectively. In addition, the Fc region may comprise only CH3.

In one embodiment, the twelfth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1405 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1386. The thirteenth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1406 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1393.

- <u>ST-038</u>

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. In addition, the Fc region may comprise only CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1407 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1160.

- ST-039

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the sixth structure of structural formula (I') and the second structure of structural formula (II), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1), a heavy chain constant region (CH1), a light chain variable region (VL1), and a light chain constant region (CL) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a sixth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain constant region (CH1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a second structure comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain constant region (CL), a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to EGFR are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. In addition, the Fc region may comprise only CH3. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1408 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1409.

- ST-040

As shown in Figure 3b, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a seventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a

first non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution in CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1410 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 207.

- ST-041

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a seventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. The Fc region or variant thereof may comprise only CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1411 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1412.

- ST-042

As shown in Figure 3c, the multispecific fusion protein dimer may be a homodimer in which two multispecific fusion proteins, each comprising the seventh structure of structural formula (IV') and the fifth structure of structural formula (V), are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an Fc region or a variant thereof (fourth component) via a third linker.

More specifically, the multispecific fusion protein may be a form in which a seventh structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to EGFR are linked to each other. In this case, it may be linked through a disulfide bond by introducing cysteine (Cys) at the 44th position of VH2 and the 100th position of VL2 according to Kabat numbering. The Fc region or variant thereof may comprise only CH3.

In one embodiment, the multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1413 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 207.

- <u>ST-043</u>

As shown in Figure 3c, the multispecific fusion protein dimer may be a heterodimer in which a fourteenth multispecific fusion protein comprising the thirteenth structure of structural formula (IV"') and the fifth structure of structural formula (V); and a fifteenth multispecific fusion protein comprising the fourteenth structure of structural formula (IV"") and the fifth structure of structural formula (V) are linked to each other.

Specifically, the multispecific fusion protein may be a form in which a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to EGFR are serially linked via a first linker (second component), is linked to an antigen binding site (sixth component) that binds to PD-L1 via a third linker.

More specifically, the fourteenth multispecific fusion protein may be a form in which a thirteenth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and a heavy chain variable region (VH3) of an antibody that binds to PD-L1; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain

constant region (CL) are linked to each other. In addition, the fifteenth multispecific fusion protein may be a form in which a fourteenth structure comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL1), a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD3, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and a light chain variable region (VL3) of an antibody that binds to PD-L1; and a fifth structure comprising a light chain variable region (VL2) of an antibody that binds to CD3, a first non-cleavable linker, and a light chain constant region (CL) are linked to each other. In addition, the third linker may comprise three disulfide bonds.

In one embodiment, the fourteenth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1414 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1415. The fifteenth multispecific fusion protein may comprise a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1416 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 1415.

<Polynucleotide encoding a fusion protein or a fusion protein dimer>

In another aspect of the present invention, there is provided a polynucleotide encoding the fusion protein or the fusion protein dimer. The fusion protein is the same as described above.

As used herein, the term "polynucleotide," also referred to as "nucleic acid," refers to a polymer of nucleotides of any length. Specifically, the polynucleotide may be DNA or RNA.

Specifically, the polynucleotide encoding the fusion protein may include a polynucleotide encoding a first structure and a second structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a fourth structure and a fifth structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a sixth structure and a second structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a seventh structure and a fifth structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding an eighth structure and a second structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a ninth structure and a fifth structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding an eleventh structure and a second structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a twelfth structure and a second structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a thirteenth structure and a fifth structure. The polynucleotide encoding the fusion protein may include a polynucleotide encoding a fourteenth structure and a fifth structure.

In this case, the polynucleotide encoding the heavy chain variable region (VH1) of the first domain of the first structure, the second structure, the fourth structure, the sixth structure to the ninth structure, the eleventh structure to the fourteenth structure may include any one

polynucleotide selected from the group consisting of SEQ ID NO: 1419 to SEQ ID NO: 1492. In addition, the light chain variable region (VL1) of the first domain may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1493 to SEQ ID NO: 1560.

In addition, the heavy chain variable region (VH2) of the second domain of the first structure, the second structure, the fourth structure, the sixth structure to the ninth structure, the eleventh structure to the fourteenth structure may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1473, SEQ ID NO: 1486, SEQ ID NO: 1491, SEQ ID NO: 1492, SEQ ID NO: 1561 to SEQ ID NO: 1586, and SEQ ID NO: 1588. In addition, the polynucleotide encoding the light chain variable region (VL2) of the second domain may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1547, SEQ ID NO: 1554, SEQ ID NO: 1560, and SEQ ID NO: 1589 to SEQ ID NO: 1615. The second domain may include a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1587.

The polynucleotide encoding the heavy chain variable region (VH2) of the second domain of the fifth structure may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1473, SEQ ID NO: 1486, SEQ ID NO: 1491, SEQ ID NO: 1492, SEQ ID NO: 1561 to SEQ ID NO: 1586, and SEQ ID NO: 1588, and the polynucleotide encoding the light chain variable region (VL2) may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1547, SEQ ID NO: 1554, SEQ ID NO: 1560, and SEQ ID NO: 1589 to SEQ ID NO: 1615. The second domain may include a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1587.

In the present invention, a fusion protein dimer may be a form in which the two fusion proteins are linked to each other. In addition, the fusion protein dimer may be a form in which the fusion protein and the fusion protein comprising the third structure, or the fusion protein comprising the fifteenth structure and the sixteenth structure are linked to each other. Therefore, the polynucleotide encoding the fusion protein dimer may include a polynucleotide encoding the fusion protein and a polynucleotide encoding the third structure, or a polynucleotide encoding the fifteenth structure and the sixteenth structure. The polynucleotide encoding the fusion protein is the same as described above. The polynucleotide encoding the heavy chain variable region (VH2) of the third structure, the fifteenth structure, and the sixteenth structure may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1473, SEQ ID NO: 1486, SEQ ID NO: 1491, SEQ ID NO: 1492, SEQ ID NO: 1561 to SEQ ID NO: 1586, and SEQ ID NO: 1588, and the polynucleotide encoding the light chain variable region (VL2) may include any one polynucleotide selected from the group consisting of SEQ ID NO: 1547, SEQ ID NO: 1554, SEQ ID NO: 1560, and SEQ ID NO: 1589 to SEQ ID NO: 1615. The second domain may include a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1587.

In addition, if the polynucleotide encodes the same polypeptide, one or more bases may be mutated by substitution, deletion, insertion, or a combination thereof. When the

polynucleotide sequence is prepared by chemical synthesis, synthetic methods well known in the art, for example, the method described in the literature (Engels and Uhlmann, Angew Chem IntEd Engl., 37:73-127, 1988), may be used, and examples thereof include triester, phosphite, phosphoramidite, and H-phosphate methods, PCR and other autoprimer methods, and oligonucleotide synthesis methods on solid supports.

Specifically, the polynucleotide may comprise a nucleotide sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% identity with the respective nucleotide sequences of the polynucleotides of SEQ ID NO: 1419 to SEQ ID NO: 1615.

The polynucleotide may further comprise a nucleic acid encoding a signal sequence or a leader sequence. As used herein, the term "signal sequence" refers to a signal peptide that directs the secretion of a target protein. The signal peptide is cleaved after translation in a host cell. Specifically, the signal sequence is an amino acid sequence that initiates the migration of a protein through the ER (endoplasmic reticulum) membrane. The characteristics of the signal sequence are well known in the art and the signal sequence typically comprises 16 to 30 amino acid residues, but may comprise more or fewer amino acid residues. A typical signal peptide consists of three regions: a basic N-terminal region, a central hydrophobic region, and a more polar C-terminal region. The central hydrophobic region comprises 4 to 12 hydrophobic residues that anchor the signal sequence through the membrane lipid bilayer during the migration of the immature polypeptide. After initiation, the signal sequence is cleaved within the lumen of the ER by a cellular enzyme commonly known as a signal peptidase. In this case, the signal sequence may be a secretion signal sequence of tPa (tissue plasminogen activation), HSV gDs (signal sequence of Herpes simplex virus glycoprotein D), or growth hormone. Preferably, a secretion signal sequence used in higher eukaryotic cells, including mammals, may be used. In addition, as the signal sequence, a wild type signal sequence can be used, or one substituted with a codon that has a high expression frequency in the host cell can be used.

<Vector comprising a polynucleotide>

In another aspect of the present invention, there is provided a vector comprising a polynucleotide encoding the fusion protein or the fusion protein dimer. The fusion protein and the polynucleotide encoding the fusion protein are the same as described above.

Specifically, the vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a first structure and a second structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a fourth structure and a fifth structure. The vector comprising the polynucleotide

encoding the fusion protein may comprise a polynucleotide encoding a sixth structure and a second structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a seventh structure and a fifth structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding an eighth structure and a second structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a ninth structure and a fifth structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding an eleventh structure and a second structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a twelfth structure and a second structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a thirteenth structure and a fifth structure. The vector comprising the polynucleotide encoding the fusion protein may comprise a polynucleotide encoding a fourteenth structure and a fifth structure. The polynucleotide encoding the fusion protein may each be included in different vectors, or may be included in a single vector in a bisitronic form. Preferably, they may each be included in different vectors.

In addition, a vector comprising a polynucleotide encoding the fusion protein dimer may be a vector comprising a polynucleotide encoding the fusion protein and a polynucleotide encoding a third structure, or a polynucleotide encoding a fifteenth structure and a sixteenth structure. A vector comprising a polynucleotide encoding the fusion protein is the same as described above.

As used herein, the term "vector" may be introduced into a host cell and recombined and inserted into the host cell genome. Alternatively, the vector is understood as a nucleic acid means comprising a nucleotide sequence capable of spontaneously replicating as an episome. The vector includes linear nucleic acids, plasmids, phagesmids, cosmids, RNA vectors, viral vectors, mini-chromosomes, and analogs thereof. Examples of viral vectors include, but are not limited to, retroviruses, adenoviruses, and adeno-associated viruses.

Specifically, the vector may be plasmid DNA, phage DNA, etc.; and may be commercially developed plasmids (pUC18, pBAD, pIDTSAMRT-AMP, etc.), plasmids derived from E. coli (pYG601BR322, pBR325, pUC118, pUC119, pcDNA, etc.), plasmids derived from Bacillus subtilis (pUB110, pTP5, etc.), plasmids derived from yeast (YEp13, YEp24, YCp50, etc.), phage DNA (Charon4A, Charon21A, EMBL3, EMBL4, λgt10, λgt11, λZAP, etc.), animal viral vectors (retroviruses, adenoviruses, vaccinia viruses, etc.), insect viral vectors (baculoviruses, etc.). Since the vector exhibits different expression levels of a protein depending on a host cell, it is desirable to select and use the host cell which is most suitable for the purpose.

In addition, the plasmid may comprise a selection marker such as an antibiotic resistance gene, and the host cell holding the plasmid may be cultured under selective conditions.

As used herein, the term "gene expression" or "expression" of the target protein are

understood to mean the transcription of a DNA sequence, the translation of an mRNA transcript, and the secretion of a fusion protein product. A useful expression vector may be RcCMV (Invitrogen, Carlsbad) or a variant thereof. The expression vector may include a human CMV (Cytomegalovirus) promoter to promote the continuous transcription of the target gene in mammalian cells and a bovine growth hormone polyadenylation signal sequence to increase the steady state level of post-transcriptional RNA.

<Transformed cell>

In another aspect of the present invention, there is provided a cell transformed with a vector comprising a polynucleotide encoding the fusion protein or the fusion protein dimer. In this case, the fusion protein, the polynucleotide, and the vector are the same as described above.

As used herein, the term "transformed cell" refers to a prokaryotic or eukaryotic cell into which a recombinant expression vector can be introduced. In addition, the transformed cell may refer to an isolated transformed cell. The transformed cell can be produced by introducing the vector into a host cell and transforming it. In addition, the polynucleotide included in the vector can be expressed to produce the fusion protein or the fusion protein dimer according to the present invention.

The transformation can be performed by various methods. As long as the fusion protein or the fusion protein dimer of the present invention can be produced, it is not particularly limited thereto. Specifically, the transformation method may be the $CaCl_2$ precipitation method, the Hanahan method whose efficiency has been increased by using a reducing agent such as dimethyl sulfoxide (DMSO) in $CaCl_2$ precipitation method, electroporation, calcium phosphate precipitation method, protoplast fusion method, agitation method using silicon carbide fibers, agrobacteria-mediated transformation method, PEG- mediated transformation method, dextran sulfate-, lipofectamine-, and dry/inhibition-mediated transformation method. In addition, a target substance can be delivered into a cell using a virus particle by means of infection. In addition, a vector can be introduced into a host cell by means of gene bombardment, and the like.

In addition, the host cell used for the production of the transformed cell is also not particularly limited thereto as long as it can produce the fusion protein or the fusion protein dimer of the present invention. Specifically, the host cell may include, but is not limited to, a prokaryotic cell, a eukaryotic cell, and a cell of mammalian, plant, insect, fungal, or bacterial origin. As an example of the prokaryotic cell, *E. coli* may be used. In addition, as an example of the eukaryotic cell, yeast may be used. In addition, for the mammalian cells, CHO cells, F2N cells, COS cells, BHK cells, Bowes melanoma cells, HeLa cells, 911 cells, AT1080 cells, A549 cells, SP2/0 cells, human lymphoblastoid, NSO cells, HT-1080 cells, PERC.6 cells, HEK293 cells, HEK293T cells, or the like may be used, but is not limited thereto. Any cells which are known to those of ordinary skill in the art to be usable as mammalian host cells may be used.

In addition, in order to optimize the properties of the fusion protein or the fusion protein

dimer as a therapeutic agent or for other purposes, the glycosylation-related genes possessed by the host cell can be manipulated through methods known to those of ordinary skill in the art to adjust the glycosylation pattern of the antibody (e.g., sialic acid, fucosylation, glycosylation).

<Method for producing a fusion protein and a fusion protein dimer>

In another aspect of the present invention, there is provided a method for producing a fusion protein or a fusion protein dimer, the method comprising the steps of: i) culturing the transformed cells; and ii) obtaining a fusion protein or a fusion protein dimer from the culture solution.

As used herein, the term "culturing" refers to a method of growing a microorganism (e.g., the transformed cells) under appropriately artificially controlled environmental conditions.

The method of culturing the transformed cells may be carried out using methods well known in the art. Specifically, the culturing is not particularly limited thereto as long as the fusion protein or the fusion protein dimer of the present invention can be expressed and produced. Specifically, the culturing may be carried out continuously in a batch process or a fed batch or repeated fed batch process.

In addition, the step of obtaining the fusion protein or the fusion protein dimer from the culture solution may be carried out by methods known in the art. Specifically, the method of obtaining is not particularly limited thereto as long as the produced fusion protein or fusion protein dimer of the present invention can be obtained. Preferably, the method of obtaining may be a method such as centrifugation, filtration, extraction, spraying, drying, evaporation, precipitation, crystallization, electrophoresis, fractional dissolution (e.g., ammonium sulfate precipitation), chromatography (e.g., ion exchange, affinity, hydrophobicity, and size exclusion).

<Fusion protein-drug conjugate and fusion protein dimer-drug conjugate>

In another aspect of the present invention, there is provided a fusion protein-drug conjugate comprising the following structural formula (IX):

X-[(L16)-Y]p (IX)

in the structural formula (IX),

X is a fusion protein,

Y is a drug,

L16 is a linker, and

p is 0 or 1.

In another aspect of the present invention, there is provided a fusion protein dimer-drug conjugate comprising the following structural formula (IX'):

X'-[(L17)-Z]q (IX')

in the structural formula (IX'),

X' is a fusion protein dimer,

L17 is a linker,

Z is a drug, and

q is 0 or 1.

In this case, the drug may be an anticancer agent, but is not limited thereto.

In addition, L16 and L17 may be a second linker.

The fusion protein-drug conjugate, the fusion protein, the fusion protein dimer, the anticancer agent, and the second linker are the same as described above.

In the present invention, the fusion protein-drug conjugate or the fusion protein dimer-drug conjugate may be prepared by conjugating the fusion protein or the fusion protein dimer and the seventh component. In this case, the conjugation method is the same as described above.

<Uses of fusion protein, fusion protein dimer, fusion protein-drug conjugate, and fusion protein dimer-drug conjugate>

In another aspect of the present invention, there is provided a pharmaceutical composition for the prevention or treatment of a disease, comprising the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, or the fusion protein dimer-drug conjugate as an active ingredient. In this case, the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, or the fusion protein dimer-drug conjugate is the same as described above.

In this case, the disease may be cancer.

As used herein, the term "cancer" refers collectively to diseases caused by cells having aggressive characteristics in which cells divide and proliferate beyond normal growth limits, invasive characteristics in which they infiltrate surrounding tissues, and metastatic characteristics in which they spread to other parts of the body, and is used with the same meaning as a malignant tumor.

The cancer may be any one selected from gastric cancer, liver cancer, lung cancer, large intestine cancer, breast cancer, prostate cancer, gallbladder cancer, bladder cancer, kidney cancer, esophageal cancer, skin cancer, rectal cancer, osteosarcoma, multiple myeloma, glioma, ovarian cancer, pancreatic cancer, cervical cancer, endometrial cancer, thyroid cancer, laryngeal cancer, testicular cancer, mesothelioma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, brain tumor, neuroblastoma, retinoblastoma, head and neck cancer, salivary gland cancer, melanoma, and lymphoma, but is not limited thereto.

The disease may be a degenerative brain disease.

As used herein, the term "degenerative brain disease" refers to a disease occurring in the brain among degenerative diseases that occur with aging. Although the exact cause of the disease has not been clearly identified, it is known to be caused by the death of brain neurons and/or problems with the formation or function of synapses that transmit information between brain neurons.

The degenerative brain disease may be any one selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, mild cognitive impairment, cerebral amyloid angiopathy, Down syndrome, amyloid stroke, systemic amyloid disease, Dutch amyloidosis, Niemann-Pick disease, senile dementia, amyotrophic lateral sclerosis, spinocerebellar atrophy, Tourette's syndrome, Friedrich's ataxia, Machado-Joseph's disease, Lewy body dementia, dystonia, progressive supranuclear palsy, and frontotemporal dementia, but is not limited thereto.

The preferred dosage of the pharmaceutical composition may vary depending on the patient's condition and body weight, the severity of the disease, the form of the drug, the route of administration, and the duration, but may be appropriately selected by those of ordinary skill in the art. In the pharmaceutical composition for the treatment or prevention of a disease according to the present invention, the active ingredient may be included in any amount (effective amount) depending on the use, formulation, purpose of combination, etc., as long as it can exhibit therapeutic activity against the disease. Here, the term "effective amount" refers to the amount of the active ingredient capable of improving the condition of the disease or inducing a treatment effect. Such effective amount may be determined experimentally within the ordinary capabilities of those of ordinary skill in the art.

As used herein, the term "treatment" may be used to include both therapeutic treatment and preventive treatment. In this case, prevention may be used to mean alleviating or reducing the pathological condition or disease of a subject. In one embodiment, the term "treatment" includes all applications or any form of medication for treating a disease in mammals, including humans. In addition, the above term includes inhibiting or slowing the progression of a disease; restoring or repairing impaired or deficient functions to partially or completely alleviate a disease; or stimulating an inefficient process; or alleviating a serious disease.

Pharmacokinetic parameters such as bioavailability and underlying parameters such as clearance rate can also affect efficacy. Therefore, "enhanced efficacy" (e.g., improvement of efficacy) can be attributed to enhanced pharmacokinetic parameters and enhanced efficacy, and can be measured by comparing parameters such as clearance rate and tumor treatment or improvement in test animals or human subjects.

Meanwhile, the pharmaceutical composition of the present invention is administered in a therapeutically effective amount.

As used herein, the term "therapeutically effective amount" or "pharmaceutically effective amount" refers to an amount of a compound or composition effective for preventing or treating a target disease, which is sufficient to treat the disease with a reasonable benefit/risk ratio applicable to medical treatment and does not cause adverse effects. The level of the effective amount may be determined by factors including the patient's health condition, type and severity of the disease, drug activity, sensitivity to the drug, method of administration, time of

administration, route of administration and elimination rate, duration of treatment, drugs used in combination or concurrently, and other factors well known in the medical field. In one embodiment, the therapeutically effective amount refers to an amount of drug effective for treating cancer. In one embodiment, the therapeutically effective amount refers to an amount of drug effective for treating degenerative brain disease.

As used herein, the term "administration" means introducing a specific substance into a subject by an appropriate method, and the composition may be administered via any general route as long as it can reach the target tissue. Preferably, it may be administered parenterally, and parenteral administration methods may include intraperitoneal, intravenous, intramuscular, subcutaneous, intradermal, topical, intranasal, intrapulmonary, and rectal administration, but are not limited thereto.

A preferred dosage of the pharmaceutical composition may be in the range of 0.01 μg/kg to 10 g/kg per day, or in the range of 0.01 mg/kg to 1 g/kg per day, depending on the patient's condition, body weight, sex, and age, severity of the patient, and route of administration. The administration may be performed once a day or divided into several times per day. This dosage should not be construed as limiting the scope of the present invention in any way.

The subject to which the pharmaceutical composition can be applied (prescribed) may be a mammal and a human, and preferably a human.

The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may be any carrier as long as it is non-toxic material suitable for delivery to a patient. Distilled water, alcohol, fats, waxes and inert solids may be included as a carrier. In addition, a pharmacologically acceptable adjuvant (buffering agent, dispersing agent) may be included in the pharmaceutical composition.

Specifically, the pharmaceutical composition may be prepared into a parenteral formulation according to the route of administration by conventional methods known in the art, including a pharmaceutically acceptable carrier in addition to the active ingredient. Here, "pharmaceuticalally acceptable" means that it does not inhibit the activity of the active ingredient and does not possess toxicity beyond what the subject of application (prescription) can tolerate.

When the pharmaceutical composition is prepared into a parenteral formulation, it may be formulated in the form of an injection, a transdermal preparation, a nasal inhalant, and a suppository together with suitable carriers according to methods known in the art. When it is formulated as an injection, as a suitable carrier, sterile water, ethanol, polyol such as glycerol or propylene glycol, or a mixture thereof may be used, and Ringer's solution, PBS (Phosphate Buffered Saline) containing triethanolamine, or sterile water for injection, an isotonic solution such as 5% dextrose, and the like may be preferably used. Methods for formulating pharmaceutical compositions are known in the art, and specifically, reference can be made to literature [Remington's Pharmaceutical Sciences (19th ed., 1995)], etc. The above literature is

considered to be part of the present specification.

In the present invention, the pharmaceutical composition may further comprise any compound or natural extract known to have a tumor-treating effect in addition to the active ingredient, or may be used in combination with a separate composition comprising said substance (hereinafter referred to as a therapeutic agent).

The "combination" includes two or more therapeutic agents being included in the same or separate formulations. When the pharmaceutical composition is prepared in a separate formulation from the therapeutic agent and used in combination, the pharmaceutical composition and the therapeutic agent may be mixed and administered "simultaneously," or they may be administered sequentially. When the pharmaceutical composition is administered sequentially with another therapeutic agent, it may be administered before and/or after the administration of the therapeutic agent. The therapeutic agent may be any compound or natural extract known to have a therapeutic effect on a disease.

In another aspect of the present invention, there is provided a use of the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, the fusion protein dimer-drug conjugate, or a pharmaceutical composition comprising the same for the prevention or treatment of a disease. The disease may be cancer or a degenerative brain disease.

In another aspect of the present invention, there is provided a use of the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, the fusion protein dimer-drug conjugate, or a pharmaceutical composition comprising the same for manufacture of a medicament for the prevention or treatment of a disease. The disease may be cancer or a degenerative brain disease. The fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, the fusion protein dimer-drug conjugate, the cancer, the degenerative brain disease, the prevention, and the treatment are the same as described above.

In another aspect of the present invention, there is provided a method for the prevention or treatment of a disease, comprising administering the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, the fusion protein dimer-drug conjugate, or a pharmaceutical composition comprising the same to a subject. The disease may be cancer or a degenerative brain disease. Here, the fusion protein, the fusion protein dimer, the fusion protein-drug conjugate, the fusion protein dimer-drug conjugate, the cancer, the degenerative brain disease, the administration, the prevention, and the treatment are the same as described above.

The "subject" may be a mammal, preferably a human. In addition, the subject may be a patient suffering from a disease or a subject with a high probability of suffering from cancer.

The route of administration, dosage, and frequency of administration of the composition may vary depending on the patient's condition and the presence or absence of side effects, and thus the composition may be administered to a subject in various ways and amounts. The optimal administration method, dosage, and frequency of administration may be selected in an

appropriate range by those of ordinary skill in the art. In addition, the composition may be administered in combination with any compound or natural extract known to have a therapeutic effect on the disease, or may be formulated in the form of a combination preparation with other drugs.

Cleavable peptide

In another aspect of the present invention, there is provided a cleavable peptide comprising any one amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 173 to SEQ ID NO: 176, and combinations thereof. In this case, the cleavable peptide may comprise an amino acid sequence of a cleavage site that is cleaved by a proteolytic enzyme that is specifically overexpressed or overactivated at a disease site compared to a non-disease site. Specifically, the cleavable peptide may be cleaved by any one proteolytic enzyme selected from the group consisting of MMP-2, MMP-9, uPA, MT-SP1, MMP-3, MMP-7, and combinations thereof.

In the present specification, the cleavable peptide may be understood as a first cleavable linker comprising the cleavable peptide. The cleavable peptide, the first cleavable linker, and the proteolytic enzyme are the same as described above.

In addition, the cleavable peptide may comprise or consist of amino acid sequences having about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identity or 100% identity with the amino acid sequences of SEQ ID NO: 159, SEQ ID NO: 160, and SEQ ID NO: 173 to SEQ ID NO: 176, respectively.

Mode for Carrying out the Invention

Hereinafter, the present invention will be described in more detail by way of the following examples. However, the following examples are intended only to illustrate the present invention, and the scope of the present invention is not limited to these examples.

Example 1. Design of dual functional domain structure

The ReleaDome (Figure 1), a dual functional domain structure according to the present invention, has a structure in which a first domain (A, first component) and a second domain (C, third component) are linked via a linker (B, second component). In this case, the first domain can bind to a protein that is specifically expressed or exposed to vascular cells or basal cells at a disease site, and the second domain can bind to a protein that is overexpressed in target cells at a disease site. In addition, the linker may comprise a substrate sequence that can be cleaved by a specific proteolytic enzyme that is specifically expressed in the microenvironment of the disease site. The first domain (outer domain) is located on the outermost side and the second domain (inner domain) is located on the inner side, and the first domain and the second domain are serially linked via a first linker. In this case, the first linker may include (first cleavable linker) or not include (first non-cleavable linker) the substrate sequence of a proteolytic enzyme that is

overexpressed or overactivated at a disease site. Although the first domain of the ReleaDome structurally masks the binding avidity to the target of the second domain, if the first linker (first cleavable linker) is cleaved by a proteolytic enzyme at a disease site, the first domain is irreversibly dissociated, exposing the binding site of the second domain, and the binding affinity to the second target can be restored.

In the present invention, the target of the first component (A) of the ReleaDome may be, for example, Annexin A1 (ANXA1). The protein is known to be overexpressed in microvascular cells present around the tumor microenvironment (TME) surrounding cancer tissue, inflammatory disease, or Alzheimer's disease site, and is exposed to the vascular lumen.

Therefore, in the present invention, an antibody that specifically binds to Annexin A1 can be configured as the first domain, and the amino acid sequences of the heavy chain variable region (VH1) and the light chain variable region (VL1) of said antibody are shown in Table 11 and Table 12, respectively. The amino acid sequences of the antibodies below are described from the N-terminus to the C-terminus. Meanwhile, the sequence analysis of the present patent mostly followed IMGT numbering, and some sequences were analyzed according to Kabat numbering. In addition, the polynucleotide sequences encoding the heavy chain variable region and the light chain variable region are shown in Table 13.

[Table 11]

Part Number	Clone name: UNIT1	VH1 or VL1 in HC	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
A1	Y004	QMQLVQSGGGLVQPGRSLRLSCAVSGFTFDDYAMHWVRQAPGKGLEWVSGINWDSSNIGYADSVKGRFTISRDNAKNSLYLQMNNLRSEDTAVYYCVKLASDSGGYFESWGQGTLVTVSS(SEQ ID NO:1)	QMQLVQSGGGLVQPGRSLRLSCAVS(SEQ ID NO:276)	GFTFDDYA(SEQ ID NO:277)	MHWVRQAPGKGLEWVSG(SEQ ID NO:278)	INWDSSNI(SEQ ID NO:279)	GYADSVKGRFTISRDNAKNSLYLQMNNLRSEDTAVYYC(SEQ ID NO:280)	VKLASDSGGYFES(SEQ ID NO:281)	WGQGTLVTVSS(SEQ ID NO:282)
A2	Y025	QVQLVESGGGLVESGGSLRLSCAASGFTFSNAWMTWVRQAPGKGLEWVGVIRSKTYGGTTEYAAPLRGRFSISRDDSKNTLYLQMNSLRAEDTAVYYCAKGAAYGPFDYWGQGTLITVSS(SEQ	QVQLVESGGGLVESGGSLRLSCAAS(SEQ ID NO:283)	GFTFSNAW(SEQ ID NO:284)	MTWVRQAPGKGLEWVGV(SEQ ID NO:285)	IRSKTYGGTT(SEQ ID NO:286)	EYAAPLRGRFSISRDDSKNTLYLQMNSLRAEDTAVYYC(SEQ ID NO:287)	AKGAAYGPFDY(SEQ ID NO:288)	WGQGTLITVSS(SEQ ID NO:289)

		ID NO:3)							
A3	Y026	QVQLVESGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:5)	QVQLVESGGGLVKPGRSLRLSCTAS(SEQ ID NO:290)	GFTFGDYA(SEQ ID NO:291)	MSWFRQAPGKGLEWVGF(SEQ ID NO:292)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A4	Y031	QVQLVQSGGGVVQPGRSLKLSCETSGFTFNMHPMHWVRQAPGKGLEWVASIKYDGSKRYYTDSVKGRFTVSRDHVDTVYLQMNSLRAEDTAVYYCSCNGLGQDDEAFDIWGQGTMVTVSS(SEQ ID NO:7)	QVQLVQSGGGVVQPGRSLKLSCETS(SEQ ID NO:297)	GFTFNMHP(SEQ ID NO:298)	MHWVRQAPGKGLEWVAS(SEQ ID NO:299)	IKYDGSK(SEQ ID NO:300)	RYYTDSVKGRFTVSRDHVDTVYLQMNSLRAEDTAVYYC(SEQ ID NO:301)	SCNGLGQDDEAFDI(SEQ ID NO:302)	WGQGTMVTVSS(SEQ ID NO:296)
A5	Y041	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYGMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRSEDTAVYYCTRYLHRLPFDVWGKGTTVTVSS(SEQ ID NO:9)	QVQLVESGGGLVQPGRSLRLSCAAS(SEQ ID NO:303)	GFTFDDYG(SEQ ID NO:304)	MHWVRQAPGKGLEWVSG(SEQ ID NO:278)	ISWNSGSI(SEQ ID NO:305)	GYADSVKGRFTISRDNAKNSLYLQMNSLRSEDTAVYYC(SEQ ID NO:306)	TRYLHRLPFDV(SEQ ID NO:307)	WGKGTTVTVSS(SEQ ID NO:308)
A6	Y060	QVQLVESGGDWVEPGRSLRLSCRTSGFTFADYALNWVRQAPGKGLEWVGFIRSKTYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARRGGWTLGYAFDIWGQGTMITVSS(SEQ ID NO:11)	QVQLVESGGDWVEPGRSLRLSCRTS(SEQ ID NO:309)	GFTFADYA(SEQ ID NO:310)	LNWVRQAPGKGLEWVGF(SEQ ID NO:311)	IRSKTYGGTT(SEQ ID NO:286)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARRGGWTLGYAFDI(SEQ ID NO:312)	WGQGTMITVSS(SEQ ID NO:313)
A7	Y062	QMQLVESGGGL	QMQL	GFTFG	MSWV	IRSKA	EYAAS	ARIV	WGQG

		VKPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRNDSKSIAYLQMNSLRAEDTAVYYCARIVAYGPFDYWGQGALVTVSS(SEQ ID NO:13)	VESGGGLVKPGRSLRLSCTAS(SEQ ID NO:314)	DYA(SEQ ID NO:291)	RQAPGKGLEWVGF(SEQ ID NO:315)	YGGTT(SEQ ID NO:293)	VKGRFTISRNDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:316)	AYGPFDY(SEQ ID NO:317)	ALVTVSS(SEQ ID NO:318)
A8	Y063	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGRSRNKANSHTTEYAASVKGRFTISRDDSKKSLYLQMNSLRAEDTAVYYCARGGAWLDYWGQGTLVTVSS(SEQ ID NO:15)	QVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:319)	GFTFSDHY(SEQ ID NO:320)	MDWVRQAPGKGLEWVGR(SEQ ID NO:321)	SRNKANSHTT(SEQ ID NO:322)	EYAASVKGRFTISRDDSKKSLYLQMNSLRAEDTAVYYC(SEQ ID NO:323)	ARGGAWLDY(SEQ ID NO:324)	WGQGTLVTVSS(SEQ ID NO:282)
A9	Y065	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDFAMTWVRQAPGKGLEWVSSISGTSGRTYYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYCARGSPSGSADYWGQGTLVTVSS(SEQ ID NO:17)	QMQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:325)	GFTFSDFA(SEQ ID NO:326)	MTWVRQAPGKGLEWVSS(SEQ ID NO:327)	ISGTSGRT(SEQ ID NO:328)	YYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYC(SEQ ID NO:329)	ARGSPSGSADY(SEQ ID NO:330)	WGQGTLVTVSS(SEQ ID NO:282)
A10	Y090	QVQLVESGGGLVQPGRSLRLSCTGSGFTFGDYVMNWVRQVPGKGLEWVGFIRSKGYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:19)	QVQLVESGGGLVQPGRSLRLSCTGS(SEQ ID NO:331)	GFTFGDYV(SEQ ID NO:332)	MNWVRQVPGKGLEWVGF(SEQ ID NO:333)	IRSKGYGGTT(SEQ ID NO:334)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A11	Y091	QVQLVQSGGGLVQPGRSLRLSCTASGITFGDYAMSWVRQAPGKGL	QVQLVQSGGGLVQPGRS	GITFGDYA(SEQ ID NO:336	MSWVRQAPGKGLEWVG	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSI	ARDGNYYDSRGYYYDT	WGQGTMVTVSS(SEQ ID

		EWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:21)	LRLSCTAS(SEQ ID NO:335)	)	F(SEQ ID NO:315)		AYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	FDL(SEQ ID NO:295)	NO:296)
A12	Y092	QMQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDLRNGETIYAQRFQGRVTMSGDTATDTAYMELSSLRSEDTAVYYCARSYYDILTGYYRDAFDIWGQGTMVTVSS(SEQ ID NO:23)	QMQLVQSGAEVKKPGASVKVSCKVS(SEQ ID NO:337)	GYTLTELS(SEQ ID NO:338)	MHWVRQAPGKGLEWMGG(SEQ ID NO:339)	FDLRNGET(SEQ ID NO:340)	IYAQRFQGRVTMSGDTATDTAYMELSSLRSEDTAVYYC(SEQ ID NO:341)	ARSYYDILTGYYRDAFDI(SEQ ID NO:342)	WGQGTMVTVSS(SEQ ID NO:296)
A13	Y097	QMQLVQSGAEVQKPGASVKVSCKASGNTFNGYYIHWVRQAPGQGLEWMGIINPSGSSTFYAQKFRGRVTMTKDTSTSTVYMKLSSLRSEDTAVYYCAQEGWTEQHPYAEYLQNWGQGTLVTVSS(SEQ ID NO:25)	QMQLVQSGAEVQKPGASVKVSCKAS(SEQ ID NO:343)	GNTFNGYY(SEQ ID NO:344)	IHWVRQAPGQGLEWMGI(SEQ ID NO:345)	INPSGSST(SEQ ID NO:346)	FYAQKFRGRVTMTKDTSTSTVYMKLSSLRSEDTAVYYC(SEQ ID NO:347)	AQEGWTEQHPYAEYLQN(SEQ ID NO:348)	WGQGTLVTVSS(SEQ ID NO:282)
A14	Y098	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRDYYYDTFDLWGQGTMVTVSS(SEQ ID NO:27)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWIGF(SEQ ID NO:350)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRDYYYDTFDL(SEQ ID NO:353)	WGQGTMVTVSS(SEQ ID NO:296)
A15	Y099	QVQLVESGGGAVKPGGSLRLSCEASGFTFSDYYMSWIRQAPGKGL	QVQLVESGGGAVKPGGSL	GFTFSDYY(SEQ ID NO:355	MSWIRQAPGKGLEWVA	ISGVNSFT(SEQ ID NO:357)	NYAASVEGRFTISRDNARNS	ARDGNYYDSRGYYYDT	WGQGTLVTVSS(SEQ ID

		EWVADISGVNSFTNYAASVEGRFTISRDNARNSLYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:29)	RLSCEAS(SEQ ID NO:354)	)	D(SEQ ID NO:356)		LYLQMNSLRAEDTAVYYC(SEQ ID NO:358)	FDM(SEQ ID NO:359)	NO:282)
A16	Y100	QMQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGDYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:31)	QMQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:360)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGDYYDSRGYYYDTFDL(SEQ ID NO:361)	WGQGTMITVSS(SEQ ID NO:313)
A17	Y102	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCAKDADFYDNSGYYDDAFDIWGQGTMVTVSS(SEQ ID NO:33)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	AKDADFYDNSGYYDDAFDI(SEQ ID NO:362)	WGQGTMVTVSS(SEQ ID NO:296)
A18	Y105	QVQLVESGGGLVQPGRSLRLSCATSGFTFGDYAMSWVRQAPGRGLEWVGFIRSKPHGGTTDFAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:35)	QVQLVESGGGLVQPGRSLRLSCATS(SEQ ID NO:363)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGRGLEWVGF(SEQ ID NO:364)	IRSKPHGGTT(SEQ ID NO:365)	DFAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:366)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A19	Y107	QVQLVQSGGGLVKPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGL	QVQLVQSGGGLVKPGRS	GFTFGDYA(SEQ ID NO:291	MSWVRQAPGKGLEWVG	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSI	ARDGNYYDSRGYYYDT	WGQGTTVTVSS(SEQ ID

		EWVGFIRSKAY GGTTEYAASVK GRFTISRDDSKSI AYLQMNSLRAE DTAVYYCARDG NYYDSRGYYYD TFDLWGQGTTV TVSS(SEQ ID NO:37)	LRLSC TAS(S EQ ID NO:367)	)	F(SEQ ID NO:315)		AYLQ MNSLR AEDTA VYYC(SEQ ID NO:294)	FDL(S EQ ID NO:29 5)	NO:36 8)
A20	Y112	QVQLVESGGGLI QPGGSLRLSCA ASGLTSSTYAM NWVRQAPGKG LEWVAGVSASG GSAYYAESVKG RFTISRDNSNNT VFLQMNSLRAE DTAVYYCARHL AWGGMDVWG QGTTITVSS(SEQ ID NO:39)	QVQL VESGG GLIQP GGSLR LSCAA S(SEQ ID NO:369)	GLTSS TYA(S EQ ID NO:370)	MNWV RQAP GKGL EWVA G(SEQ ID NO:371)	VSASG GSA(SE Q ID NO:372)	YYAES VKGRF TISRD NSNNT VFLQ MNSLR AEDTA VYYC(SEQ ID NO:373)	ARHL AWG GMD V(SE Q ID NO:37 4)	WGQG TTITV SS(SE Q ID NO:37 5)
A21	Y122	QMQLVESGGGL VQPGRSLRLSCT ASGFTFGDYAM SWVRQAPGKGL EWVGFIRSKAY GGTTEYAASVK GRFTISRDDSKSI AYLQMNSLRAE DTAVYYCARDG NYYDSRGYYYD TFDLWGQGTM VTVSS(SEQ ID NO:41)	QMQL VESGG GLVQP GRSLR LSCTA S(SEQ ID NO:360)	GFTFG DYA(S EQ ID NO:291)	MSWV RQAP GKGL EWVG F(SEQ ID NO:315)	IRSKA YGGTT (SEQ ID NO:293)	EYAAS VKGRF TISRD DSKSI AYLQ MNSLR AEDTA VYYC(SEQ ID NO:294)	ARDG NYYD SRGY YYDT FDL(S EQ ID NO:29 5)	WGQG TMVT VSS(S EQ ID NO:29 6)
A22	Y123	QVQLVESGGGL VKPGGSLRLSC AASGFTFSDYY MSWIRQAPGKG LEWVSYISSSGS TIYYADSVKGRF TISRDNAKNSLY LQMNSLRAEDT AVYYCARATYY DILTGYYNDGY FDYWGQGTLVT VSS(SEQ ID NO:43)	QVQL VESGG GLVKP GGSLR LSCAA S(SEQ ID NO:376)	GFTFS DYY(S EQ ID NO:355)	MSWI RQAP GKGL EWVS Y(SEQ ID NO:377)	ISSSGS TI(SEQ ID NO:378)	YYADS VKGRF TISRD NAKNS LYLQ MNSLR AEDTA VYYC(SEQ ID NO:379)	ARAT YYDI LTGY YNDG YFDY (SEQ ID NO:38 0)	WGQG TLVT VSS(S EQ ID NO:28 2)
A23	Y124	QMQLVESGGGL VQPGRSLRLSCA ASGFNFNTYAM HWVRQAPGRGL EWVGFIRSKAY	QMQL VESGG GLVQP GRSLR LSCAA	GFNFN TYA(S EQ ID NO:382)	MHWV RQAP GRGLE WVGF(SEQ ID	IRSKA YGGTT (SEQ ID NO:293)	EYAAS VKGRF TISRD DSKSI AYLQ	ARDG NYYD SRGY YYDT FDL(S	WGQG TMVT VSS(S EQ ID NO:29

		GGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:45)	S(SEQ ID NO:381)		NO:383)		MNSLRAEDTAVYYC(SEQ ID NO:294)	EQ ID NO:295)	6)
A24	Y125	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKTYGGTTEYAASVTGRFTISRDDSRGIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:47)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKTYGGTT(SEQ ID NO:286)	EYAASVTGRFTISRDDSRGIAYLQMNSLRAEDTAVYYC(SEQ ID NO:384)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)
A25	Y126	QVQLVESGGGLIQPGRSLRLSCTTSGFTFGDYAMSWVRQAPGKGLEWVGFIRTKTYGGTPEYAASLKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCVRDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:49)	QVQLVESGGGLIQPGRSLRLSCTTS(SEQ ID NO:385)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRTKTYGGTP(SEQ ID NO:386)	EYAASLKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:387)	VRDGNYYDSRGYYYDTFDL(SEQ ID NO:388)	WGQGTMITVSS(SEQ ID NO:313)
A26	Y127	QVQLVESGGGLIQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:51)	QVQLVESGGGLIQPGRSLRLSCTAS(SEQ ID NO:389)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)
A27	Y096	QVQLVESGGDLVKPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAY	QVQLVESGGDLVKPGRSLRLSCTA	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQ	ARDGNYYDSRGYYYDTFDL(S	WGQGTMITVSS(SEQ ID NO:31

		GGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:53)	S(SEQ ID NO:390)		ID NO:315)		MNSLRAEDTAVYYC(SEQ ID NO:294)	EQ ID NO:295)	3)
A28	Y108	QVQLVESGGGLVPPGGSLRLSCAASGFSFSDHYMDWVRQAPGKGLEWVGFIRSAAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:55)	QVQLVESGGGLVPPGGSLRLSCAAS(SEQ ID NO:391)	GFSFSDHY(SEQ ID NO:392)	MDWVRQAPGKGLEWVGF(SEQ ID NO:393)	IRSAAYGGTT(SEQ ID NO:394)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A29	Y132	QVQLVQSGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:57)	QVQLVQSGGGLVQPGRSLRLSCTAS(SEQ ID NO:335)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A30	Y133	QVQLVESGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVGFIRSKAYGGTTEHAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:59)	QVQLVESGGGLVKPGRSLRLSCTAS(SEQ ID NO:290)	GFTFGDYA(SEQ ID NO:291)	MSWFRQAPGKGLEWVGF(SEQ ID NO:292)	IRSKAYGGTT(SEQ ID NO:293)	EHAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:395)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A31	Y140	QMQLVESGGGLVQPGRSLRLSCTASGFTFRDYAMSWVRQAPGKGLEWIGFIRSKAYG	QMQLVESGGGLVQPGRSLRLSCTA	GFTFRDYA(SEQ ID NO:396)	MSWVRQAPGKGLEWIGF(SEQ	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQ	ARDGNYYDSRGYYYDTFDL(S	WGQGTMVTVSS(SEQ ID NO:29

		GTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:61)	S(SEQ ID NO:360)		ID NO:350)		MNSLRAEDTAVYYC(SEQ ID NO:294)	EQ ID NO:295)	6)
A32	Y145	QVQLVESGGGVVQPGGSLRLSCDVSGLTFSIYGMHWVRQAPGKGLEWVAVIGYDGGNSFYAESVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSLGTFDIWGQGTVVTVSS(SEQ ID NO:63)	QVQLVESGGGVVQPGGSLRLSCDVS(SEQ ID NO:397)	GLTFSIYG(SEQ ID NO:398)	MHWVRQAPGKGLEWVAV(SEQ ID NO:399)	IGYDGGNS(SEQ ID NO:400)	FYAESVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC(SEQ ID NO:401)	ARGSLGTFDI(SEQ ID NO:402)	WGQGTVVTVSS(SEQ ID NO:403)
A33	Y559	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQTRLGPTTFDYWGQGSLVTVSS(SEQ ID NO:65)	QVQLVESGGGVVQPGRSLRLSCAAS(SEQ ID NO:404)	GFTFSSYA(SEQ ID NO:405)	MHWVRQAPGKGLEWVAV(SEQ ID NO:399)	ISYDGSNK(SEQ ID NO:406)	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC(SEQ ID NO:407)	ARDQTRLGPTTFDY(SEQ ID NO:408)	WGQGSLVTVSS(SEQ ID NO:409)
A34	Y569	QVQLVESGAEVKKPGESLKISCKGSGYSFTSFWISWVRQMPGKGLEWMGRIDPSDGYTSYSPSFQGHVTISVDKSINTAYLQWNSLKASDTAMYYCARHNRKTLGRVDVWGQGTTVTVSS(SEQ ID NO:67)	QVQLVESGAEVKKPGESLKISCKGS(SEQ ID NO:410)	GYSFTSFW(SEQ ID NO:411)	ISWVRQMPGKGLEWMGR(SEQ ID NO:412)	IDPSDGYT(SEQ ID NO:413)	SYSPSFQGHVTISVDKSINTAYLQWNSLKASDTAMYYC(SEQ ID NO:414)	ARHNRKTLGRVDV(SEQ ID NO:415)	WGQGTTVTVSS(SEQ ID NO:368)
A35	Y683	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLTWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:29	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416	GFNFGDYP(SEQ ID NO:417)	LTWVRQAPGKGLEWIGF(SEQ ID NO:418)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

		TAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:69)	)				SEQ ID NO:352)		
A36	Y705	QVQLVESGGGVVQPGGSLRLSCAASGFNFENYAMHWVRQVPGKGLEWVSLISGDGSSTHYTDSLRGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCARGGGKLDYWGQGTLVTVSS(SEQ ID NO:71)	QVQLVESGGGVVQPGGSLRLSCAAS(SEQ ID NO:419)	GFNFENYA(SEQ ID NO:420)	MHWVRQVPGKGLEWVSL(SEQ ID NO:421)	ISGDGSST(SEQ ID NO:422)	HYTDSLRGRFTISRDNSKNSLYLQMNSLRAEDTAVYYC(SEQ ID NO:423)	ARGGGKLDY(SEQ ID NO:424)	WGQGTLVTVSS(SEQ ID NO:282)
A37	Y711	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:73)	QVQLVQSGGGLVQPGGSLRLSCAAS(SEQ ID NO:425)	GFTFSDHY(SEQ ID NO:320)	MDWVRQAPGKGLEWVGF(SEQ ID NO:393)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A38	Y712	QVQLVESGGGLIQPGRSLRLSCRTSGFSFGDYAMTWVRQAPGKGLEWVGFIRSKRFGGTTEYAASVKGRFTISRDDSTSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:75)	QVQLVESGGGLIQPGRSLRLSCRTS(SEQ ID NO:426)	GFSFGDYA(SEQ ID NO:427)	MTWVRQAPGKGLEWVGF(SEQ ID NO:428)	IRSKRFGGTT(SEQ ID NO:429)	EYAASVKGRFTISRDDSTSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:430)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A39	Y715	QVQLVESGGGLVQPGHSLRLSCTSSGFNFGDHAVSWVRQAPGKGLEWVGFIRSKTYGGTPEYAASVKDRFSISRDDSKSSAYLQMNSLRAEDTAVYYCARD	QVQLVESGGGLVQPGHSLRLSCTSS(SEQ ID NO:431)	GFNFGDHA(SEQ ID NO:432)	VSWVRQAPGKGLEWVGF(SEQ ID NO:433)	IRSKTYGGTP(SEQ ID NO:434)	EYAASVKDRFSISRDDSKSSAYLQMNSLRAEDTAVYYC(SEQ ID	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)

		GNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:77)					NO:435)		
A40	Y716	QVQLVESGGGLVQPGRSLRLSCTASGFIFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTDYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:79)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFIFGDYA(SEQ ID NO:436)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	DYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:437)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A41	Y719	QVQLVESGGGLVQPGRSLRISCKASGFNFGDYPLTWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:81)	QVQLVESGGGLVQPGRSLRISCKAS(SEQ ID NO:438)	GFNFGDYP(SEQ ID NO:417)	LTWVRQAPGKGLEWIGF(SEQ ID NO:418)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A42	Y722	QMQLVQSGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:83)	QMQLVQSGGGLVKPGRSLRLSCTAS(SEQ ID NO:439)	GFTFGDYA(SEQ ID NO:291)	MSWFRQAPGKGLEWVGF(SEQ ID NO:292)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A43	Y723	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCA	QMQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:325)	GFTFSDHY(SEQ ID NO:320)	MDWVRQAPGKGLEWVGF(SEQ ID NO:393)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)

		RDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:85)					NO:294)		
A44	Y727	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:87)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A45	Y728	QMQLVESGGDLVQPGRSLRLSCRTSGFTFGEYAMSWVRQAPGKGLEWVGFIRSKAFGGTPEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:89)	QMQLVESGGDLVQPGRSLRLSCRTS(SEQ ID NO:440)	GFTFGEYA(SEQ ID NO:441)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAFGGTP(SEQ ID NO:442)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A46	Y735	QVQLVESGGGLIHPGESLRLSCAASGFSFSSHAMSWVRQAPGKGLEWVATISETGGIAFYADSVKGLFTISRDNSKNTLSLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTVVTVSS(SEQ ID NO:91)	QVQLVESGGGLIHPGESLRLSCAAS(SEQ ID NO:443)	GFSFSSHA(SEQ ID NO:444)	MSWVRQAPGKGLEWVAT(SEQ ID NO:445)	ISETGGIA(SEQ ID NO:446)	FYADSVKGLFTISRDNSKNTLSLQMNSLRAEDTAVYYC(SEQ ID NO:447)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTVVTVSS(SEQ ID NO:403)
A47	Y738	QVQLVQSGGGVVQPGTSLRLSCAASGFTFSSSTMHWVRQAPGKGLEWVAGFSYDGDTQWYADSVKGRFTISRDNSRNTLYLQMNSLRSEDTAVYYCARENVA	QVQLVQSGGGVVQPGTSLRLSCAAS(SEQ ID NO:448)	GFTFSSST(SEQ ID NO:449)	MHWVRQAPGKGLEWVAG(SEQ ID NO:450)	FSYDGDTQ(SEQ ID NO:451)	WYADSVKGRFTISRDNSRNTLYLQMNSLRSEDTAVYYC(SEQ ID	ARENVAADWFDA(SEQ ID NO:453)	WGQGALITVSS(SEQ ID NO:454)

		ADWFDAWGQGALITVSS(SEQ ID NO:93)					NO:452)		
A48	Y741	QVQLVESGGGWVQPGGSLRLSCAGSGFTTNSYTMAWVRQAPGKGLEWVSSISSSTNYMYYADSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:95)	QVQLVESGGGWVQPGGSLRLSCAGS(SEQ ID NO:455)	GFTTNSYT(SEQ ID NO:456)	MAWVRQAPGKGLEWVSS(SEQ ID NO:457)	ISSSTNYM(SEQ ID NO:458)	YYADSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYC(SEQ ID NO:459)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)
A49	Y748	QVQLVESGGGLVKPGGSLRLSCAASGFTFGDYYMNWIRQAPGKGLEWVAYISSSSAYTRYADSVKGRFTISRDNTKNSLYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:97)	QVQLVESGGGLVKPGGSLRLSCAAS(SEQ ID NO:376)	GFTFGDYY(SEQ ID NO:460)	MNWIRQAPGKGLEWVAY(SEQ ID NO:461)	ISSSSAYT(SEQ ID NO:462)	RYADSVKGRFTISRDNTKNSLYLQMNSLRAEDTAVYYC(SEQ ID NO:463)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A50	Y758	QVQLVESGGVAVQPGGSLRLSCTASGFTLDDYSMHWVRQRPGKGLEWVSVIYTGGNTYYSESVKGRFNIARDNSKNSLYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:99)	QVQLVESGGVAVQPGGSLRLSCTAS(SEQ ID NO:464)	GFTLDDYS(SEQ ID NO:465)	MHWVRQRPGKGLEWVSV(SEQ ID NO:466)	IYTGGNT(SEQ ID NO:467)	YYSESVKGRFNIARDNSKNSLYLQMNSLRAEDTAVYYC(SEQ ID NO:468)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A51	Y765	QVQLVQSGAEVKKPGASVKVSCKVSGYTLSELSIHWVRQAPGKGLEWMGRFDPEDGETSYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCARDGNYYDSRGYYYD	QVQLVQSGAEVKKPGASVKVSCKVS(SEQ ID NO:469)	GYTLSELS(SEQ ID NO:470)	IHWVRQAPGKGLEWMGR(SEQ ID NO:471)	FDPEDGET(SEQ ID NO:472)	SYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYC(SEQ ID NO:473	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)

		TFDMWGQGTLVTVSS(SEQ ID NO:100)					)		
A52	Y769	QVQLVESGGGLIQPGRSLRLSCVGSGFKFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFDISRDDSESIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:103)	QVQLVESGGGLIQPGRSLRLSCVGS(SEQ ID NO:474)	GFKFGDYA(SEQ ID NO:475)	MSWVRQAPGKGLEWVGF(SEQ ID NO:315)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFDISRDDSESIAYLQMNSLRAEDTAVYYC(SEQ ID NO:476)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A53	Y781	QVQLVQSGAEVKKPGASVKLSCKASGYTFSSYWMHWVRQAPGQRLEWMGEINPGNGHTNYNEKFKSRVTITVDKSASTAYMELSSLRSEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLVTVSS(SEQ ID NO:105)	QVQLVQSGAEVKKPGASVKLSCKAS(SEQ ID NO:477)	GYTFSSYW(SEQ ID NO:478)	MHWVRQAPGQRLEWMGE(SEQ ID NO:479)	INPGNGHT(SEQ ID NO:480)	NYNEKFKSRVTITVDKSASTAYMELSSLRSEDTAVYYC(SEQ ID NO:481)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLVTVSS(SEQ ID NO:282)
A54	Y813	QMQLVESGGGFVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGRGLEWLGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:107)	QMQLVESGGGFVQPGRSLRLSCTAS(SEQ ID NO:482)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGRGLEWLGF(SEQ ID NO:483)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A55	Y829	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDT	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

		FDLWGQGTMITVSS(SEQ ID NO:109)					)		
A56	Y842	QMQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLTWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDMWGQGTLITVSS(SEQ ID NO:111)	QMQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:485)	GFNFGDYP(SEQ ID NO:417)	LTWVRQAPGKGLEWIGF(SEQ ID NO:418)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDM(SEQ ID NO:359)	WGQGTLITVSS(SEQ ID NO:289)
A57	Y843	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYALNWVRQAPGKGLEWVGFIRSQTYGGTTEYAASVKGRFTISRDDSRSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSS(SEQ ID NO:113)	QVQLVESGGGLVQPGRSLRLSCTAS(SEQ ID NO:349)	GFTFGDYA(SEQ ID NO:291)	LNWVRQAPGKGLEWVGF(SEQ ID NO:311)	IRSQTYGGTT(SEQ ID NO:486)	EYAASVKGRFTISRDDSRSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:487)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMVTVSS(SEQ ID NO:296)
A58	S001	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGYYMSWVRQAPGKGLEWVSSISPSGSSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSPGFDYWGQGTLVTVSS(SEQ ID NO:115)	EVQLLESGGGLVQPGGSLRLSCAAS(SEQ ID NO:488)	GFTFSGYY(SEQ ID NO:489)	MSWVRQAPGKGLEWVSS(SEQ ID NO:490)	ISPSGSSI(SEQ ID NO:491)	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC(SEQ ID NO:407)	AKGSPGFDY(SEQ ID NO:492)	WGQGTLVTVSS(SEQ ID NO:282)
A59	Y1471	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMIT	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

		VSS(SEQ ID NO:109)							
A60	Y1471.1	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:118)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A61	Y1494	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKRIGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:119)	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKRIGGTT(SEQ ID NO:494)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A62	Y1494.1	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKRIGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:120)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKRIGGTT(SEQ ID NO:494)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A63	Y1494.2	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKRYGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMI	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKRYGGTT(SEQ ID NO:495)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

		TVSS(SEQ ID NO:121)							
A64	Y1501	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKTVGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:122)	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKTVGGTT(SEQ ID NO:496)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A65	Y1501.1	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKTVGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:123)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKTVGGTT(SEQ ID NO:496)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A66	Y1501.2	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKTYGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:124)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRDKTYGGTT(SEQ ID NO:497)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A67	Y1502	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRPKWLGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMI	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRPKWLGGTT(SEQ ID NO:498)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

		TVSS(SEQ ID NO:125)							
A68	Y1502.1	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRPKWLGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:126)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRPKWLGGTT(SEQ ID NO:498)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A69	Y829.2	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:118)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
A82	Y829 VH-VL cross	VL1	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR-4
		DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:780)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)

[Table 12]

Part Number	Clone name; UNIT 1	VL1 or VH1 in HC	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
A1	Y004	QLVLTQPHSVSESPGKTVTISCARSSGSIASKYVQWYQQRPGSAPTAVIYE	QLVLTQPHSVSESPGKT	SGSIASKY(SEQ ID NO:500	VQWYQQRPGSAPTAVIY(SE	EDNQR(SEQ ID NO:50	PSGVPDRFSGSIDTSSNSASLTI	QSYDSSSVV(SEQ ID	FGGGTKLTVL(SEQ ID

		DNQRPSGVPDRFSGSIDTSSNSASLTISGLKTEDEADYYCQSYDSSSVVFGGGTKLTVL(SEQ ID NO:2)	VTISCARS(SEQ ID NO:499)	)	Q ID NO:501)	2)	SGLKTEDEADYYC(SEQ ID NO:503)	NO:504)	NO:505)
A2	Y025	NFMLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSVPITVIYEDDQRPSGVPDRFSGSIDSFSNSASLTITGLKTEDEAEYYCQSYDDNTVVFGGGTKLTVL(SEQ ID NO:4)	NFMLTQPHSVSESPGKTVTISCTRS(SEQ ID NO:506)	SGSIASKY(SEQ ID NO:500)	VQWYQQRPGSVPITVIY(SEQ ID NO:507)	EDDQR(SEQ ID NO:508)	PSGVPDRFSGSIDSFSNSASLTITGLKTEDEAEYYC(SEQ ID NO:509)	QSYDDNTVV(SEQ ID NO:510)	FGGGTKLTVL(SEQ ID NO:505)
A3	Y026	DIVMTQTPLSLHVTPGEPASISCRSSQSLLHSNGYNYLEWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCTQSIQVPYTFGQGTKLEIK(SEQ ID NO:6)	DIVMTQTPLSLHVTPGEPASISCRSS(SEQ ID NO:511)	QSLLHSNGYNY(SEQ ID NO:512)	LEWYLQKPGQSPQLLIY(SEQ ID NO:513)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	TQSIQVPYT(SEQ ID NO:516)	FGQGTKLEIK(SEQ ID NO:517)
A4	Y031	QLVLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYCQSYDSSSVVFGGGTKLTVL(SEQ ID NO:8)	QLVLTQPHSVSESPGKTVTISCTRS(SEQ ID NO:518)	SGSIASKY(SEQ ID NO:500)	VQWYQQRPGSAPTTVIY(SEQ ID NO:519)	EDNQR(SEQ ID NO:502)	PSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYC(SEQ ID NO:520)	QSYDSSSVV(SEQ ID NO:504)	FGGGTKLTVL(SEQ ID NO:505)
A5	Y041	NFMLTQPHSVSESPGKMVTISCTRSSGSIASKYVQWYQQRPGSAPITVIYEDNKRPSGVPDRFSGSIDSFSNSASLTITGLKTEDEADYYCQSYDDNTVVFGGGTKLTVL(SEQ ID NO:10)	NFMLTQPHSVSESPGKMVTISCTRS(SEQ ID NO:521)	SGSIASKY(SEQ ID NO:500)	VQWYQQRPGSAPITVIY(SEQ ID NO:522)	EDNKR(SEQ ID NO:523)	PSGVPDRFSGSIDSFSNSASLTITGLKTEDEADYYC(SEQ ID NO:1417)	QSYDDNTVV(SEQ ID NO:510)	FGGGTKLTVL(SEQ ID NO:505)
A6	Y060	SYELTQPLSVSVSPGQTATITCSGHQLGNRYLSWYQKKPGQSPVLLISQDTNRPSGIPERFSGSDSGTTATLTIRE	SYELTQPLSVSVSPGQTATITCSGH(SE	QLGNRY(SEQ ID NO:525)	LSWYQKKPGQSPVLLIS(SEQ ID NO:526)	QDT(SEQ ID NO:527)	NRPSGIPERFSGSDSGTTATLTIRETQAMDEADY	QAWDSTTAV(SEQ ID NO:529)	FGGGTKLTVL(SEQ ID NO:505)

		TQAMDEADYYC QAWDSTTAVFG GGTKLTVL(SEQ ID NO:12)	Q ID NO:524)				YC(SEQ ID NO:528)		
A7	Y062	DIQMTQSPSTLSA SVGDRVTITCRAS QSISSWLAWYQQ KPGIAPKLLIYQA STLETGVPLRFSG RGSGTEFTLTINS LQPDDFATYYCQ QYDDYSPLTFGG GTKVEIK(SEQ ID NO:14)	DIQM TQSPS TLSAS VGDR VTITC RAS(S EQ ID NO:530)	QSISS W(SEQ ID NO:531)	LAWY QQKPG IAPKLL IY(SEQ ID NO:532)	QAS(S EQ ID NO:533)	TLETG VPLRFS GRGSG TEFTLT INSLQP DDFAT YYC(SE Q ID NO:534)	QQYD DYSP LT(SE Q ID NO:535)	FGGG TKVE IK(SE Q ID NO:536)
A8	Y063	DIQMTQSPSSLSA SVGDRLTITCRAS QSILTYLNWYQQ KPGKAPKLLVYA ASSLQRGVPSRFS GRGSGTDFTLTIS GLQPDDFALYYC QQSYSSPYSFGPG TKVDIK(SEQ ID NO:16)	DIQM TQSPS SLSAS VGDR LTITC RAS(S EQ ID NO:537)	QSILT Y(SEQ ID NO:538)	LNWY QQKPG KAPKL LVY(SE Q ID NO:539)	AAS(S EQ ID NO:540)	SLQRG VPSRFS GRGSG TDFTLT ISGLQP DDFAL YYC(SE Q ID NO:541)	QQSY SSPYS (SEQ ID NO:542)	FGPG TKVD IK(SE Q ID NO:543)
A9	Y065	QLVLTQPHSVSES PGKTVTISCTRSS GSIASKYVQWYQ QRPGSAPTTVIYE DNQRPSGVPDRF SGSIDISSNSASLT ISGLKTEDEADY YCQSYDSSTVVF GGGTKLTVL(SEQ ID NO:18)	QLVL TQPH SVSES PGKT VTISC TRS(S EQ ID NO:518)	SGSIA SKY(S EQ ID NO:500)	VQWY QQRPG SAPTT VIY(SE Q ID NO:519)	EDNQ R(SEQ ID NO:502)	PSGVP DRFSGS IDISSNS ASLTIS GLKTE DEADY YC(SEQ ID NO:520)	QSYD SSTV V(SEQ ID NO:544)	FGGG TKLT VL(SE Q ID NO:505)
A10	Y090	DIVMTQTPLSLPV TPGEPASISCRSS QSLLHSNGYNYL DWYLQKPGQSPR LLIYSGSSRASGV PDRFSGSGSGTDF TLKISSVEAEDVG TYYCMQTLETPL TFGGGTKVEIK(S EQ ID NO:20)	DIVM TQTPL SLPVT PGEP ASISC RSS(S EQ ID NO:545)	QSLLH SNGY NY(SE Q ID NO:512)	LDWYL QKPGQ SPRLLI Y(SEQ ID NO:546)	SGS(S EQ ID NO:547)	SRASG VPDRFS GSGSG TDFTL KISSVE AEDVG TYYC(S EQ ID NO:548)	MQTL ETPLT (SEQ ID NO:549)	FGGG TKVE IK(SE Q ID NO:536)
A11	Y091	DIQMTQSPSSVFA SVGDRVTITCRAS QAISSWLAWYQQ KPGKAPKLLIYA TSYLQTGVPSRFS GSGSGTDFTLSIN NLQPEDSATYFC EQAHSFPLTFGPG	DIQM TQSPS SVFAS VGDR VTITC RAS(S EQ LIST	QAISS W(SEQ ID NO:551)	LAWY QQKPG KAPKL LIY(SE Q ID NO:552)	ATS(S EQ ID NO:553)	YLQTG VPSRFS GSGSG TDFTLS INNLQP EDSAT YFC(SE Q ID	EQAH SFPLT (SEQ ID NO:555)	FGPG TKVD IK(SE Q ID NO:543)

		TKVDIK(SEQ ID NO:22)	550)				NO:554)		
A12	Y092	DIQMTQSPDSLAVSLGERATINCNSSRSVLHSSSNQNYLAWYQQKPGQPPKLLISWASGRQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQCYSTPYTFGQGTKLDIK(SEQ ID NO:24)	DIQMTQSPDSLAVSLGERATINCNSS(SEQ ID NO:556)	RSVLHSSSNQNY(SEQ ID NO:557)	LAWYQQKPGQPPKLLIS(SEQ ID NO:558)	WAS(SEQ ID NO:559)	GRQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC(SEQ ID NO:560)	QQCYSTPYT(SEQ ID NO:561)	FGQGTKLDIK(SEQ ID NO:562)
A13	Y097	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYDASTLQPGVPSRFSGGGSGTDFTLTIRSSVQPEDYATYFCQQSYITPFAFGQGTKLEIK(SEQ ID NO:26)	DIQMTQSPSFLSASVGDRVTITCRAS(SEQ ID NO:563)	QYIGTY(SEQ ID NO:564)	LAWYQQQPGKAPKLLIY(SEQ ID NO:565)	DAS(SEQ ID NO:566)	TLQPGVPSRFSGGGSGTDFTLTIRSVQPEDYATYFC(SEQ ID NO:567)	QQSYITPFA(SEQ ID NO:568)	FGQGTKLEIK(SEQ ID NO:517)
A14	Y098	DIQMTQSPSSVSASVGDRVTITCRASQDISRWLAWYQQKPGKAPKLLIYAASILQTGVPSRFSGSGSGTDFTLSINNLQPEDSATYFCEQAHSFPLTFGPGTKVDIK(SEQ ID NO:28)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	QDISRW(SEQ ID NO:570)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	ILQTGVPSRFSGSGSGTDFTLSINNLQPEDSATYFC(SEQ ID NO:553)	EQAHSFPLT(SEQ ID NO:555)	FGPGTKVDIK(SEQ ID NO:543)
A15	Y099	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK(SEQ ID NO:30)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQALQTPRT(SEQ ID NO:572)	FGQGTKVEIK(SEQ ID NO:573)
A16	Y100	DIQMTQSPSSVSASVGDSVTITCRASQDISTWLAWYQQKPGRAPKVLIYAASRLQDGVSSRFSGSGSGTDFNLSISSLQPEDFATYYCQQANSFPLTFGGGTKVEIK(SEQ	DIQMTQSPSSVSASVGDSVTITCRAS(SEQ ID NO:574)	QDISTW(SEQ ID NO:575)	LAWYQQKPGRAPKVLIY(SEQ ID NO:576)	AAS(SEQ ID NO:540)	RLQDGVSSRFSGSGSGTDFNLSISSLQPEDFATYYC(SEQ ID NO:577)	QQANSFPLT(SEQ ID NO:578)	FGGGTKVEIK(SEQ ID NO:536)

		ID NO:32)							
A17	Y102	DIQMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASTRATGTPDRFSGSGSGTDFTLTISSLEPEDFAVYYCQQRAKWPATFGQGTKLDIK(SEQ ID NO:34)	DIQMTQSPATLSLSPGERATLSCRAS(SEQ ID NO:579)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	GAS(SEQ ID NO:582)	TRATGTPDRFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:583)	QQRAKWPAT(SEQ ID NO:584)	FGQGTKLDIK(SEQ ID NO:562)
A18	Y105	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQPPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQTPRTFGQGTKVEIK(SEQ ID NO:36)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQPPQLLIY(SEQ ID NO:585)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQTLQTPRT(SEQ ID NO:586)	FGQGTKVEIK(SEQ ID NO:573)
A19	Y107	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLDSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLHTLYTFGQGTKLDIK(SEQ ID NO:38)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LDS(SEQ ID NO:587)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQTLHTLYT(SEQ ID NO:588)	FGQGTKLDIK(SEQ ID NO:562)
A20	Y112	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYGASILQNGVPSRFSGSGSGTEFTLTITNLQPEDFASYYCQQLSSYPYTFGQGTKLDIK(SEQ ID NO:40)	DIQMTQSPSFLSASVGDRVTITCRAS(SEQ ID NO:563)	QYIGTY(SEQ ID NO:564)	LAWYQQQPGKAPKLLIY(SEQ ID NO:565)	GAS(SEQ ID NO:582)	ILQNGVPSRFSGSGSGTEFTLTITNLQPEDFASYYC(SEQ ID NO:589)	QQLSSYPYT(SEQ ID NO:590)	FGQGTKLDIK(SEQ ID NO:562)
A21	Y122	DIVMTQSPLSLPVIPGEPASISCRSSKSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLTISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK(SEQ ID NO:42)	DIVMTQSPLSLPVIPGEPASISCRSS(SEQ ID NO:591)	KSLLHSNGYNY(SEQ ID NO:592)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLTISRVEAEDVGVYYC(SEQ ID NO:593)	MQALQTPRT(SEQ ID NO:572)	FGQGTKVEIK(SEQ ID NO:573)

A22	Y123	DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYGASNLKSGVPSRFSGSGSGTHFTLTISSLHPEDFATYYCQQSYITQTWTFGQGTKVEIK(SEQ ID NO:44)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QSISNW(SEQ ID NO:595)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	GAS(SEQ ID NO:582)	NLKSGVPSRFSGSGSGTHFTLTISSLHPEDFATYYC(SEQ ID NO:596)	QQSYITQTWT(SEQ ID NO:597)	FGQGTKVEIK(SEQ ID NO:573)
A23	Y124	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVDIK(SEQ ID NO:46)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQALQTPRT(SEQ ID NO:572)	FGQGTKVDIK(SEQ ID NO:598)
A24	Y125	DIQMTQSPSSVSASVGDRVTITCRASQGIGNWLAWYQQKPGEAPNLLIYGASNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:48)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	QGIGNW(SEQ ID NO:599)	LAWYQQKPGEAPNLLIY(SEQ ID NO:600)	GAS(SEQ ID NO:582)	NLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:601)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A25	Y126	DIQMTQSPSSVSASVGDRVTITCRASQGISNWVAWYQQKPGKAPKLLIYAASTLHSGVPSRFSGSASGTDFTLTISSLQPEDFAIYYCQQGHSFPYTFGQGTKLEIK(SEQ ID NO:50)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	QGISNW(SEQ ID NO:603)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	AAS(SEQ ID NO:540)	TLHSGVPSRFSGSASGTDFTLTISSLQPEDFAIYYC(SEQ ID NO:605)	QQGHSFPYT(SEQ ID NO:606)	FGQGTKLEIK(SEQ ID NO:517)
A26	Y127	DIVMTQTPLSLPVTPGEPAFISCRSSQNLLHSNGYNYLDWYLQKPGQSPQLLIYMGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQPLQIPFTFGGGTKVEIK(SEQ ID NO:52)	DIVMTQTPLSLPVTPGEPAFISCRSS(SEQ ID NO:607)	QNLLHSNGYNY(SEQ ID NO:608)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	MGS(SEQ ID NO:609)	YRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:610)	MQPLQIPFT(SEQ ID NO:611)	FGGGTKVEIK(SEQ ID NO:536)
A27	Y096	DIVMTQTPLSLPVTPGEPASISCRSS	DIVMTQTPL	QSLLHSNGY	LDWYLQKPGQ	LGS(SEQ ID	NRASGVPDRFS	MHTLQLPFT	FGPGTKVE

		QSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTEFTLKISRVEAEDVGVYYCMHTLQLPFTFGPGTKVEIK(SEQ ID NO:54)	SLPVTPGEPASISCRSS(SEQ ID NO:545)	NY(SEQ ID NO:512)	SPQLLIY(SEQ ID NO:571)	NO:514)	GSGSGTEFTLKISRVEAEDVGVYYC(SEQ ID NO:612)	(SEQ ID NO:613)	IK(SEQ ID NO:614)
A28	Y108	DIQMTQSPSSLSASVGDKVTITCRASQGISSYLAWYQQKPGKAPKLLIYVASSLQTGVPSRFSGSRSGTDFTLTISSLQSEDFGTYYCQQSYRTPYTFGQGTKLEIK(SEQ ID NO:56)	DIQMTQSPSSLSASVGDKVTITCRAS(SEQ ID NO:615)	QGISSY(SEQ ID NO:616)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	VAS(SEQ ID NO:617)	SLQTGVPSRFSGSRSGTDFTLTISSLQSEDFGTYYC(SEQ ID NO:618)	QQSYRTPYT(SEQ ID NO:619)	FGQGTKLEIK(SEQ ID NO:517)
A29	Y132	DIQMTQSPSSVSASLGDRVTITCRASQDIGHWLAWYQQKPGKAPKHLIYAASSLHSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYCQQANSFPYTFGQGTKVDIK(SEQ ID NO:58)	DIQMTQSPSSVSASLGDRVTITCRAS(SEQ ID NO:620)	QDIGHW(SEQ ID NO:621)	LAWYQQKPGKAPKHLIY(SEQ ID NO:622)	AAS(SEQ ID NO:540)	SLHSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYC(SEQ ID NO:623)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVDIK(SEQ ID NO:598)
A30	Y133	DIVMTQTPLSLPVTPGEPASISCRSSQNLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQTLYTFGQGTKVEIK(SEQ ID NO:60)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QNLLHSNGYNY(SEQ ID NO:608)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQTLQTLYT(SEQ ID NO:624)	FGQGTKVEIK(SEQ ID NO:573)
A31	Y140	DIQMTQSPSSVSASVGDSVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIDSLQPEDFATYYCQQADSFPYTFGQGTKVEIK(SEQ ID NO:62)	DIQMTQSPSSVSASVGDSVTITCRAS(SEQ ID NO:574)	QGISSW(SEQ ID NO:625)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	SLQSGVPSRFSGSGSGTDFTLTIDSLQPEDFATYYC(SEQ ID NO:626)	QQADSFPYT(SEQ ID NO:627)	FGQGTKVEIK(SEQ ID NO:573)
A32	Y145	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKRLMY	DIQMTQSPSSVSASVGDR	QGISSW(SEQ ID NO:625	LAWYQQKPGKAPKRLMY(S	AAS(SEQ ID NO:540)	VLDAGVPSRFSGSGSGTDFTLT	QQGDSFPRT(SEQ ID	FGPGTKVDIK(SEQ ID

		AASVLDAGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQGDSFPRTFGPGTKVDIK(SEQ ID NO:64)	VTITCRAS(SEQ ID NO:569)	)	EQ ID NO:628)		VSSLQPEDFATYYC(SEQ ID NO:629)	NO:630)	NO:543)
A33	Y559	DIQMTQSPSTLSASVGDRVTITCRASQNVDKWLAWYQQKPGKAPKLLIYKASGLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDSYPLTFGGGTKVEIK(SEQ ID NO:66)	DIQMTQSPSTLSASVGDRVTITCRAS(SEQ ID NO:530)	QNVDKW(SEQ ID NO:631)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	KAS(SEQ ID NO:632)	GLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYC(SEQ ID NO:633)	QQYDSYPLT(SEQ ID NO:634)	FGGGTKVEIK(SEQ ID NO:536)
A34	Y569	QSALTQPPSASGSPGQSVTISCSGGSRDVGAYNYVSWYQQHPGKAPKLMIYEVNKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCTSFAGENNFGVFGGGTKLTVL(SEQ ID NO:68)	QSALTQPPSASGSPGQSVTISCSGG(SEQ ID NO:635)	SRDVGAYNY(SEQ ID NO:636)	VSWYQQHPGKAPKLMIY(SEQ ID NO:637)	EVN(SEQ ID NO:639)	KRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYC(SEQ ID NO:640)	TSFAGENNFGV(SEQ ID NO:641)	FGGGTKLTVL(SEQ ID NO:505)
A35	Y683	DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIYAASALESGVPSRFSASGYGTDFTLTISSLQPEDFATYFCQQGKSFPYTFGQGTKVEIK(SEQ ID NO:70)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	QGISNW(SEQ ID NO:603)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	ALESGVPSRFSASGYGTDFTLTISSLQPEDFATYFC(SEQ ID NO:642)	QQGKSFPYT(SEQ ID NO:643)	FGQGTKVEIK(SEQ ID NO:573)
A36	Y705	QAVVTQEPSFSVSPGGTVTLTCGLTSGSVSTSHFPSWYQQTPGQAPRTLIYFTDTHSSGVPDRFSGSILGNKAALTITGAQADDESDYYCVLYMGSGIYAFGTGTKVTVL(SEQ ID NO:72)	QAVVTQEPSFSVSPGGTVTLTCGLT(SEQ ID NO:644)	SGSVSTSHF(SEQ ID NO:645)	PSWYQQTPGQAPRTLIY(SEQ ID NO:646)	FTD(SEQ ID NO:647)	THSSGVPDRFSGSILGNKAALTITGAQADDESDYYC(SEQ ID NO:648)	VLYMGSGIYA(SEQ ID NO:649)	FGTGTKVTVL(SEQ ID NO:650)
A37	Y711	DIQMTQSPSSLSASVGDRVTITCRASQSISNYLNWYQQKPGKAPKLLMSAASSLQSGVPSRFSGSGSGTDFTLTIS	DIQMTQSPSSLSASVGDRVTITCRAS(S	QSISNY(SEQ ID NO:651)	LNWYQQKPGKAPKLLMS(SEQ ID NO:141	AAS(SEQ ID NO:540)	SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT	QQSYNTPRT(SEQ ID NO:653)	FGQGTKVDIK(SEQ ID NO:598)

		SLQPEDFATYYC QQSYNTPRTFGQ GTKVDIK(SEQ ID NO:74)	EQ ID NO:594)		8)		YYC(SEQ ID NO:652)		
A38	Y712	DIQMTQSPSSVSA SVGDRVTITCRAS QPISTWLVWYQH KPEKAPKLLIYA ASNLQSGVPSRFS GSGSGTDFTLTIN SLQPDDFATYYC QQANSFPYTFGQ GTKLDIK(SEQ ID NO:76)	DIQM TQSPS SVSAS VGDR VTITC RAS(SEQ ID NO:569)	QPIST W(SEQ ID NO:654)	LVWY QHKPE KAPKL LIY(SE Q ID NO:655)	AAS(SEQ ID NO:540)	NLQSG VPSRFS GSGSG TDFTLT INSLQP DDFAT YYC(SEQ ID NO:656)	QQAN SFPYT (SEQ ID NO:602)	FGQG TKLD IK(SEQ ID NO:562)
A39	Y715	DIVMTQTPLSLPV IPGEPASISCRSSQ SLLHSNGYNYLD WYLQKPGQSPQL LIYLGSNRASGVP DRFSGSGSGTDFT LKISRVEAEDVG VYYCMQTLQTL YTFGQGTKLEIK(SEQ ID NO:78)	DIVM TQTPL SLPVI PGEP ASISC RSS(SEQ ID NO:657)	QSLLH SNGY NY(SEQ ID NO:512)	LDWYL QKPGQ SPQLLI Y(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASG VPDRFS GSGSG TDFTL KISRVE AEDVG VYYC(SEQ ID NO:515)	MQTL QTLY T(SEQ ID NO:624)	FGQG TKLEI K(SEQ ID NO:517)
A40	Y716	DIQMTQSPSSLSA SVGDRITISCQAS QDIKNYLNWYQ KKPGKAPKLLIY GASNLAAGVPSR FSGSGYGTDFTFII SSGLQPEDVATYY CQQYEELAALTF GGGTKVEIK(SEQ ID NO:80)	DIQM TQSPS SLSAS VGDR ITISC QAS(SEQ ID NO:658)	QDIKN Y(SEQ ID NO:659)	LNWY QKKPG KAPKL LIY(SE Q ID NO:660)	GAS(SEQ ID NO:582)	NLAAG VPSRFS GSGYG TDFTFII SGLQPE DVATY YC(SEQ ID NO:661)	QQYE ELAA LT(SEQ ID NO:662)	FGGG TKVE IK(SEQ ID NO:536)
A41	Y719	DIQMTQSPSSLSA SVGDRVTITCRAS QSISSWLAWYQQ KPGKAPKLLIYTS STLQSEVPSRFSG SGSGTDFTLTISG LQPEDFATYYCQ QSYSLPRTFGPGT KVDIK(SEQ ID NO:82)	DIQM TQSPS SLSAS VGDR VTITC RAS(SEQ ID NO:594)	QSISS W(SEQ ID NO:531)	LAWY QQKPG KAPKL LIY(SE Q ID NO:552)	TSS(SEQ ID NO:663)	TLQSE VPSRFS GSGSG TDFTLT ISGLQP EDFAT YYC(SEQ ID NO:664)	QQSY SLPRT (SEQ ID NO:665)	FGPG TKVD IK(SEQ ID NO:543)
A42	Y722	DIQMTQSPSSVSA SIGDRITITCRASQ GISTWLAWYQQ KPGKAPKLLIYA ASSLHSGVPSRFS GSGSGTDFTLTIS SLQPDDFATYYC QQSYSIPRTFGQG	DIQM TQSPS SVSAS IGDRI TITCR AS(SEQ ID NO:66	QGIST W(SEQ ID NO:667)	LAWY QQKPG KAPKL LIY(SE Q ID NO:552)	AAS(SEQ ID NO:540)	SLHSG VPSRFS GSGSG TDFTLT ISSLQP DDFAT YYC(SEQ ID	QQSY SIPRT(SEQ ID NO:669)	FGQG TKVE IK(SEQ ID NO:573)

		TKVEIK(SEQ ID NO:84)	6)				NO:668)		
A43	Y723	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLGWYQQKPGRAPKLLIYAASSLQSGVPSRFRGSGSGTDFTLTISSLQPEDFATYYCLQDHDYPYTFGQGTKVEIK(SEQ ID NO:86)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QGIRNY(SEQ ID NO:670)	LGWYQQKPGRAPKLLIY(SEQ ID NO:671)	AAS(SEQ ID NO:540)	SLQSGVPSRFRGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:672)	LQDHDYPYT(SEQ ID NO:673)	FGQGTKVEIK(SEQ ID NO:573)
A44	Y727	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLEWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSLQTPPYTFGQGTKVEIK(SEQ ID NO:88)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LEWYLQKPGQSPQLLIY(SEQ ID NO:513)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQSLQTPPYT(SEQ ID NO:674)	FGQGTKVEIK(SEQ ID NO:573)
A45	Y728	DIQMTQSPSSVSASVGDRVTITCRASHDISSWLAWYQQKPGKAPKLLIYATSSLQNGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQGKSFPYTFGQGTKVEIK(SEQ ID NO:90)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	HDISSW(SEQ ID NO:675)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	ATS(SEQ ID NO:553)	SLQNGVPSRFSGSGSGTDFTLTISSLQPEDFATYFC(SEQ ID NO:676)	QQGKSFPYT(SEQ ID NO:643)	FGQGTKVEIK(SEQ ID NO:573)
A46	Y735	DIVMTQTPLSLPVTLGEPASISCRSSQSLLHTNGYNYLDWYLQKPGQSPQLLVYSASTRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQALQTPWTFGQGTKVEIK(SEQ ID NO:92)	DIVMTQTPLSLPVTLGEPASISCRSS(SEQ ID NO:677)	QSLLHTNGYNY(SEQ ID NO:678)	LDWYLQKPGQSPQLLVY(SEQ ID NO:679)	SAS(SEQ ID NO:680)	TRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYC(SEQ ID NO:681)	MQALQTPWT(SEQ ID NO:682)	FGQGTKVEIK(SEQ ID NO:573)
A47	Y738	QSALTQPASVSGSPGQSITFSCTGTSSDFGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNHFSGSKSGNTASLTISGLQAEDEADYYCSSFTGDSVIFGGGTKLTVL(SEQ ID NO:94)	QSALTQPASVSGSPGQSITFSCTGT(SEQ ID NO:683)	SSDFGGYNY(SEQ ID NO:684)	VSWYQQHPGKAPKLMIY(SEQ ID NO:637)	DVS(SEQ ID NO:685)	KRPSGVSNHFSGSKSGNTASLTISGLQAEDEADYYC(SEQ ID NO:686)	SSFTGDSVI(SEQ ID NO:687)	FGGGTKLTVL(SEQ ID NO:505)

A48	Y741	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVQAEDVGTYYCMQTLQTLPYTFGQGTKLEIK (SEQ ID NO:96)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVQAEDVGTYYC(SEQ ID NO:688)	MQTLQTLPYT(SEQ ID NO:689)	FGQGTKLEIK(SEQ ID NO:517)
A49	Y748	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYYYLDWYLQKPGQSPQVLIYLGSNRAPGVPDRFSGSGSGTDFTLKISRVEADDVGIYYCMQGLMTPFTFGPGTKLDIK(SEQ ID NO:98)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYYY(SEQ ID NO:690)	LDWYLQKPGQSPQVLIY(SEQ ID NO:691)	LGS(SEQ ID NO:514)	NRAPGVPDRFSGSGSGTDFTLKISRVEADDVGIYYC(SEQ ID NO:692)	MQGLMTPFT(SEQ ID NO:693)	FGPGTKLDIK(SEQ ID NO:694)
A50	Y758	DIVMTQTPLSLPVTPGGPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALRTPYTFGQGTKVDIK(SEQ ID NO:100)	DIVMTQTPLSLPVTPGGPASISCRSS(SEQ ID NO:695)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	LGS(SEQ ID NO:514)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQALRTPYT(SEQ ID NO:696)	FGQGTKVDIK(SEQ ID NO:598)
A51	Y765	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYMGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQTPYTFGQGTKVEIK(SEQ ID NO:102)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	MGS(SEQ ID NO:609)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQGLQTPYT(SEQ ID NO:697)	FGQGTKVEIK(SEQ ID NO:573)
A52	Y769	DIQMTQSPSSVSASVGDRVTITCRASQEITTWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQADSFPYTFGQGTKVEIK(SEQ ID NO:104)	DIQMTQSPSSVSASVGDRVTITCRAS(SEQ ID NO:569)	QEITTW(SEQ ID NO:698)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:652)	QQADSFPYT(SEQ ID NO:627)	FGQGTKVEIK(SEQ ID NO:573)
A53	Y781	DIVMTQTPLSLPVTPGEPASISCRSS	DIVMTQTPL	QSLLHSNGY	LGWYRQKPGQ	LGS(SEQ ID	NRAFGVPDRFS	MQALRTPY	FGQGAKLD

		QSLLHSNGYNYL GWYRQKPGQSP QLLIYLGSNRAFG VPDRFSGSGSGT DYTLKISRVEAE DVGVYYCMQAL RTPYTFGQGAKL DIK(SEQ ID NO:106)	SLPVT PGEP ASISC RSS(S EQ ID NO:54 5)	NY(SE Q ID NO:512)	SPQLLI Y(SEQ ID NO:700)	NO:51 4)	GSGSG TDYTL KISRVE AEDVG VYYC(S EQ ID NO:701)	T(SEQ ID NO:69 6)	IK(SE Q ID NO:70 2)
A54	Y813	DIQMTQSPSSVSA SVGDKVTIACRA SQGIVSWLAWYQ QKPGKAPRLLIY AASNLQDGVPSR FSGSGSGTVFTLT ISSLQPEDFATYY CQQANSFPYTFG QGTKLEIK(SEQ ID NO:108)	DIQM TQSPS SVSAS VGDK VTIAC RAS(S EQ ID NO:70 3)	QGIVS W(SEQ ID NO:704)	LAWY QQKPG KAPRL LIY(SE Q ID NO:705)	AAS(S EQ ID NO:54 0)	NLQDG VPSRFS GSGSG TVFTLT ISSLQP EDFAT YYC(SE Q ID NO:706)	QQAN SFPYT (SEQ ID NO:60 2)	FGQG TKLEI K(SEQ ID NO:51 7)
A55	Y829	DIQMTQSPSSVSA SVGDRVTLTCRA SQGIRSWLAWYQ QKPGKAPKLLIY AASNLQSGVPSR FSGSGSGTDFILTI NSLQPDDFATYY CQQANSFPYTFG QGTKVEIK(SEQ ID NO:110)	DIQM TQSPS SVSAS VGDR VTLT CRAS(SEQ ID NO:70 7)	QGIRS W(SEQ ID NO:708)	LAWY QQKPG KAPKL LIY(SE Q ID NO:552)	AAS(S EQ ID NO:54 0)	NLQSG VPSRFS GSGSG TDFILTI NSLQP DDFAT YYC(SE Q ID NO:709)	QQAN SFPYT (SEQ ID NO:60 2)	FGQG TKVE IK(SE Q ID NO:57 3)
A56	Y842	DIQMTQSPSSVSA SIGDRVTITCRAS EDISRQLAWYQQ KPGKAPKLLIYA ASSLQSGVPSRFS GSGSGTDFTLTIS SLQPEDFATYYC QQANSFPYTFGQ GTKLDIK(SEQ ID NO:112)	DIQM TQSPS SVSAS IGDR VTITC RAS(S EQ ID NO:71 0)	EDISR Q(SEQ ID NO:711)	LAWY QQKPG KAPKL LIY(SE Q ID NO:552)	AAS(S EQ ID NO:54 0)	SLQSG VPSRFS GSGSG TDFTLT ISSLQP EDFAT YYC(SE Q ID NO:652)	QQAN SFPYT (SEQ ID NO:60 2)	FGQG TKLD IK(SE Q ID NO:56 2)
A57	Y843	DIVMTQTPLSLPV TPGEPASISCRSS QSLLHTNGYNYL DWYLQKPGQSPQ LLVYSASTRASG VPDRFSGSGSGT DFTLKISRLEAED VGVYYCMQALQ TPWTFGQGTKVE IK(SEQ ID NO:114)	DIVM TQTPL SLPVT PGEP ASISC RSS(S EQ ID NO:54 5)	QSLLH TNGY NY(SE Q ID NO:678)	LDWYL QKPGQ SPQLL VY(SEQ ID NO:679)	SAS(S EQ ID NO:68 0)	TRASG VPDRFS GSGSG TDFTL KISRLE AEDVG VYYC(S EQ ID NO:712)	MQAL QTPW T(SEQ ID NO:68 2)	FGQG TKVE IK(SE Q ID NO:57 3)
A58	S001	QSVLTQPPSASG APGQRVTISCSGS SFNIGSNDVSWY	QSVL TQPPS ASGA	SFNIG SND(S EQ ID	VSWYQ QLPGT APKLLI	SDS(S EQ ID NO:71	HRPSG VPDRFS GSKSG	GSWD YSLS AYV(S	FGGG TKLT VL(SE

		QQLPGTAPKLLIYSDSHRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCGSWDYSLSAYVFGGGTKLTVL(SEQ ID NO:116)	PGQRVTISCSGS(SEQ ID NO:713)	NO:714)	Y(SEQ ID NO:715)	6)	TSASLAISGLQSEDEADYYC(SEQ ID NO:717)	EQ ID NO:718)	Q ID NO:505)
A59	Y1471	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYMGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTQLTFGGGTKVEIK(SEQ ID NO:117)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	MGS(SEQ ID NO:609)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQALQTQLT(SEQ ID NO:719)	FGGGTKVEIK(SEQ ID NO:536)
A60	Y1471.1	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYMGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTQLTFGGGTKVEIK(SEQ ID NO:117)	DIVMTQTPLSLPVTPGEPASISCRSS(SEQ ID NO:545)	QSLLHSNGYNY(SEQ ID NO:512)	LDWYLQKPGQSPQLLIY(SEQ ID NO:571)	MGS(SEQ ID NO:609)	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:515)	MQALQTQLT(SEQ ID NO:719)	FGGGTKVEIK(SEQ ID NO:536)
A61	Y1494	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A62	Y1494.1	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A63	Y1494.2	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSR	DIQMTQSPSSVSASVGDRVTLT	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQP	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)

		FSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	CRAS(SEQ ID NO:707)		NO:552)		DDFATYYC(SEQ ID NO:709)	2)	3)
A64	Y1501	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A65	Y1501.1	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A66	Y1501.2	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A67	Y1502	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A68	Y1502.1	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYY	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SE	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)

		CQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	NO:707)				Q ID NO:709)		
A69	Y829.2	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
A82	Y829 VH-VL cross	VH1	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
		QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:109)	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)

[Table 13]

Part Number	Clone name; UNIT1	SEQ ID NO (VH1 or VL1 in HC)	SEQ ID NO (VL1 or VH1 in LC)
A1	Y004	1419	1493
A2	Y025	1420	1494
A3	Y026	1421	1495
A4	Y031	1422	1496
A5	Y041	1423	1497
A6	Y060	1424	1498
A7	Y062	1425	1499
A8	Y063	1426	1500
A9	Y065	1427	1501
A10	Y090	1428	1502
A11	Y091	1429	1503
A12	Y092	1430	1504
A13	Y097	1431	1505
A14	Y098	1432	1506
A15	Y099	1433	1507
A16	Y100	1434	1508
A17	Y102	1435	1509
A18	Y105	1436	1510

A19	Y107	1437	1511
A20	Y112	1438	1512
A21	Y122	1439	1513
A22	Y123	1440	1514
A23	Y124	1441	1515
A24	Y125	1442	1516
A25	Y126	1443	1517
A26	Y127	1444	1518
A27	Y096	1445	1519
A28	Y108	1446	1520
A29	Y132	1447	1521
A30	Y133	1448	1522
A31	Y140	1449	1523
A32	Y145	1450	1524
A33	Y559	1451	1525
A34	Y569	1452	1526
A35	Y683	1453	1527
A36	Y705	1454	1528
A37	Y711	1455	1529
A38	Y712	1456	1530
A39	Y715	1457	1531
A40	Y716	1458	1532
A41	Y719	1459	1533
A42	Y722	1460	1534
A43	Y723	1461	1535
A44	Y727	1462	1536
A45	Y728	1463	1537
A46	Y735	1464	1538
A47	Y738	1465	1539
A48	Y741	1466	1540
A49	Y748	1467	1541
A50	Y758	1468	1542
A51	Y765	1469	1543
A52	Y769	1470	1544
A53	Y781	1471	1545
A54	Y813	1472	1546
A55	Y829	1473	1547
A56	Y842	1474	1548
A57	Y843	1475	1549
A58	S001	1476	1550
A59	Y1471	1473	1551
A60	Y1471.1	1477	1552
A61	Y1494	1478	1547
A62	Y1494.1	1479	1553
A63	Y1494.2	1480	1553
A64	Y1501	1481	1547
A65	Y1501.1	1482	1553
A66	Y1501.2	1483	1553
A67	Y1502	1484	1547

A68	Y1502.1	1485	1553
A69	Y829.2	1477	1553
A82	Y829 VH-VL cross	VL1	VH1
		1547	1473

In addition, in the present invention, the target of the first domain (first component, A) of the ReleaDome may be a protein that is specifically overexpressed in vascular cells, immune cells, basal cells, or cancer cells present in the microenvironment surrounding cancer tissue. Examples may include TEM8, albumin, KDR(VEGF2), PSMA, ICAM1, FAPα, and B7H3. The amino acid sequences of the heavy chain variable region (VH1) and the light chain variable region (VL1) of the antibody (Fv) that specifically binds to the protein are shown in Tables 14 and 15, respectively. The amino acid sequences of the antibodies below are described from the N-terminus to the C-terminus. In addition, the polynucleotides encoding the heavy chain variable region (VH1) and the light chain variable region (VL1) are shown in Table 16.

[Table 14]

Part Number	TME Target	Clone name; UNIT1	VH1	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
A70	TEM8	m825	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSS(SEQ ID NO:127)	QVQLVQSGAEVKKPGTSVKVSCKVP(SEQ ID NO:720)	GYTFSSYA(SEQ ID NO:721)	ISWVRQAPGQGLEWMGG(SEQ ID NO:722)	IIPIFGTT(SEQ ID NO:723)	NYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYC(SEQ ID NO:724)	ARDTDYMFDY(SEQ ID NO:725)	WGQGTLVTVSS(SEQ ID NO:282)
A71	Albumin	anti-Albumin	EVQLLESGGGLVQPGGSLRLSCAVSGIDLSNYAINWVRQAPGKGLEWIGIIWASGTTFYATWAKGRFTISRDNSKNTVYLQMNSLRAEDTAVYYCARTVPGYSTAPYFDLWGQGTLVTVSS(SEQ ID NO:129)	EVQLLESGGGLVQPGGSLRLSCAVS(SEQ ID NO:726)	GIDLSNYA(SEQ ID NO:727)	INWVRQAPGKGLEWIGI(SEQ ID NO:728)	IWASGTT(SEQ ID NO:729)	FYATWAKGRFTISRDNSKNTVYLQMNSLRAEDTAVYYC(SEQ ID NO:730)	ARTVPGYSTAPYFDL(SEQ ID NO:731)	WGQGTLVTVSS(SEQ ID NO:282)

A72	KDR(VEGFR2)	Ramucirumab	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVTDAFDIWGQGTMVTVSS(SEQ ID NO:131)	EVQLVQSGGGLVKPGGSLRLSCAAS(SEQ ID NO:732)	GFTFSSYS(SEQ ID NO:733)	MNWVRQAPGKGLEWVSS(SEQ ID NO:734)	ISSSSSYI(SEQ ID NO:735)	YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC(SEQ ID NO:379)	ARVTDAFDI(SEQ ID NO:736)	WGQGTMVTVSS(SEQ ID NO:296)
A73	PSMA	MEDI3726	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWVKQAPGKGLEWIGNINPNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNFDYWGQGTLLTVSS(SEQ ID NO:133)	EVQLVQSGPEVKKPGATVKISCKTS(SEQ ID NO:737)	GYTFTEYTIH(SEQ ID NO:738)	WVKQAPGKGLEWIGN(SEQ ID NO:739)	INPNNGGT(SEQ ID NO:740)	TYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYC(SEQ ID NO:741)	AAGWNFDY(SEQ ID NO:742)	WGQGTLLTVSS(SEQ ID NO:743)
A74	ICAM1	Icmo0191fgi	QVQLQESGPGLVKPSETLSLTCAVSGYPISSGYFWGWIRQPPGKGLEWIGSIYQSGSTYYNPSLKRRVTMSLDTSKNQFSLKLSSVTAADTAVYYCARDGYCSGGSCYPFDYWGQGTLVTVSS(SEQ ID NO:135)	QVQLQESGPGLVKPSETLSLTCAVS(SEQ ID NO:744)	GYPISSGYF(SEQ ID NO:745)	WGWIRQPPGKGLEWIGS(SEQ ID NO:746)	IYQSGST(SEQ ID NO:747)	YYNPSLKRRVTMSLDTSKNQFSLKLSSVTAADTAVYYC(SEQ ID NO:748)	ARDGYCSGGSCYPFDY(SEQ ID NO:749)	WGQGTLVTVSS(SEQ ID NO:282)
A75	FAPα	humanized MFP5	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNNGINWLRQAPGQGLEWMGEIYPRSTNTLYAQKFQGRVTITADRSSNTAYMELSSLRSEDTAVYFCARTLTAPFAFWGQGTLVTVSS(SEQ ID NO:137)	QVQLVQSGAEVKKPGASVKVSCKAS(SEQ ID NO:750)	GYTFTNNG(SEQ ID NO:751)	INWLRQAPGQGLEWMGE(SEQ ID NO:752)	IYPRSTNT(SEQ ID NO:753)	LYAQKFQGRVTITADRSSNTAYMELSSLRSEDTAVYFC(SEQ ID NO:754)	ARTLTAPFAF(SEQ ID NO:755)	WGQGTLVTVSS(SEQ ID NO:282)

A76	B7H3	m8524	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS(SEQ ID NO:139)	QVQLQQSGAEVKKPGSSVKVSCKAS(SEQ ID NO:756)	GGTFSSYA(SEQ ID NO:757)	ISWVRQAPGQGLEWMGG(SEQ ID NO:758)	IIPILGIA(SEQ ID NO:759)	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC(SEQ ID NO:760)	ARGGSGSYHMDV(SEQ ID NO:761)	WGKGTTVTVSS(SEQ ID NO:308)

[Table 15]

Part Number	TME Target	Clone name; UNIT1	VL1	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
A70	TEM8	m825	SSELTQDPVVSVALGETVSITCQGDNLRDFYASWYQQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVL(SEQ ID NO:128)	SSELTQDPVVSVALGETVSITCQGD(SEQ ID NO:762)	NLRDFY(SEQ ID NO:763)	ASWYQQKPGQAPLLVMY(SEQ ID NO:764)	GKN(SEQ ID NO:765)	RRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYC(SEQ ID NO:766)	SSRDNSKHVV(SEQ ID NO:767)	FGGGTKVTVL(SEQ ID NO:768)
A71	Albumin	anti-Albumin	DIQMTQSPSSVSASVGDRVTITCQSSPSVWSNFLSWYQQKPGKAPKLLIYEASKLTSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCGGGYSSISDTTFGGGTKVEIK(SEQ ID NO:130)	DIQMTQSPSSVSASVGDRVTITCQSS(SEQ ID NO:769)	PSVWSNF(SEQ ID NO:770)	LSWYQQKPGKAPKLLIY(SEQ ID NO:771)	EAS(SEQ ID NO:772)	KLTSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:773)	GGGYSSISDTT(SEQ ID NO:774)	FGGGTKVEIK(SEQ ID NO:536)
A72	KDR(VEGFR2)	Ramucirumab	DIQMTQSPSSVSASIGDRVTITCRASQGIDNWLGWYQQKPGKAPKLLIYDASNLDTGVPSRFSGSGS	DIQMTQSPSSVSASIGDRVTITCRAS(SEQ ID NO:710)	QGIDNW(SEQ ID NO:775)	LGWYQQKPGKAPKLLIY(SEQ ID NO:776)	DAS(SEQ ID NO:566)	NLDTGVPSRFSGSGSGTYFTLTISSLQAEDFAVYFC	QQAKAFPPT(SEQ ID NO:778)	FGGGTKVDIK(SEQ ID NO:779)

			GTYFTLTISSLQAEDFAVYFCQQAKAFPPTFGGGTKVDIK(SEQ ID NO:132)					(SEQ ID NO:777)		
A73	PSMA	MEDI3726	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWASTRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKVDIK(SEQ ID NO:134)	DIQMTQSPSSLSTSVGDRVTLTCKAS(SEQ ID NO:780)	QDVGTA(SEQ ID NO:781)	VDWYQQKPGPSPKLLIY(SEQ ID NO:782)	WAS(SEQ ID NO:559)	TRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYC(SEQ ID NO:783)	QQYNSYPLT(SEQ ID NO:784)	FGPGTKVDIK(SEQ ID NO:543)
A74	ICAM1	Icmo0191fgi	QSVLTQPPSVSGTPGQRVTISCSGSSSNIGGSTVNWYQQLPGTAPKLLIYNNDQRPSGVPDRFSGSKSGTSGSLAISGLQSEDEADYYCESWDDSLSGRVFGGGTKLTVL(SEQ ID NO:136)	QSVLTQPPSVSGTPGQRVTISCSGS(SEQ ID NO:785)	SSNIGGST(SEQ ID NO:786)	VNWYQQLPGTAPKLLIY(SEQ ID NO:787)	NND(SEQ ID NO:788)	QRPSGVPDRFSGSKSGTSGSLAISGLQSEDEADYYC(SEQ ID NO:789)	ESWDDSLSGRV(SEQ ID NO:790)	FGGGTKLTVL(SEQ ID NO:505)
A75	FAPα	humanized MFP5	QIVLTQSPATLSLSPGERATLSCSASSGVNFMHWYQQKPGQAPRRLIFDTSKLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQWSFNPPTFGQGTKVEIK(SEQ ID NO:138)	QIVLTQSPATLSLSPGERATLSCSAS(SEQ ID NO:791)	SGVNF(SEQ ID NO:792)	MHWYQQKPGQAPRRLIF(SEQ ID NO:793)	DTS(SEQ ID NO:794)	KLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYC(SEQ ID NO:795)	QQWSFNPPT(SEQ ID NO:796)	FGQGTKVEIK(SEQ ID NO:573)
A76	B7H3	m8524	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGS	EIVLTQSPATLSLSPGERATLSCRAS(SEQ ID NO:797)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY	QQRSNWPPRIT(SEQ ID NO:799)	FGQGTRLEIK(SEQ ID NO:800)

			GTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK(SEQ ID NO:140)					YC(SEQ ID NO:798)		

[Table 16]

Part Number	Clone name; UNIT1	SEQ ID NO (VH)	SEQ ID NO (VL)
A70	m825	1486	1554
A71	anti-Albumin	1487	1555
A72	Ramucirumab	1488	1556
A73	MEDI3726	1489	1557
A74	Icmo0191fgi	1490	1558
A75	humanized MFP5	1491	1559
A76	m8524	1492	1560

In the present invention, the first linker, which is the second component, may comprise a cleavable peptide comprising the substrate sequence of proteolytic enzymes that are specifically expressed at a disease site. In this case, the proteolytic enzyme (protease) may be, for example, MMP-2, MMP-9, uPA, Matriptase, etc. The cleavable peptide may be composed of three or more amino acids and may include a variant (PRS variant) formed by combining different compositions and arrangements of each substrate sequence. In this case, the proteolytic enzyme recognizing the PRS variant may be one or more than one types, and the cleavage efficiency of the cleavable peptide may vary depending on the substrate sequence and the proteolytic enzyme. In addition, the masking effect of the first domain (first component) masking the second domain (third component) may vary depending on the length of the PRS variant and the composition and arrangement of amino acids.

An example of the amino acid sequence of the substrate peptide of the PRS variant and the proteolytic enzyme cleaving the variant substrate peptide is shown in Table 17. The following amino acid sequences are described from the N-terminus to the C-terminus.

[Table 17]

Part Number	PRS Number	Sequence; (), additional amino acids in Variable Light chain	Protease type	*In vitro* cutting efficiency
B1	PRS 0	PLSAAAGSDN(SEQ ID NO: 159)	MMP-2/-9	High

		PLSAAAGSDN(H)(SEQ ID NO: 160)		
B2	PRS 1	LSGRSDN(SEQ ID NO: 161)	MT-SP1, uPA	High
		LSGRSDN(H)(SEQ ID NO: 162)		
B3	PRS 2	PLGLSGRSDN(SEQ ID NO: 163)	MMP-2/-9, MT-SP1, uPA	High
		PLGLSGRSDN(H)(SEQ ID NO: 164)		
B4	PRS 3	LSGRSANPAGL(SEQ ID NO: 165)	MMP-2/-9, MT-SP1, uPA	High
		LSGRSANPAGL(Y)(SEQ ID NO: 166)		
B5	PRS 4	PLSGRSDN(SEQ ID NO: 167)	MT-SP1, uPA	High
		PLSGRSDNH(SEQ ID NO: 168)		
B6	PRS 5	PLGL(SEQ ID NO: 169)	MMP-2/-9	Low
		PLGLY(SEQ ID NO: 170)		
B7	PRS 6	ASTKG(SEQ ID NO: 171)	Not specified	Medium
		ASTKGP(SEQ ID NO: 172)		
B8	PRS 7	PLSAAA(SEQ ID NO: 173)	MMP-2/-9	High
		PLSAAAH(SEQ ID NO: 174)		
B9	PRS 8	EAD(SEQ ID NO: 175)	Not specified	No or few
		EADH(SEQ ID NO: 176)		

In the present invention, the second domain (second component) may be an antibody having a protein that is specifically expressed in target cells at a disease site as an antigen. The amino acid sequences of the heavy chain variable region (VH2) and the light chain variable region (VL2) of the antibody that specifically binds to the antigen protein are shown in Tables 18 and 19, respectively. The amino acid sequences of each antibody below are described from the N-terminus to the C-terminus. In addition, the polynucleotide sequences encoding the heavy chain variable region (VH2) and the light chain variable region (VL2) of the antibody are shown in Table 20.

The second domain is linked to the first domain via a first linker, and the antigen binding avidity of the second domain may exist in a masked state due to structural position. The degree of masking of the second domain may vary depending on the sequence of the first domain or the sequence of the cleavable peptide within the first linker. When a cleavable peptide comprising a substrate sequence is cleaved by a disease site-specific proteolytic enzyme and the first domain is dissociated from the second domain, the binding affinity of the second domain to the target

protein (antigen) can be restored.

[Table 18]

Part Number	Clone name; UNIT2	VH2 or VL2 in HC	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
C1	Trastuzumab	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS (SEQ ID NO:184)	EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFNIKDTY(SEQ ID NO:802)	IHWVRQAPGKGLEWVAR(SEQ ID NO:803)	IYPTNGYT (SEQ ID NO:804)	RYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC(SEQ ID NO:805)	SRWGGDGFYAMDY(SEQ ID NO:806)	WGQGTLVTVSS(SEQ ID NO:282)
C2	Trastuzumab (disulfide)	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS (SEQ ID NO:186)	EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFNIKDTY(SEQ ID NO:802)	IHWVRQAPGKCLEWVAR(SEQ ID NO:807)	IYPTNGYT(SEQ ID NO:804)	RYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC(SEQ ID NO:805)	SRWGGDGFYAMDY(SEQ ID NO:806)	WGQGTLVTVSS(SEQ ID NO:282)
C3	Candidate14	QVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRGLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARGGYTMDYWGQGTSVTVSS(SEQ ID NO:188)	QVQLQQPGAELVKPGASLRVSCKAS(SEQ ID NO:808)	GYTFTNYW(SEQ ID NO:809)	MYWVRQRPGRGLEWIGW(SEQ ID NO:810)	IDPNSGGTK(SEQ ID NO:811)	YNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNC(SEQ ID NO:812)	ARGGYTMDY(SEQ ID NO:813)	WGQGTSVTVSS(SEQ ID NO:814)
C4	Candidate14 (disulfide)	QVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRCLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARG	QVQLQQPGAELVKPGASLRVSCKAS(SEQ ID NO:808)	GYTFTNYW(SEQ ID NO:809)	MYWVRQRPGRCLEWIGW(SEQ ID NO:638)	IDPNSGGTK(SEQ ID NO:811)	YNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNC(SEQ ID NO:812)	ARGGYTMDY(SEQ ID NO:813)	WGQGTSVTVSS(SEQ ID NO:814)

		GYTMDYWGQG TSVTVSS(SEQ ID NO:190)							
C5	Magrolimab	QVQLVQSGAEV KKPGASVKVSC KASGYTFTNYN MHWVRQAPGQ RLEWMGTIYPG NDDTSYNQKFK DRVTITADTSAS TAYMELSSLRS EDTAVYYCARG GYRAMDYWGQ GTLVTVSS(SEQ ID NO:192)	QVQLV QSGAE VKKPG ASVKV SCKAS(SEQ ID NO:750)	GYTFT NYN(S EQ ID NO:815)	MHW VRQA PGQR LEW MGT(SEQ ID NO:69 9)	IYPGND DT(SEQ ID NO:817)	SYNQKF KDRVTI TADTSA STAYME LSSLRSE DTAVYY C(SEQ ID NO:818)	ARGGY RAMD Y(SEQ ID NO:819)	WGQG TLVTV SS(SEQ ID NO:282)
C6	Magrolimab (disulfide)	QVQLVQSGAEV KKPGASVKVSC KASGYTFTNYN MHWVRQAPGQ CLEWMGTIYPG NDDTSYNQKFK DRVTITADTSAS TAYMELSSLRS EDTAVYYCARG GYRAMDYWGQ GTLVTVSS(SEQ ID NO:194)	QVQLV QSGAE VKKPG ASVKV SCKAS(SEQ ID NO:750)	GYTFT NYN(S EQ ID NO:815)	MHW VRQA PGQC LEW MGT(SEQ ID NO:81 6)	IYPGND DT(SEQ ID NO:817)	SYNQKF KDRVTI TADTSA STAYME LSSLRSE DTAVYY C(SEQ ID NO:818)	ARGGY RAMD Y(SEQ ID NO:819)	WGQG TLVTV SS(SEQ ID NO:282)
C7	CC-90002	QMQLVQSGAE VKKTGSSVKVS CKASGFNIKDY YLHWVRQAPG QALEWMGWID PDQGDTEYAQK FQDRVTITRDRS MSTAYMELSSL RSEDTAMYYCN AAYGSSSYPMD YWGQGTIVTVS S(SEQ ID NO:196)	QMQL VQSGA EVKKT GSSVK VSCKA S(SEQ ID NO:820)	GFNIK DYY(S EQ ID NO:821)	LHW VRQA PGQA LEW MGW(SEQ ID NO:82 2)	IDPDQG DT(SEQ ID NO:823)	EYAQKF QDRVTI TRDRSM STAYME LSSLRSE DTAMY YC(SEQ ID NO:824)	NAAYG SSSYP MDY(S EQ ID NO:825)	WGQG TIVTVS S(SEQ ID NO:826)
C8	CC-90002 (disulfide)	QMQLVQSGAE VKKTGSSVKVS CKASGFNIKDY YLHWVRQAPG QCLEWMGWID PDQGDTEYAQK FQDRVTITRDRS MSTAYMELSSL RSEDTAMYYCN AAYGSSSYPMD YWGQGTIVTVS S(SEQ ID	QMQL VQSGA EVKKT GSSVK VSCKA S(SEQ ID NO:820)	GFNIK DYY(S EQ ID NO:821)	LHW VRQA PGQC LEW MGW(SEQ ID NO:82 7)	IDPDQG DT (SEQ ID NO:823)	EYAQKF QDRVTI TRDRSM STAYME LSSLRSE DTAMY YC(SEQ ID NO:824)	NAAYG SSSYP MDY SEQ ID NO:825)	WGQG TIVTVS S(SEQ ID NO:826)

		NO:198)							
C9	Cetuximab	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA(SEQ ID NO:200)	QVQLKQSGPGLVQPSQSLSITCTVS(SEQ ID NO:828)	GFSLTNYG(SEQ ID NO:829)	VHWVRQSPGKGLEWLGV(SEQ ID NO:830)	IWSGGNT(SEQ ID NO:832)	DYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYC(SEQ ID NO:833)	ARALTYYDYEFAY(SEQ ID NO:834)	WGQGTLVTVSA(SEQ ID NO:835)
C10	Cetuximab (disulfide)	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKCLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA(SEQ ID NO:202)	QVQLKQSGPGLVQPSQSLSITCTVS(SEQ ID NO:828)	GFSLTNYG(SEQ ID NO:829)	VHWVRQSPGKCLEWLGV(SEQ ID NO:836)	IWSGGNT(SEQ ID NO:832)	DYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYC(SEQ ID NO:833)	ARALTYYDYEFAY(SEQ ID NO:834)	WGQGTLVTVSA(SEQ ID NO:835)
C11	Panitumumab	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS(SEQ ID NO:204)	QVQLQESGPGLVKPSETLSLTCTVS(SEQ ID NO:837)	GGSVSSGDYY(SEQ ID NO:838)	WTWIRQSPGKGLEWIGH(SEQ ID NO:839)	IYYSGNT(SEQ ID NO:840)	NYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYC(SEQ ID NO:841)	VRDRVTGAFDI(SEQ ID NO:842)	WGQGTMVTVSS(SEQ ID NO:296)
C12	Panitumumab (disulfide)	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKCLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS(SEQ ID NO:206)	QVQLQESGPGLVKPSETLSLTCTVS(SEQ ID NO:837)	GGSVSSGDYY(SEQ ID NO:838)	WTWIRQSPGKCLEWIGH(SEQ ID NO:831)	IYYSGNT(SEQ ID NO:840)	NYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYC(SEQ ID NO:841)	VRDRVTGAFDI(SEQ ID NO:842)	WGQGTMVTVSS(SEQ ID NO:296)
C13	Necitumumab	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYY	QVQLQESGPGLVKPS	GGSISSGDYY(SEQ ID	WSWIRQPPGKGL	IYYSGST(SEQ ID NO:846)	DYNPSLKSRVTMSVDTSK	ARVSIFGVGTFDY(SE	WGQGTLVTVSS(SEQ

		WSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSS(SEQ ID NO:208)	QTLSLTCTVS(SEQ ID NO:843)	NO:844)	EWIGY(SEQ ID NO:845)		NQFSLKVNSVTAADTAVYYC(SEQ ID NO:847)	Q ID NO:848)	ID NO:282)
C14	Necitumumab (disulfide)	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKCLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSS(SEQ ID NO:210)	QVQLQESGPGLVKPSQTLSLTCTVS(SEQ ID NO:843)	GGSISSGDYY(SEQ ID NO:844)	WSWIRQPPGKCLEWIGY(SEQ ID NO:849)	IYYSGST(SEQ ID NO:846)	DYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYC(SEQ ID NO:847)	ARVSIFGVGTFDY(SEQ ID NO:848)	WGQGTLVTVSS(SEQ ID NO:282)
C15	Ipilimumab (disulfide)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKCLEWVTFISYDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSS(SEQ ID NO:212)	QVQLVESGGGVVQPGRSLRLSCAAS(SEQ ID NO:404)	GFTFSSYT(SEQ ID NO:850)	MHWVRQAPGKCLEWVTF(SEQ ID NO:851)	ISYDGNNK(SEQ ID NO:852)	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYC(SEQ ID NO:853)	ARTGWLGPFDY(SEQ ID NO:854)	WGQGTLVTVSS(SEQ ID NO:282)
C16	Tremelimumab (disulfide)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKCLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPRGATLYYYYYGMDVWGQGTTVTVSS(SEQ ID NO:214)	QVQLVESGGGVVQPGRSLRLSCAAS(SEQ ID NO:404)	GFTFSSYG(SEQ ID NO:855)	MHWVRQAPGKCLEWVAV(SEQ ID NO:856)	IWYDGSNK(SEQ ID NO:857)	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC(SEQ ID NO:407)	ARDPRGATLYYYYGMDV(SEQ ID NO:858)	WGQGTTVTVSS(SEQ ID NO:368)
C17	m8524	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPILGIANYAQKFQGR	QVQLQQSGAEVKKPGSSVKVSCKAS(SEQ ID	GGTFSSYA(SEQ ID NO:757)	ISWVRQAPGQGLEWMGG(SEQ ID	IIPILGIA(SEQ ID NO:759)	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYY	ARGGSGSYHMDV(SEQ ID NO:761)	WGKGTTVTVSS(SEQ ID NO:308)

		VTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS(SEQ ID NO:139)	NO:756)		NO:758)		C(SEQ ID NO:760)		
C18	m8524 (disulfide)	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQCLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS(SEQ ID NO:216)	QVQLQQSGAEVKKPGSSVKVSCKAS(SEQ ID NO:756)	GGTFSSYA(SEQ ID NO:757)	ISWVRQAPGQCLEWMGG(SEQ ID NO:859)	IIPILGIA(SEQ ID NO:759)	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC(SEQ ID NO:760)	ARGGSGSYHMDV(SEQ ID NO:761)	WGKGTTVTVSS(SEQ ID NO:308)
C19	ANXA1 (Y829)	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:109)	QVQLVQSGGGLVQPGRSLRISCKAS(SEQ ID NO:416)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
C20	DLK1(18A5)	QVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSS(SEQ ID NO:218)	QVQLVQSGGAVVQPGHSLRLSCEAS(SEQ ID NO:860)	GFKFKDYG(SEQ ID NO:861)	MHWVRQAPGKGLEWLAV(SEQ ID NO:862)	ISHDGRNK(SEQ ID NO:863)	NYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYC(SEQ ID NO:864)	VRDWSYAFDI(SEQ ID NO:865)	WGQGTLVTVSS(SEQ ID NO:282)
C21	CD3(SP34#8)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCA	EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFTFSTYA(SEQ ID NO:866)	MNWVRQAPGKGLEWVGR(SEQ ID NO:867)	IRSKYNNYAT(SEQ ID NO:868)	YYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYC(SEQ ID NO:869)	ARHGNFGNSYVSYFAY(SEQ ID NO:870)	WGQGTLVTVSS(SEQ ID NO:282)

		RHGNFGNSYVSYFAYWGQGTLVTVSS(SEQ ID NO:220)							
C22	CLDN18.2(Zolbetuximab)	QVQLQQPGAELVRPGASVKLSCKASGYTFTSYWINWVKQRPGQGLEWIGNIYPSDSYTNYNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTRSWRGNSFDYWGQGTTLTVSS(SEQ ID NO:222)	QVQLQQPGAELVRP(SEQ ID NO:871)	GASVKLSCKASGYTFT(SEQ ID NO:872)	SYWINWVKQRPGQGLEWIGN(SEQ ID NO:873)	IYPSDSYT(SEQ ID NO:874)	NYNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYC(SEQ ID NO:875)	TRSWRGNSFDY(SEQ ID NO:876)	WGQGTTLTVSS(SEQ ID NO:877)
C23	CLDN18.2(PR002726)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFVMSWVRQAPGKGLEWVSTISGSGRSTYYADSVKGRFTISRDNSKNTLHLQMNSLRAEDTAVYYCAKDAAAAGTKFDYWGQGTLVTVSS(SEQ ID NO:224)	EVQLLESGGGLVQPGGSLRLSCAAS(SEQ ID NO:488)	GFTFSSFV(SEQ ID NO:878)	MSWVRQAPGKGLEWVST(SEQ ID NO:879)	ISGSGRST(SEQ ID NO:880)	YYADSVKGRFTISRDNSKNTLHLQMNSLRAEDTAVYYC(SEQ ID NO:881)	AKDAAAAGTKFDY(SEQ ID NO:882)	WGQGTLVTVSS(SEQ ID NO:282)
C24	TEM8(m825)	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSS (SEQ ID NO:127)	QVQLVQSGAEVKKPGTSVKVSCKVP(SEQ ID NO:720)	GYTFSSYA(SEQ ID NO:721)	ISWVRQAPGQGLEWMGG(SEQ ID NO:722)	IIPIFGTT(SEQ ID NO:723)	NYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYC(SEQ ID NO:724)	ARDTDYMFDY(SEQ ID NO:725)	WGQGTLVTVSS(SEQ ID NO:282)
C25	FAP(humanized MFP5)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNNGINWLRQAPGQGLEWMGEIYPRSTNTLYAQKFQGRVTITADRSSNTAYMELSSLRSEDTAVYFCARTLTAPFAFWGQGTLVTVSS(SEQ ID NO:137)	QVQLVQSGAEVKKPGASVKVSCKAS(SEQ ID NO:750)	GYTFTNNG(SEQ ID NO:751)	INWLRQAPGQGLEWMGE(SEQ ID NO:752)	IYPRSTNT(SEQ ID NO:753)	LYAQKFQGRVTITADRSSNTAYMELSSLRSEDTAVYFC(SEQ ID NO:754)	ARTLTAPFAF(SEQ ID NO:755)	WGQGTLVTVSS(SEQ ID NO:282)

C26	EpCAM (ING-1)	QIQLVQSGPEVKKPGESVKISCKASGYTFTKYGMNWVKQAPGQGLKWMGWINTYTEEPTYGDDFKGRFTFTLDTSTSTAYLEISSLRSEDTATYFCARFGSAVDYWGQGTLVTVSS(SEQ ID NO:226)	QIQLVQSGPEVKKPGESVKISCKAS(SEQ ID NO:883)	GYTFTKYGMN(SEQ ID NO:884)	WVKQAPGQGLKWMGW(SEQ ID NO:885)	INTYTEEPTYGDD(SEQ ID NO:886)	FKGRFTFTLDTSTSTAYLEISSLRSEDTATYFC(SEQ ID NO:887)	ARFGSAVDY(SEQ ID NO:888)	WGQGTLVTVSS(SEQ ID NO:282)
C27	PD-1(Nivolumab)	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS(SEQ ID NO:228)	QVQLVESGGGVVQPGRSLRLDCKAS(SEQ ID NO:889)	GITFSNSGMH(SEQ ID NO:890)	WVRQAPGKGLEWVAV(SEQ ID NO:891)	IWYDGSKR(SEQ ID NO:892)	YYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYC(SEQ ID NO:893)	ATNDDY(SEQ ID NO:894)	WGQGTLVTVSS(SEQ ID NO:282)
C28	PD-L1(Atezolimumab)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS(SEQ ID NO:230)	EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFTFSDSWIH(SEQ ID NO:895)	WVRQAPGKGLEWVAW(SEQ ID NO:896)	ISPYGGST(SEQ ID NO:898)	YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC(SEQ ID NO:899)	ARRHWPGGFDY(SEQ ID NO:900)	WGQGTLVTVSS(SEQ ID NO:282)
C29	SP34#8(disdulfide)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKCLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSYFAYWGQGTLVTVSS(SEQ ID NO:232)	EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFTFSTYA(SEQ ID NO:866)	MNWVRQAPGKCLEWVGR(SEQ ID NO:901)	IRSKYNNYAT(SEQ ID NO:868)	YYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYC(SEQ ID NO:869)	ARHGNFGNSYVSYFAY(SEQ ID NO:870)	WGQGTLVTVSS(SEQ ID NO:282)
C33	amyloid-beta (Lecane	EVQLVESGGGLVQPGGSLRLSCSASGFTFSSFGM	EVQLVESGGGLVQPG	GFTFSSFG(SEQ ID	MHWVRQAPGKG	ISSGSSTI(SEQ ID NO:910)	YYGDTVKGRFTISRDNAK	AREGGYYYGRSYYTM	WGQGTTVTVSS(SEQ

	mab)	HWVRQAPGKGLEWVAYISSGSSTIYYGDTVKGRFTISRDNAKNSLFLQMSSLRAEDTAVYYCAREGGYYYGRSYYTMDYWGQGTTVTVSS(SEQ ID NO:239)	GSLRLSCSAS(SEQ ID NO:907)	NO:908)	LEWVAY(SEQ ID NO:909)		NSLFLQMSSLRAEDTAVYYC(SEQ ID NO:911)	DY(SEQ ID NO:912)	ID NO:368)
C30	EGFR(Panitumumab_cross)	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIK(SEQ ID NO:205)	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
			DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFC(SEQ ID NO:902)	QDISNY(SEQ ID NO:903)	LNWYQQKPGKAPKLLIY(SEQ ID NO:904)	DAS(SEQ ID NO:566)	NLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFC(SEQ ID NO:905)	QHFDHLPLA(SEQ ID NO:906)	FGGGTKVEIK(SEQ ID NO:536)
C31	PD-L1 Atezolizumab(disulfide, cross)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGCGTKVEIK(SEQ ID NO:236)	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
			DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:594)	QDVSTA(SEQ ID NO:982)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	SAS(SEQ ID NO:680)	FLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:983)	QQYLYHPAT(SEQ ID NO:984)	FGCGTKVEIK(SEQ ID NO:916)
C32	PD-L1 Atezolizumab scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
			EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFTFSDSWIH(SEQ ID NO:895)	WVRQAPGKCLEWVAW(SEQ ID NO:897)	ISPYGGST(SEQ ID NO:898)	YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC(SEQ ID NO:899)	ARRHWPGGFDY(SEQ ID NO:900)	WGQGTLVTVSS(SEQ ID NO:282)
			L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	K-FR4
			DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:594)	QDVSTA(SEQ ID NO:982)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	SAS(SEQ ID NO:680)	FLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:983)	QQYLYHPAT(SEQ ID NO:984)	FGQGTKVEIK(SEQ ID NO:573)

		YHPATFGQGTKVEIK(SEQ ID NO:238)							
N/D, Not determined; N/A or '-', Not associated									

[Table 19]

Part Number	Clone name; UNIT2	VL2 or VH2 in LC	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
C1	Trastuzumab	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK(SEQ ID NO:185)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QDVNTA(SEQ ID NO:913)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	SAS(SEQ ID NO:680)	FLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:914)	QQHYTTPPT(SEQ ID NO:915)	FGQGTKVEIK(SEQ ID NO:573)
C2	Trastuzumab (disulfide)	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:187)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QDVNTA(SEQ ID NO:913)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	SAS(SEQ ID NO:680)	FLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:914)	QQHYTTPPT(SEQ ID NO:915)	FGCGTKVEIK(SEQ ID NO:916)
C3	Candidate14	DVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGAGTKLELK(SEQ ID NO:189)	DVVMTQTPLSLPVSLGDQASISCRAS(SEQ ID NO:917)	QSLVHSNGNTY(SEQ ID NO:918)	LHWYLQKPGQSPKLLIY(SEQ ID NO:919)	KVS(SEQ ID NO:920)	NRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFC(SEQ ID NO:921)	SQSTHVPLT(SEQ ID NO:922)	FGAGTKLELK(SEQ ID NO:923)
C4	Candidate14 (disulfide)	DVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPK	DVVMTQTPLSLPVSLGDQASISCRAS	QSLVHSNGNTY(SEQ ID NO:918)	LHWYLQKPGQSPKLLIY(SEQ ID	KVS(SEQ ID NO:920)	NRFSGVPDRFSGSGSGTDFTLKISRVEAEDL	SQSTHVPLT(SEQ ID NO:922)	FGCGTKLELK(SEQ ID NO:924)

		LLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGCGTKLELK(SEQ ID NO:191)	(SEQ ID NO:917)		NO:919)		GVYFC(SEQ ID NO:921)		
C5	Magrolimab	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIK(SEQ ID NO:193)	DIVMTQSPLSLPVTPGEPASISCRSS(SEQ ID NO:925)	QSIVYSNGNTY(SEQ ID NO:926)	LGWYLQKPGQSPQLLIY(SEQ ID NO:927)	KVS(SEQ ID NO:920)	NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:928)	FQGSHVPYT(SEQ ID NO:929)	FGQGTKLEIK(SEQ ID NO:517)
C6	Magrolimab (disulfide)	DIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGCGTKLEIK(SEQ ID NO:195)	DIVMTQSPLSLPVTPGEPASISCRSS(SEQ ID NO:925)	QSIVYSNGNTY(SEQ ID NO:926)	LGWYLQKPGQSPQLLIY(SEQ ID NO:927)	KVS(SEQ ID NO:920)	NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:929)	FQGSHVPYT(SEQ ID NO:929)	FGCGTKLEIK(SEQ ID NO:930)
C7	CC-90002	NIQMTQSPSAMSASVGDRVTITCKASQDIHRYLSWFQQKPGKVPKHLIYRANRLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQYDEFPYTFGGGTKVEIK(SEQ ID NO:197)	NIQMTQSPSAMSASVGDRVTITCKAS(SEQ ID NO:931)	QDIHRY(SEQ ID NO:932)	LSWFQQKPGKVPKHLIY(SEQ ID NO:933)	RAN(SEQ ID NO:934)	RLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC(SEQ ID NO:935)	LQYDEFPYT(SEQ ID NO:936)	FGGGTKVEIK(SEQ ID NO:536)
C8	CC-90002 (disulfide)	NIQMTQSPSAMSASVGDRVTITCKASQDIHRYLSWFQQKPGKVPKHLIYRANRLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQYDE	NIQMTQSPSAMSASVGDRVTITCKAS(SEQ ID NO:931)	QDIHRY(SEQ ID NO:932)	LSWFQQKPGKVPKHLIY(SEQ ID NO:933)	RAN(SEQ ID NO:934)	RLVSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC(SEQ ID NO:935)	LQYDEFPYT(SEQ ID NO:936)	FGCGTKVEIK(SEQ ID NO:916)

		FPYTFGCGTKVEIK(SEQ ID NO:199)							
C9	Cetuximab	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELK(SEQ ID NO:201)	DILLTQSPVILSVSPGERVSFSCRAS(SEQ ID NO:938)	QSIGTN(SEQ ID NO:939)	IHWYQQRTNGSPRLLIK(SEQ ID NO:940)	YAS(SEQ ID NO:941)	ESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYC(SEQ ID NO:942)	QQNNNWPTT(SEQ ID NO:943)	FGAGTKLELK(SEQ ID NO:923)
C10	Cetuximab (disulfide)	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGCGTKLELK(SEQ ID NO:203)	DILLTQSPVILSVSPGERVSFSCRAS(SEQ ID NO:938)	QSIGTN(SEQ ID NO:939)	IHWYQQRTNGSPRLLIK(SEQ ID NO:940)	YAS(SEQ ID NO:941)	ESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYC(SEQ ID NO:942)	QQNNNWPTT(SEQ ID NO:943)	FGCGTKLELK(SEQ ID NO:924)
C11	Panitumumab	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIK(SEQ ID NO:205)	DIQMTQSPSSLSASVGDRVTITCQAS(SEQ ID NO:902)	QDISNY(SEQ ID NO:903)	LNWYQQKPGKAPKLLIY(SEQ ID NO:904)	DAS(SEQ ID NO:566)	NLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFC(SEQ ID NO:905)	QHFDHLPLA(SEQ ID NO:906)	FGGGTKVEIK(SEQ ID NO:536)
C12	Panitumumab (disulfide)	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGCGTKVEIK(SEQ ID NO:207)	DIQMTQSPSSLSASVGDRVTITCQAS(SEQ ID NO:902)	QDISNY(SEQ ID NO:903)	LNWYQQKPGKAPKLLIY(SEQ ID NO:904)	DAS(SEQ ID NO:566)	NLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFC(SEQ ID NO:905)	QHFDHLPLA(SEQ ID NO:906)	FGCGTKVEIK(SEQ ID NO:916)
C13	Necitum	EIVMTQSPAT	EIVMT	QSVSS	LAWY	DAS(SE	NRATGI	HQYGS	FGGGTK

	umab	LSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAEIK(SEQ ID NO:209)	QSPATLSLSPGERATLSCRAS(SEQ ID NO:945)	Y(SEQ ID NO:580)	QQKPGQAPRLLIY(SEQ ID NO:581)	Q ID NO:566)	PARFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:798)	TPLT(SEQ ID NO:937)	AEIK(SEQ ID NO:944)
C14	Necitumumab (disulfide)	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGCGTKAEIK(SEQ ID NO:211)	EIVMTQSPATLSLSPGERATLSCRAS(SEQ ID NO:945)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:798)	HQYGSTPLT(SEQ ID NO:937)	FGCGTKAEIK(SEQ ID NO:946)
C15	Ipilimumab (disulfide)	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGCGTKVEIK(SEQ ID NO:213)	EIVLTQSPGTLSLSPGERATLSCRAS(SEQ ID NO:947)	QSVGSSY(SEQ ID NO:948)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	GAF(SEQ ID NO:949)	SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC(SEQ ID NO:950)	QQYGSSPWT(SEQ ID NO:951)	FGCGTKVEIK(SEQ ID NO:916)
C16	Tremelimumab (disulfide)	DIQMTQSPSSLSASVGDRVTITCRASQSINSYLDWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPFTFGCGTKVEIK(SEQ ID NO:215)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QSINSY(SEQ ID NO:952)	LDWYQQKPGKAPKLLIY(SEQ ID NO:953)	AAS(SEQ ID NO:540)	SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:652)	QQYYSTPFT(SEQ ID NO:954)	FGCGTKVEIK(SEQ ID NO:916)
C17	m8524	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDA	EIVLTQSPATLSLSPGERATLSCRAS(S	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDF	QQRSNWPPRIT(SEQ ID NO:799)	FGQGTRLEIK(SEQ ID NO:800)

		SNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK(SEQ ID NO:140)	EQ ID NO:797)		NO:581)		AVYYC(SEQ ID NO:798)		
C18	m8524 (disulfide)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGCGTRLEIK(SEQ ID NO:217)	EIVLTQSPATLSLSPGERATLSCRAS(SEQ ID NO:797)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:798)	QQRSNWPPRIT(SEQ ID NO:799)	FGCGTRLEIK(SEQ ID NO:955)
C19	ANXA1(Y829)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
C20	DLK1(18A5)	DIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIK(SEQ ID NO:219)	DIQMTQSPSFLSASVGDRVNITCRAS(SEQ ID NO:956)	QDISRR(SEQ ID NO:957)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	GAA(SEQ ID NO:958)	SLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYC(SEQ ID NO:959)	QQIYTTPLT(SEQ ID NO:960)	FGGGTKVEIK(SEQ ID NO:536)
C21	CD3(SP34#8)	DIQMTQSPSSLSASVGDRVTITCRSSTGAVTTSNYANWVQQKPGKAPKALIGGTNKRAPGVPSRFSGSLIGDKATLTISSLQPEDFATYYCA	DIQMTQSPSSLSASVGDRVTITCRSS(SEQ ID NO:961)	TGAVTTSNY(SEQ ID NO:962)	ANWVQQKPGKAPKALIG(SEQ ID NO:963)	GTN(SEQ ID NO:964)	KRAPGVPSRFSGSLIGDKATLTISSLQPEDFATYYC(SEQ ID NO:965)	ALWYSNLWV(SEQ ID NO:966)	FGQGTKVEIK(SEQ ID NO:573)

		LWYSNLWVFGQGTKVEIK(SEQ ID NO:221)							
C22	CLDN18.2(Zolbetuximab)	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPFTFGSGTKLEIK(SEQ ID NO:223)	DIVMTQSPSSLTVTAGEKVTMSCKSS(SEQ ID NO:967)	QSLLNSGNQKNY(SEQ ID NO:968)	LTWYQQKPGQPPKLLIY(SEQ ID NO:969)	WAS(SEQ ID NO:559)	TRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC(SEQ ID NO:970)	QNDYSYPFT(SEQ ID NO:971)	FGSGTKLEIK(SEQ ID NO:972)
C23	CLDN18.2(PR002726)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK(SEQ ID NO:225)	EIVLTQSPATLSLSPGERATLSCRAS(SEQ ID NO:797)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:798)	QQRSNWPLT(SEQ ID NO:973)	FGGGTKVEIK(SEQ ID NO:536)
C24	TEM8(m825)	SSELTQDPVVSVALGETVSITCQGDNLRDFYASWYQQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVL(SEQ ID NO:128)	SSELTQDPVVSVALGETVSITCQGD(SEQ ID NO:762)	NLRDFY(SEQ ID NO:763)	ASWYQQKPGQAPLLVMY(SEQ ID NO:764)	GKN(SEQ ID NO:765)	RRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYC(SEQ ID NO:766)	SSRDNSKHVV(SEQ ID NO:767)	GGGTKVTVL(SEQ ID NO:768)
C25	FAP(humanized MFP5)	QIVLTQSPATLSLSPGERATLSCSASSGVNFMHWYQQKPGQAPRRLIFDTSKLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQWSFNPPTFGQGTKVEIK(SEQ ID NO:138)	QIVLTQSPATLSLSPGERATLSCSAS(SEQ ID NO:791)	SGVNF(SEQ ID NO:792)	MHWYQQKPGQAPRRLIF(SEQ ID NO:793)	DTS(SEQ ID NO:794)	KLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYC(SEQ ID NO:795)	QQWSFNPPT(SEQ ID NO:796)	FGQGTKVEIK(SEQ ID NO:573)

C26	EpCAM(ING-1)	DIVMTQSALSNPVTLGESGSISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNRASGVPDRFSSSGSGTDFTLKISRVEAEDVGVYYCAQNLELPRTFGQGTKLEMK(SEQ ID NO:227)	DIVMTQSALSNPVTLGESGSISCRSS(SEQ ID NO:974)	KSLLHSNGITY(SEQ ID NO:975)	LYWYLQKPGQSPQLLIY(SEQ ID NO:976)	QMS(SEQ ID NO:977)	NRASGVPDRFSSSGSGTDFTLKISRVEAEDVGVYYC(SEQ ID NO:978)	AQNLELPRT(SEQ ID NO:979)	FGQGTKLEMK(SEQ ID NO:980)
C27	PD-1(Nivolumab)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK(SEQ ID NO:229)	EIVLTQSPATLSLSPGERATLSCRAS(SEQ ID NO:797)	QSVSSY(SEQ ID NO:580)	LAWYQQKPGQAPRLLIY(SEQ ID NO:581)	DAS(SEQ ID NO:566)	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC(SEQ ID NO:798)	QQSSNWPRT(SEQ ID NO:981)	FGQGTKVEIK(SEQ ID NO:573)
C28	PD-L1(Atezolimumab)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIK(SEQ ID NO:231)	DIQMTQSPSSLSASVGDRVTITCRAS(SEQ ID NO:594)	QDVSTA(SEQ ID NO:982)	VAWYQQKPGKAPKLLIY(SEQ ID NO:604)	SAS(SEQ ID NO:680)	FLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC(SEQ ID NO:983)	QQYLYHPAT(SEQ ID NO:984)	FGQGTKVEIK(SEQ ID NO:573)
C29	SP34#8(disdulfide)	DIQMTQSPSSLSASVGDRVTITCRSSTGAVTTSNYANWVQQKPGKAPKALIGGTNKRAPGVPSRFSGSLIGDKATLTISSLQPEDFATYYCALWYSNLWVFGCGTKVEIK(SEQ ID NO:233)	DIQMTQSPSSLSASVGDRVTITCRSS(SEQ ID NO:961)	TGAVTTSNY(SEQ ID NO:962)	ANWVQQKPGKAPKALIG(SEQ ID NO:963)	GTN(SEQ ID NO:964)	KRAPGVPSRFSGSLIGDKATLTISSLQPEDFATYYC(SEQ ID NO:965)	ALWYSNLWV(SEQ ID NO:966)	FGCGTKVEIK(SEQ ID NO:916)
C33	amyloid-beta (Lecanemab)	DVVMTQSPLSLPVTPGAPASISCRSSQSIVHSNGNTYLEWY	DVVMTQSPLSLPVTPGAPASI	QSIVHSNGNTY(SEQ ID	LEWYLQKPGQSPKLLIY(SEQ	KVS(SEQ ID NO:920)	NRFSGVPDRFSGSGSGTDFTLRISR	FQGSHVPPT(SEQ ID NO:989)	FGPGTKLEIK(SEQ ID NO:990)

		LQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCFQGSHVPPTFGPGTKLEIK(SEQ ID NO:240)	SCRSS(SEQ ID NO:985)	NO:986)	ID NO:987)		VEAEDVGIYYC(SEQ ID NO:988)		
C30	EGFR(Panitumumab_cross)	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS(SEQ ID NO:204)	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
			QVQLQESGPGLVKPSETLSLTCTVS(SEQ ID NO:837)	GGSVSSGDYY(SEQ ID NO:838)	WTWIRQSPGKGLEWIGH(SEQ ID NO:839)	IYYSGNT(SEQ ID NO:840)	NYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYC(SEQ ID NO:841)	VRDRVTGAFDI(SEQ ID NO:842)	WGQGTMVTVSS(SEQ ID NO:296)
C31	PD-L1 Atezolizumab(disulfide, cross)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKCLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS(SEQ ID NO:237)	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
			EVQLVESGGGLVQPGGSLRLSCAAS(SEQ ID NO:801)	GFTFSDSWIH(SEQ ID NO:895)	WVRQAPGKCLEWVAW(SEQ ID NO:897)	ISPYGGST(SEQ ID NO:898)	YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC(SEQ ID NO:899)	ARRHWPGGFDY(SEQ ID NO:900)	WGQGTLVTVSS(SEQ ID NO:282)
N/D, Not determined; N/A or '-', Not associated									

[Table 20]

Part Number	Clone name; UNIT2	SEQ ID NO: (VH2 or VL2(DNA))	SEQ ID NO: (VL2 or VH2(DNA))
C1	Trastuzumab	1561	1589
C2	Trastuzumab (disulfide)	1562	1590
C3	Candidate14	1563	1591
C4	Candidate14 (disulfide)	1564	1592
C5	Magrolimab	1565	1593
C6	Magrolimab (disulfide)	1566	1594
C7	CC-90002	1567	1595
C8	CC-90002 (disulfide)	1568	1596
C9	Cetuximab	1569	1597
C10	Cetuximab (disulfide)	1570	1598

C11	Panitumumab	1571	1599
C12	Panitumumab (disulfide)	1572	1600
C13	Necitumumab	1573	1601
C14	Necitumumab (disulfide)	1574	1602
C15	Ipilimumab (disulfide)	1575	1603
C16	Tremelimumab (disulfide)	1576	1604
C17	m8524	1492	1560
C18	m8524 (disulfide)	1577	1605
C19	ANXA1(Y829)	1473	1547
C20	DLK1(18A5)	1578	1606
C21	CD3(SP34#8)	1579	1607
C22	CLDN18.2(Zolbetuximab)	1580	1608
C23	CLDN18.2(PR002726)	1581	1609
C24	TEM8(m825)	1486	1554
C25	FAP(humanized MFP5)	1491	1559
C26	EpCAM(ING-1)	1583	1610
C27	PD-1(Nivolumab)	1584	1611
C28	PD-L1(Atezolimumab)	1585	1612
C29	SP34#8(disdulfide)	1582	1613
C32	PD-L1 Atezolizumab scFv	1587	-
C33	amyloid-beta (Lecanemab)	1588	1615
C30	EGFR(Panitumumab_cross)	VL2	VH2
		1599	1571
C31	PD-L1 Atezolizumab(disulfide, cross)	VL2	VH2
		1614	1586

In the present invention, the first domain may be Fv (Tables 11 and 12). In this case, the VH1 of the first domain and the VH2 or VL2 of the second domain may be linked serially via a first linker. Alternatively, VL1 of the first domain and VH2 or VL2 of the second domain may be linked serially via a first linker. In this case, for structural stability, an additional disulfide bond may be inserted at a specific location between the VH2 and VL2 of the second domain (Tables 18 and 19).

In the present invention, the first domain (first component, A) of the ReleaDome may be a scFv (single chain Fv). In this case, the scFv of the first domain and the VH2 or VL2 of the second domain may be linked serially via a first linker, and for structural stability, an additional disulfide bond may be inserted at a specific location between the VH2 and VL2 of the second domain. An example of an amino acid sequence of a scFv antibody that binds to a TME (e.g., ANXA1) that may be included in the heavy chain or the light chain of the multispecific fusion protein according to the present invention and a polynucleotide encoding the same is shown in Table 21. The amino acid sequences of the antibodies are described from the N-terminus to the C-terminus.

[Table 21]

Part Number	TME Target	Clone name; UNIT1					
		In HC	In LC				
A77	ANXA1	Y829.2 scFv	-				
A77-1	ANXA1	Y829.2 scFv	-				
Amino acid sequence of scFv							
QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:141)							
VH1	H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSS(SEQ ID NO:118)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(SEQ ID NO:313)
Linker	GGGGSGGGGSGGGGS(SEQ ID NO:274)						
VL1	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4
DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIK(SEQ ID NO:110)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)
Nucleic acid sequence of scFv (SEQ ID NO:1627)							

In the present invention, the first domain (first component, A) of the ReleaDome may be VHH. In this case, the first domain and the VH2 or VL2 of the second domain may be linked serially via a first linker. In addition, for structural stability, an additional disulfide bond may be inserted at a specific location between the VH2 and VL2 of the second domain. An example of an amino acid sequence of a VHH antibody that binds to TME (e.g., ANXA1) that may be included in the heavy chain or the light chain of the multispecific fusion protein according to the present invention and a polynucleotide encoding the same is shown in Table 22 below. The amino acid sequences of the antibodies are described from the N-terminus to the C-terminus.

[Table 22]

Part Number	TME Target	Clone name; UNIT1	
		In HC	In LC
A78	ANXA1	Y107 VHH	-
A78-1	ANXA	Y107 VHH	-

	1					
Amino acid sequence of VHH						
QVQLVQSGGGSVKAGRSLRLSCTASGFTFGDYAMSWVRQAPGKEREFVAFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTTVTVSS(SEQ ID NO:142)						
H-FR1	H-CDR1	H-FR2	H-CDR2	H-FR3	H-CDR3	H-FR4
QVQLVQSGGGSVKAGRSLRLSCTAS(SEQ ID NO:1625)	GFTFGDYA(SEQ ID NO:291)	MSWVRQAPGKEREFVAF(SEQ ID NO:1626)	IRSKAYGGTT(SEQ ID NO:293)	EYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYC(SEQ ID NO:294)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTTVTVSS(SEQ ID NO:368)
Nucleic acid sequence of VHH(SEQ ID NO:1628)						

In the present invention, the first domain (first component, A) of the ReleaDome may be a peptide that binds to TME. In this case, the C-terminus of the peptide of the first domain and the VH2 or VL2 of the second domain may be linked serially via a first linker. In this case, for structural stability, an additional disulfide bond may be inserted at a specific location between the VH2 and VL2 of the second domain. An example of an amino acid sequence of a peptide that binds to TME (e.g., ANXA1) that may be included in the heavy chain or the light chain of the multispecific fusion protein according to the present invention and a polynucleotide encoding the same is shown in Table 23. The amino acid sequence of the peptide is described from the N-terminus to the C-terminus.

[Table 23]

Part Number	TME target	Clone name; UNIT1	Amino acid sequence	Nucleic acid sequence
A80	ANXA1	IF7 in HC	IFLLWQR (SEQ ID NO: 145)	ATCTTCCTGCTGTGGCAGAGA(SEQ ID NO: 1629)
A80-1	ANXA1	IF7 in LC		

In the present invention, the first domain (first component, A) of the ReleaDome may be Fab. In this case, the CH1 of the first domain and the VH2 or VL2 of the second domain may be linked serially via a linker. In addition, for structural stability, an additional disulfide bond may be inserted at a specific location between the VH2 and VL2 of the second domain. An example of the amino acid sequences of the heavy chain variable region and the light chain variable region of a Fab antibody that binds to the TME (e.g., ANXA1, TEM8) and a polynucleotide encoding the same is shown in Tables 24 and 25 below. The amino acid sequences of the antibodies are described from the N-terminus to the C-terminus.

[Table 24]

Part	TME	Clone	Fab(VH1+CH	H-FR1	H-	H-FR2	H-	H-FR3	H-	H-FR4	H-CH1

Number	Target	name; UNIT 1	1)		CDR1		CDR2		CDR3		
A79	ANXA1	Y829.2 Fab	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:143)	QVQLVQSGGGLVQPGRSLRLSCKAS(SEQ ID NO:493)	GFNFGDYP(SEQ ID NO:417)	LSWVRQAPGKGLEWIGF(SEQ ID NO:484)	IRSKSFGGTT(SEQ ID NO:351)	EYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC(SEQ ID NO:352)	ARDGNYYDSRGYYYDTFDL(SEQ ID NO:295)	WGQGTMITVSS(번호 313)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:241)
			Nucleic acid sequence	SEQ ID NO:1630							
A81	TEM8	m825 Fab	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL	QVQLVQSGAEVKKPGTSVKVSCKVP(SEQ ID NO:720)	GYTFSSYA(SEQ ID NO:721)	ISWVRQAPGQGLEWMGG(SEQ ID NO:722)	IIPIFGTT(SEQ ID NO:723)	NYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYC(SEQ ID NO:724)	ARDTDYMFDY(SEQ ID NO:725)	WGQGTLVTVSS(SEQ ID NO:282)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT

			TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:146)								YICNVNHKPSNTKVDKKVEPKSC(SEQ ID NO:241)
			Nucleic acid sequence	SEQ ID NO:1634							

[Table 25]

Part Number	TME Target	Clone name; UNIT1	Fab (VL1+CL1)	L-FR1	L-CDR1	L-FR2	L-CDR2	L-FR3	L-CDR3	L-FR4	CL1
A79	ANXA1	Y829.2 Fab	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:144)	DIQMTQSPSSVSASVGDRVTLTCRAS(SEQ ID NO:707)	QGIRSW(SEQ ID NO:708)	LAWYQQKPGKAPKLLIY(SEQ ID NO:552)	AAS(SEQ ID NO:540)	NLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYC(SEQ ID NO:709)	QQANSFPYT(SEQ ID NO:602)	FGQGTKVEIK(SEQ ID NO:573)	RSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:247)
			Nucleic acid sequence	SEQ ID NO:1631							
A81	TEM8	m825 Fab	SSELTQDPVVSVALGETVSITCQGDNLRDFYA	SSELTQDPVVSV	NLRDFY(SEQ ID NO:76	ASWYQQKPGQAPLLVM	GKN(SEQ ID NO:76	RRPSGIPDRFSGSTSG	SSRDNSKHVV(SEQ ID	FGGGTKVTVL(SE	RSVAAPSVFIFPPSDEQLKSGTASVVCLL

			SWYQQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVLRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:147)	ALGETVSITCQGD(SEQ ID NO:762)	3)	Y(SEQ ID NO:764)	5)	NTLSLTITGAQAEDEADYYC(SEQ ID NO:766)	NO:767)	Q ID NO:768)	NNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:247)
			Nucleic acid sequence	SEQ ID NO:1635							

Example 2. Preparation and analysis of multispecific fusion protein

Example 2.1. Production of multispecific fusion protein expression vector

Each polynucleotide encoding a fusion protein, which is one embodiment of the present invention as described in Tables 24 to 41 below, was produced by commissioning gene synthesis to Bioneer or by performing PCR using an oligomer (Bioneer). Among the polynucleotides produced by the above methods, the polynucleotides encoding the heavy chain (HC) and the light chain (LC) were treated with a restriction enzyme and loaded into the PC3.1-HC vector (TriOar) and the PC3.1-LC vector (TriOar), respectively.

The vector produced by the above process was used as an expression vector to express the fusion protein of the present invention. In this case, all restriction enzymes used were products from New England Biolabs Products. Specifically, for example, for heavy chain cloning, NheI-XhoI, NotI-NheI, NotI-PmlI, NotI-XhoI, PmlI-XhoI, SfiI-NheI, SfiI-NotI, etc. were used in pairs, and for light chain cloning, BglII-XhoI, EagI_HF-BglII, NotI-BglII, NotI-NheI, NotI-XhoI, SfiI-BglII, SfiI-NheI, SfiI-NotI, etc. were used in pairs.

Example 2.2. Expression and analysis of multispecific fusion protein

In order to express the fusion protein, which is one embodiment of the present invention

described in Tables 27 to 41 below, each heavy chain (HC) expression vector (PC3.1-HC vector) and light chain (LC) expression vector (PC3.1-LC vector) produced by the method of Example 2.1 above were transfected into each cell according to the manufacturer's method. After simultaneous transfection into ExpiCHO-S™ cell line (#A29127, ThermoFisher) using the ExpiFectamine™ CHO Transfection kit (#A29129, ThermoFisher), the cells were cultured with shaking (120 rpm, 5% CO_2, 32 ℃; CO_2 shaking incubator, N-biotek) in ExpiCHO™ Expression Medium (#A2910001, ThermoFisher) for about 7 to about 10 days. In addition, after simultaneous transfection into Expi293F™ cell line (#A14527, Thermo) using the ExpiFectamine™ 293 Transfection Kit (#A14524, Thermo), the cells were cultured with shaking (120 rpm, 8% CO_2, 37 ℃; CO_2 shaking incubator, N-biotek) in Expi293™ Expression Medium (#A1435101, Thermo) for 5 days. After collecting the cell culture solution from each cell cultured as described above, the the cell culture solution was centrifuged (5,000 rpm, 4 ℃, 30 minutes) to obtain the supernatant, which was then filtered through a 0.22 um filter.

The fusion protein included in the supernatant obtained as described above was first purified using a Protein A affinity column (HiTrap™ MabSelect SuRe, Cytiva) on an AKTA Pure 25 (Cytiva) or AKTA Avant 150 (Cytiva) instrument, and then the buffer was exchanged using a desalting column (PD-10 Desalting Column, Cytiva). The concentration of the finally obtained purified product was quantified by measuring the absorbance at 280 nm using a microvolume spectrophotometer (Optizen NanoQ, KLAB). A size exclusion chromatography (SEC; TSK gel SuperSW mAbm, TOSOH) column was mounted on an ACQUITY H-Class PLUS Bio System (#176015105, Waters). Each sample (purified product) was diluted in phosphate buffer solution (pH 7.4), loaded onto the column, and then analyzed at room temperature for 40 minutes at a flow rate of 0.5 mL/min to confirm purity. The final purified product was subjected to SDS-PAGE under reducing or non-reducing conditions (4-20% Mini-PROTEAN® TGX™ Precast Protein Gels, Bio-Rad).

As another purification method, the culture supernatant was added to a Gravity column (#29924, Thermo) packed with Protein A affinity resin (#17127903, Cytiva) and mixed by rotating at 4 ℃ for 1 hour. Then, the mixture was washed with PBS (PH 7.4) buffer solution, and then the fusion protein bound to Protein A was eluted using IgG elution buffer (#21009, Thermo). The eluent was concentrated using a desalting filter (Vivaspin 20; #28-9323-61, Cytiva). The final concentration of the purified product obtained as described above was quantified using a microvolume spectrophotometer, and SEC-UPLC analysis (purity verification) and SDS-PAGE analysis were performed (Figures 4 to 14).

Hereinafter, the multispecific fusion proteins, which are one embodiment of the present invention, were used after expressing the expression vector of Example 2.1 by the above method and then isolating and purifying them.

Example 2.3. DVD-Ig type multispecific fusion protein comprising a ReleaDome

Example 2.3.1. DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to Annexin A1 (ANXA1), and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to HER2 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a DVD-Ig form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to HER2, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector.

The amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 27. The amino acid sequences are described sequentially from the N-terminus to the C-terminus. In addition, the components of the terms "DH" or "DL" described in Table 26 below are shown in Table 26.

The multispecific fusion protein produced as described above formed a dimer.

[Table 26]

Part Number	Component	CH1
DH1	CH1+DHH1+DDH1	IgG1-WT
DH2	CH1+DHH1+DDH2	IgG1-LALA
DH3	CH1+DHH1+DDH3	IgG1-LALAPG
DH4	CH1+DHH1+DDH4	IgG1-LALAPG-knob
DH5	DL1+DHH1+DDH5	-
DH6	DHH5+DDH1	-
DH7	DHH5+DDH3	-
DH8	DHH1+DDH1	-
DH9	DHH1+DDH3	-

DH10	DHH1+DDH4	-
DH11	DHH1+DDH5	-
DH12	CH1+DHH1+DDH5	IgG1-WT
DH13	CH1+DHH1+E4(linker)+VH(Ate)	IgG1-WT
DH14	CH1+DHH1+E4(linker)+VL(Ate)	IgG1-WT
DH15	DHH1+DDH7	-
DH16	DHH1+DDH8	-
DH17	DHH1+DDH9	-
DH18	CH1+DHH1+DDH12	IgG1-WT
DH19	CH1+DHH2+DDH10	IgG2-WT
DH20	CH1+DHH4+DDH11	IgG4-WT
DH21	CH1+DHH6+DDH11	IgG4-WT
DL1	DL1	-
DL2	DL2	-
DL3	CH1	IgG1-Variant
DL4	DL1+E6(linker)+CVIM	-
DL5	DL5	-

[Table 27]

Part Number					Protein code	HC	LC
A58	B2	C1	DH1	DL2	BA-0102-001	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGYYMSWVRQAPGKGLEWVSSISPSGSSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSPGFDYWGQGTLVTVSSLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAQSVLTQPPSASGAPGQRVTISCSGSSFNIGSNDVSWYQQLPGTAPKLLIYSDSHRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCGSWDYSLSAYVFGGGTKLTVLLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT	

						VEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK(SEQ ID NO:991)	HQGLSSPVTKSFNRGEC (SEQ ID NO:992)
A5 8	B 3	C 1	DH 3	DL 2	BA- 0102- 002	EVQLLESGGGLVQPGGSLRLSCAASGF TFSGYYMSWVRQAPGKGLEWVSSISP SGSSIYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKGSPGFDYW GQGTLVTVSSPLGLSGRSDNEVQLVES GGGLVQPGGSLRLSCAASGFNIKDTYI HWVRQAPGKGLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCSRWGGDGFYAMDY WGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK(SEQ ID NO:993)	QSVLTQPPSASGAPGQR VTISCSGSSFNIGSNDVS WYQQLPGTAPKLLIYS DSHRPSGVPDRFSGSKS GTSASLAISGLQSEDEA DYYCGSWDYSLSAYVF GGGTKLTVLPLGLSGRS DNHDIQMTQSPSSLSAS VGDRVTITCRASQDVN TAVAWYQQKPGKAPK LLIYSASFLYSGVPSRFS GSRSGTDFTLTISSLQPE DFATYYCQQHYTTPPT FGQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:994)
A4	B 3	C 1	DH 3	DL 2	BA- 0102- 003	QVQLVQSGGGVVQPGRSLKLSCETSG FTFNMHPMHWVRQAPGKGLEWVASI KYDGSKRYYTDSVKGRFTVSRDHVDT VYLQMNSLRAEDTAVYYCSCNGLGQ DDEAFDIWGQGTMVTVSSPLGLSGRS DNEVQLVESGGGLVQPGGSLRLSCAA SGFNIKDTYIHWVRQAPGKGLEWVAR IYPTNGYTRYADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCSRWGGD GFYAMDYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALGAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG K(SEQ ID NO:995)	QLVLTQPHSVSESPGKT VTISCTRSSGSIASKYVQ WYQQRPGSAPTTVIYE DNQRPSGVPDRFSGSID ISSNSASLTISGLKTEDE ADYYCQSYDSSSVVFG GGTKLTVLPLGLSGRSD NHDIQMTQSPSSLSASV GDRVTITCRASQDVNT AVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPED FATYYCQQHYTTPPTF GQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:996)
A5	B 3	C 1	DH 3	DL 2	BA- 0102- 004	QVQLVESGGGLVQPGRSLRLSCAASGF TFDDYGMHWVRQAPGKGLEWVSGIS WNSGSIGYADSVKGRFTISRDNAKNSL	NFMLTQPHSVSESPGK MVTISCTRSSGSIASKY VQWYQQRPGSAPITVIY

						YLQMNSLRSEDTAVYYCTRYLHRLPF DVWGKGTTVTVSSPLGLSGRSDNEVQ LVESGGGLVQPGGSLRLSCAASGFNIK DTYIHWVRQAPGKGLEWVARIYPTNG YTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALGAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:997)	EDNKRPSGVPDRFSGSI DSFSNSASLTITGLKTE DEADYYCQSYDDNTV VFGGGTKLTVLPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:998)
A9	B3	C1	DH3	DL2	BA-0102-005	QMQLVESGGGLVQPGGSLRLSCAASG FTFSDFAMTWVRQAPGKGLEWVSSIS GTSGRTYYADSVKGRSTVSTDNSKNT VYLRMNSLRAEDTAVYYCARGSPSGS ADYWGQGTLVTVSSPLGLSGRSDNEV QLVESGGGLVQPGGSLRLSCAASGFNI KDTYIHWVRQAPGKGLEWVARIYPTN GYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALGAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:999)	QLVLTQPHSVSESPGKT VTISCTRSSGSIASKYVQ WYQQRPGSAPTTVIYE DNQRPSGVPDRFSGSID ISSNSASLTISGLKTEDE ADYYCQSYDSSTVVFG GGTKLTVLPLGLSGRSD NHDIQMTQSPSSLSASV GDRVTITCRASQDVNT AVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPED FATYYCQQHYTTPPTF GQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1000)
A9	B2	C1	DH3	DL2	BA-0102-005.1	QMQLVESGGGLVQPGGSLRLSCAASG FTFSDFAMTWVRQAPGKGLEWVSSIS GTSGRTYYADSVKGRSTVSTDNSKNT VYLRMNSLRAEDTAVYYCARGSPSGS ADYWGQGTLVTVSSLSGRSDNEVQLV ESGGGLVQPGGSLRLSCAASGFNIKDT YIHWVRQAPGKGLEWVARIYPTNGYT RYADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCSRWGGDGFYAMDY	QLVLTQPHSVSESPGKT VTISCTRSSGSIASKYVQ WYQQRPGSAPTTVIYE DNQRPSGVPDRFSGSID ISSNSASLTISGLKTEDE ADYYCQSYDSSTVVFG GGTKLTVLLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV

						WGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1001)	AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1002)
A13	B3	C1	DH3	DL2	BA-0102-006	QMQLVQSGAEVQKPGASVKVSCKAS GNTFNGYYIHWVRQAPGQGLEWMGII NPSGSSTFYAQKFRGRVTMTKDTSTST VYMKLSSLRSEDTAVYYCAQEGWTEQ HPYAEYLQNWGQGTLVTVSSPLGLSG RSDNEVQLVESGGGLVQPGGSLRLSC AASGFNIKDTYIHWVRQAPGKGLEWV ARIYPTNGYTRYADSVKGRFTISADTS KNTAYLQMNSLRAEDTAVYYCSRWG GDGFYAMDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALGAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1003)	DIQMTQSPSFLSASVGD RVTITCRASQYIGTYLA WYQQQPGKAPKLLIYD ASTLQPGVPSRFSGGGS GTDFTLTIRSVQPEDYA TYFCQQSYITPFAFGQG TKLEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1004)
A28	B3	C1	DH3	DL2	BA-0102-007	QVQLVESGGGLVPPGGSLRLSCAASGF SFSDHYMDWVRQAPGKGLEWVGFIRS AAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT	DIQMTQSPSSLSASVGD KVTITCRASQGISSYLA WYQQKPGKAPKLLIYV ASSLQTGVPSRFSGSRS GTDFTLTISSLQSEDFGT YYCQQSYRTPYTFGQG TKLEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC

						PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1005)	LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1006)
A48	B3	C1	DH3	DL2	BA-0102-008	QVQLVESGGGWVQPGGSLRLSCAGSG FTTNSYTMAWVRQAPGKGLEWVSSIS SSTNYMYYADSVKGRFTISRDNAKNS VYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDMWGQGTLVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1007)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVQ AEDVGTYYCMQTLQTL PYTFGQGTKLEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1008)
A55	B3	C1	DH3	DL2	BA-0102-009	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR	DIQMTQSPSSVSASVGD RVTLTCRASQGIRSWL AWYQQKPGKAPKLLIY AASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFA TYYCQQANSFPYTFGQ GTKVEIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1010)

						WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1009)	
A11	B3	C1	DH3	DL2	BA-0102-010	QVQLVQSGGGLVQPGRSLRLSCTASGI TFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1011)	DIQMTQSPSSVFASVGD RVTITCRASQAISSWLA WYQQKPGKAPKLLIYA TSYLQTGVPSRFSGSGS GTDFTLSINNLQPEDSA TYFCEQAHSFPLTFGPG TKVDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1012)
A25	B3	C1	DH3	DL2	BA-0102-011	QVQLVESGGGLIQPGRSLRLSCTTSGFT FGDYAMSWVRQAPGKGLEWVGFIRT KTYGGTPEYAASLKGRFTISRDDSKSIA YLQMNSLRAEDTAVYYCVRDGNYYD SRGYYYDTFDLWGQGTMITVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1013)	DIQMTQSPSSVSASVGD RVTITCRASQGISNWVA WYQQKPGKAPKLLIYA ASTLHSGVPSRFSGSAS GTDFTLTISSLQPEDFAI YYCQQGHSFPYTFGQG TKLEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1014)
A30	B3	C1	DH3	DL2	BA-0102-012	QVQLVESGGGLVKPGRSLRLSCTASGF TFGDYAMSWFRQAPGKGLEWVGFIRS KAYGGTTEHAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY	DIVMTQTPLSLPVTPGE PASISCRSSQNLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF

						DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1015)	SGSGSGTDFTLKISRVE AEDVGVYYCMQTLQT LYTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1016)
A42	B3	C1	DH3	DL2	BA-0102-013	QMQLVQSGGGLVKPGRSLRLSCTASG FTFGDYAMSWFRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1017)	DIQMTQSPSSVSASIGD RITITCRASQGISTWLA WYQQKPGKAPKLLIYA ASSLHSGVPSRFSGSGS GTDFTLTISSLQPDDFA TYYCQQSYSIPRTFGQG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1018)
A43	B3	C1	DH3	DL2	BA-0102-014	QMQLVESGGGLVQPGGSLRLSCAASG FTFSDHYMDWVRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST	DIQMTQSPSSLSASVGD RVTITCRASQGIRNYLG WYQQKPGRAPKLLIYA ASSLQSGVPSRFRGSGS GTDFTLTISSLQPEDFAT YYCLQDHDYPYTFGQG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY

						KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1019)	SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1020)
A55	B1	C1	DH3	DL2	BA-0102-015	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLSA AAGSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1021)	DIQMTQSPSSVSASVGD RVTLTCRASQGIRSWL AWYQQKPGKAPKLLIY AASNLQSGVPSRFSGSG SGTDFILTINSLQPDDFA TYYCQQANSFPYTFGQ GTKVEIKPLSAAAGSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1022)
A33	B3	C1	DH3	DL2	BA-0102-016	QVQLVESGGGVVQPGRSLRLSCAASG FTFSSYAMHWVRQAPGKGLEWVAVIS YDGSNKYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCARDQTRLG PTTFDYWGQGSLVTVSSPLGLSGRSDN EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK	DIQMTQSPSTLSASVGD RVTITCRASQNVDKWL AWYQQKPGKAPKLLIY KASGLESGVPSRFSGSG SGTEFTLTISSLQPDDFA TYYCQQYDSYPLTFGG GTKVEIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC

						TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1023)	VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1024)
A1	B3	C1	DH3	DL2	BA-0102-017	QMQLVQSGGGLVQPGRSLRLSCAVSG FTFDDYAMHWVRQAPGKGLEWVSGI NWDSSNIGYADSVKGRFTISRDNAKNS LYLQMNNLRSEDTAVYYCVKLASDSG GYFESWGQGTLVTVSSPLGLSGRSDNE VQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1025)	QLVLTQPHSVSESPGKT VTISCARSSGSIASKYV QWYQQRPGSAPTAVIY EDNQRPSGVPDRFSGSI DTSSNSASLTISGLKTE DEADYYCQSYDSSSVV FGGGTKLTVLPLGLSGR SDNHDIQMTQSPSSLSA SVGDRVTITCRASQDV NTAVAWYQQKPGKAP KLLIYSASFLYSGVPSRF SGSRSGTDFTLTISSLQP EDFATYYCQQHYTTPP TFGQGTKVEIKRSVAAP SVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1026)
A2	B3	C1	DH3	DL2	BA-0102-018	QVQLVESGGGLVESGGSLRLSCAASGF TFSNAWMTWVRQAPGKGLEWVGVIR SKTYGGTTEYAAPLRGRFSISRDDSKN TLYLQMNSLRAEDTAVYYCAKGAAY GPFDYWGQGTLITVSSPLGLSGRSDNE VQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(	NFMLTQPHSVSESPGKT VTISCTRSSGSIASKYVQ WYQQRPGSVPITVIYED DQRPSGVPDRFSGSIDS FSNSASLTITGLKTEDE AEYYCQSYDDNTVVFG GGTKLTVLPLGLSGRSD NHDIQMTQSPSSLSASV GDRVTITCRASQDVNT AVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPED FATYYCQQHYTTPPTF GQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1028)

						SEQ ID NO:1027)	
A3	B3	C1	DH3	DL2	BA-0102-019	QVQLVESGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1029)	DIVMTQTPLSLHVTPGEPASISCRSSQSLLHSNGYNYLEWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCTQSIQVPYTFGQGTKLEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1030)
A6	B3	C1	DH3	DL2	BA-0102-020	QVQLVESGGDWVEPGRSLRLSCRTSGFTFADYALNWVRQAPGKGLEWVGFIRSKTYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARRGGWTLGYAFDIWGQGTMITVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1031)	SYELTQPLSVSVSPGQTATITCSGHQLGNRYLSWYQKKPGQSPVLLISQDTNRPSGIPERFSGSDSGTTATLTIRETQAMDEADYYCQAWDSTTAVFGGGTKLTVLPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1032)
A7	B3	C1	DH3	DL2	BA-0102-021	QMQLVESGGGLVKPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRNDSKSIAYLQMNSLRAEDTAVYYCARIVAYGPFDYWGQGALVTVSSPLGLSGRSDNEDIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGIAPKLLIYQASTLETGVPLRFSGRGSGTEFTLTINSLQPDDFA	

						VQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1033)	TYYCQQYDDYSPLTFG GGTKVEIKPLGLSGRSD NHDIQMTQSPSSLSASV GDRVTITCRASQDVNT AVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPED FATYYCQQHYTTPPTF GQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1034)
A8	B3	C1	DH3	DL2	BA-0102-022	QVQLVESGGGLVQPGGSLRLSCAASG FTFSDHYMDWVRQAPGKGLEWVGRS RNKANSHTTEYAASVKGRFTISRDDSK KSLYLQMNSLRAEDTAVYYCARGGA WLDYWGQGTLVTVSSPLGLSGRSDNE VQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1035)	DIQMTQSPSSLSASVGD RLTITCRASQSILTYLN WYQQKPGKAPKLLVY AASSLQRGVPSRFSGRG SGTDFTLTISGLQPDDF ALYYCQQSYSSPYSFGP GTKVDIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1036)
A10	B3	C1	DH3	DL2	BA-0102-023	QVQLVESGGGLVQPGRSLRLSCTGSGF TFGDYVMNWVRQVPGKGLEWVGFIR SKGYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPR LLIYSGSSRASGVPDRF SGSGSGTDFTLKISSVE AEDVGTYYCMQTLETP LTFGGGTKVEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR

						DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1037)	FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1038)
A27	B3	C1	DH3	DL2	BA-0102-024	QVQLVESGGDLVKPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMITVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1039)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTEFTLKISRVE AEDVGVYYCMHTLQLP FTFGPGTKVEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1040)
A14	B3	C1	DH3	DL2	BA-0102-025	QVQLVESGGGLVQPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWIGFIRS KSFGGTTEYAASVKGRFTISRDDSRDI AYLQMNSLRAEDTAVYYCARDGNYY DSRDYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT	DIQMTQSPSSVSASVGD RVTITCRASQDISRWLA WYQQKPGKAPKLLIYA ASILQTGVPSRFSGSGS GTDFTLSINNLQPEDSA TYFCEQAHSFPLTFGPG TKVDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ

						VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1041)	DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1042)
A15	B3	C1	DH3	DL2	BA-0102-026	QVQLVESGGGAVKPGGSLRLSCEASG FTFSDYYMSWIRQAPGKGLEWVADIS GVNSFTNYAASVEGRFTISRDNARNSL YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDMWGQGTLVTVSSPLGL SGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:51043)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQALQT PRTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1044)
A16	B3	C1	DH3	DL2	BA-0102-027	QMQLVESGGGLVQPGRSLRLSCTASG FTFGDYAMSWVRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGDYY DSRGYYYDTFDLWGQGTMITVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1045)	DIQMTQSPSSVSASVGD SVTITCRASQDISTWLA WYQQKPGRAPKVLIYA ASRLQDGVSSRFSGSGS GTDFNLSISSLQPEDFAT YYCQQANSFPLTFGGG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1046)

A17	B3	C1	DH3	DL2	BA-0102-028	QVQLVESGGGLVQPGRSLRLSCTASGFTFGDYAMSWVRQAPGKGLEWVGFIRSKAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCAKDADFYDNSGYYDDAFDIWGQGTMVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1047)	DIQMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASTRATGTPDRFSGSGSGTDFTLTISSLEPEDFAVYYCQQRAKWPATFGQGTKLDIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1048)
A18	B3	C1	DH3	DL2	BA-0102-029	QVQLVESGGGLVQPGRSLRLSCATSGFTFGDYAMSWVRQAPGRGLEWVGFIRSKPHGGTTDFAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1049)	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQPPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQTPRTFGQGTKVEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1050)
A20	B3	C1	DH3	DL2	BA-0102-030	QVQLVESGGGLIQPGGSLRLSCAASGLTSSTYAMNWVRQAPGKGLEWVAGVSASGGSAYYAESVKGRFTISRDNSNNTVFLQMNSLRAEDTAVYYCARHLAWGGMDVWGQGTTITVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNI	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYGASILQNGVPSRFSGSGSGTEFTLTITNLQPEDFASYYCQQLSSYPYTFGQG

						KDTYIHWVRQAPGKGLEWVARIYPTN GYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALGAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1051)	TKLDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1052)
A21	B3	C1	DH3	DL2	BA-0102-031	QMQLVESGGGLVQPGRSLRLSCTASG FTFGDYAMSWVRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1053)	DIVMTQSPLSLPVIPGEP ASISCRSSKSLLHSNGY NYLDWYLQKPGQSPQL LIYLGSNRASGVPDRFS GSGSGTDFTLTISRVEA EDVGVYYCMQALQTP RTFGQGTKVEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1054)
A22	B3	C1	DH3	DL2	BA-0102-032	QVQLVESGGGLVKPGGSLRLSCAASG FTFSDYYMSWIRQAPGKGLEWVSYISS SGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARATYYDILT GYYNDGYFDYWGQGTLVTVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ	DIQMTQSPSSLSASVGD RVTITCRASQSISNWLA WYQQKPGKAPKLLIYG ASNLKSGVPSRFSGSGS GTHFTLTISSLHPEDFAT YYCQQSYITQTWTFGQ GTKVEIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF

						SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1055)	ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1056)
A23	B3	C1	DH3	DL2	BA-0102-033	QMQLVESGGGLVQPGRSLRLSCAASG FNFNTYAMHWVRQAPGRGLEWVGFI RSKAYGGTTEYAASVKGRFTISRDDSK SIAYLQMNSLRAEDTAVYYCARDGNY YDSRGYYYDTFDLWGQGTMVTVSSPL GLSGRSDNEVQLVESGGGLVQPGGSL RLSCAASGFNIKDTYIHWVRQAPGKGL EWVARIYPTNGYTRYADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1057)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQALQT PRTFGQGTKVDIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1058)
A24	B3	C1	DH3	DL2	BA-0102-034	QVQLVESGGGLVQPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWVGFIRS KTYGGTTEYAASVTGRFTISRDDSRGI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDMWGQGTLVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE	DIQMTQSPSSVSASVGD RVTITCRASQGIGNWLA WYQQKPGEAPNLLIYG ASNLASGVPSRFSGSGS GTDFTLTISSLQPEDFAT YYCQQANSFPYTFGQG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK

						KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1059)	ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1060)
A26	B3	C1	DH3	DL2	BA-0102-035	QVQLVESGGGLIQPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDMWGQGTLVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1061)	DIVMTQTPLSLPVTPGE PAFISCRSSQNLLHSNG YNYLDWYLQKPGQSPQ LLIYMGSYRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQPLQIP FTFGGGTKVEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1062)
A29	B3	C1	DH3	DL2	BA-0102-036	QVQLVQSGGGLVQPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1063)	DIQMTQSPSSVSASLGD RVTITCRASQDIGHWLA WYQQKPGKAPKHLIYA ASSLHSGVPSRFSGSGS GTEFTLTISNLQPEDFAT YYCQQANSFPYTFGQG TKVDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1064)
A3	B	C	DH	DL	BA-	QMQLVESGGGLVQPGRSLRLSCTASG	DIQMTQSPSSVSASVGD

1	3	1	3	2	0102-037	FTFRDYAMSWVRQAPGKGLEWIGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1065)	SVTITCRASQGISSWLA WYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGS GTDFTLTIDSLQPEDFA TYYCQQADSFPYTFGQ GTKVEIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1066)
A32	B3	C1	DH3	DL2	BA-0102-038	QVQLVESGGGVVQPGGSLRLSCDVSG LTFSIYGMHWVRQAPGKGLEWVAVIG YDGGNSFYAESVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARGSLGTFD IWGQGTVVTVSSPLGLSGRSDNEVQLV ESGGGLVQPGGSLRLSCAASGFNIKDT YIHWVRQAPGKGLEWVARIYPTNGYT RYADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCSRWGGDGFYAMDY WGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1067)	DIQMTQSPSSVSASVGD RVTITCRASQGISSWLA WYQQKPGKAPKRLMY AASVLDAGVPSRFSGS GSGTDFTLTVSSLQPED FATYYCQQGDSFPRTF GPGTKVDIKPLGLSGRS DNHDIQMTQSPSSLSAS VGDRVTITCRASQDVN TAVAWYQQKPGKAPK LLIYSASFLYSGVPSRFS GSRSGTDFTLTISSLQPE DFATYYCQQHYTTPPT FGQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1068)
A34	B3	C1	DH3	DL2	BA-0102-039	QVQLVESGAEVKKPGESLKISCKGSGY SFTSFWISWVRQMPGKGLEWMGRIDP SDGYTSYSPSFQGHVTISVDKSINTAYL QWNSLKASDTAMYYCARHNRKTLGR VDVWGQGTTVTVSSPLGLSGRSDNEV QLVESGGGLVQPGGSLRLSCAASGFNI KDTYIHWVRQAPGKGLEWVARIYPTN	QSALTQPPSASGSPGQS VTISCSGGSRDVGAYN YVSWYQQHPGKAPKL MIYEVNKRPSGVPDRFS GSKSGNTASLTISGLQA EDEADYYCTSFAGENN FGVFGGGTKLTVLPLG

						GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1069)	LSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1070)
A35	B3	C1	DH3	DL2	BA-0102-040	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLTWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1071)	DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIYAASALESGVPSRFSASGYGTDFTLTISSLQPEDFATYFCQQGKSFPYTFGQGTKVEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1072)
A36	B3	C1	DH3	DL2	BA-0102-041	QVQLVESGGGVVQPGGSLRLSCAASGFNFENYAMHWVRQVPGKGLEWVSLISGDGSSTHYTDSLRGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCARGGGKLDYWGQGTLVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDQAVVTQEPSFSVSPGGTVTLTCGLTSGSVSTSHFPSWYQQTPGQAPRTLIYFTDTHSSGVPDRFSGSILGNKAALTITGAQADDESDYYCVLYMGSGIYAFGTGTKVTVLPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPT	

						KKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALGAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1073)	FGQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1074)
A37	B3	C1	DH3	DL2	BA-0102-042	QVQLVQSGGGLVQPGGSLRLSCAASG FTFSDHYMDWVRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFTISRDDSKS IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1075)	DIQMTQSPSSLSASVGD RVTITCRASQSISNYLN WYQQKPGKAPKLLMS AASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFA TYYCQQSYNTPRTFGQ GTKVDIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGEC (SEQ ID NO:1076)
A38	B3	C1	DH3	DL2	BA-0102-043	QVQLVESGGGLIQPGRSLRLSCRTSGFS FGDYAMTWVRQAPGKGLEWVGFIRS KRFGGTTEYAASVKGRFTISRDDSTSIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMVTVSSPLGL SGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ	DIQMTQSPSSVSASVGD RVTITCRASQPISTWLV WYQHKPEKAPKLLIYA ASNLQSGVPSRFSGSGS GTDFTLTINSLQPDDFA TYYCQQANSFPYTFGQ GTKLDIKPLGLSGRSDN HDIQMTQSPSSLSASVG DRVTITCRASQDVNTA VAWYQQKPGKAPKLLI YSASFLYSGVPSRFSGS RSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFG QGTKVEIKRSVAAPSVF IFPPSDEQLKSGTASVV CLLNNFYPREAKVQWC VDNALQSGNSQESVTE QDSKDSTYSLSSTLTLS KADYEKHKVYACEVT

						VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1077)	HQGLSSPVTKSFNRGEC (SEQ ID NO:1078)
A39	B3	C1	DH3	DL2	BA-0102-044	QVQLVESGGGLVQPGHSLRLSCTSSGF NFGDHAVSWVRQAPGKGLEWVGFIRS KTYGGTPEYAASVKDRFSISRDDSKSS AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDMWGQGTLVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1079)	DIVMTQTPLSLPVIPGEP ASISCRSSQSLLHSNGY NYLDWYLQKPGQSPQL LIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEA EDVGVYYCMQTLQTL YTFGQGTKLEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1080)
A40	B3	C1	DH3	DL2	BA-0102-045	QVQLVESGGGLVQPGRSLRLSCTASGF IFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTDYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1081)	DIQMTQSPSSLSASVGD RITISCQASQDIKNYLN WYQKKPGKAPKLLIYG ASNLAAGVPSRFSGSG YGTDFTFIISGLQPEDV ATYYCQQYEELAALTF GGGTKVEIKPLGLSGRS DNHDIQMTQSPSSLSAS VGDRVTITCRASQDVN TAVAWYQQKPGKAPK LLIYSASFLYSGVPSRFS GSRSGTDFTLTISSLQPE DFATYYCQQHYTTPPT FGQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1082)
A41	B3	C1	DH3	DL2	BA-0102-	QVQLVESGGGLVQPGRSLRISCKASGF NFGDYPLTWVRQAPGKGLEWIGFIRSK	DIQMTQSPSSLSASVGD RVTITCRASQSISSWLA

					046	SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMVTVSSPLGL SGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1083)	WYQQKPGKAPKLLIYT SSTLQSEVPSRFSGSGS GTDFTLTISGLQPEDFA TYYCQQSYSLPRTFGPG TKVDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1084)
A44	B3	C1	DH3	DL2	BA-0102-047	QVQLVESGGGLVQPGRSLRLSCTASGF TFGDYAMSWVRQAPGKGLEWVGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1085)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLEWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQSLQTP PYTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1086)
A45	B3	C1	DH3	DL2	BA-0102-048	QMQLVESGGDLVQPGRSLRLSCRTSGF TFGEYAMSWVRQAPGKGLEWVGFIRS KAFGGTPEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD	DIQMTQSPSSVSASVGD RVTITCRASHDISSWLA WYQQKPGKAPKLLIYA TSSLQNGVPSRFSGSGS GTDFTLTISSLQPEDFAT YFCQQGKSFPYTFGQG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD

						TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1087)	RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1088)
A46	B3	C1	DH3	DL2	BA-0102-049	QVQLVESGGGLIHPGESLRLSCAASGF SFSSHAMSWVRQAPGKGLEWVATISE TGGIAFYADSVKGLFTISRDNSKNTLSL QMNSLRAEDTAVYYCARDGNYYDSR GYYYDTFDMWGQGTVVTVSSPLGLSG RSDNEVQLVESGGGLVQPGGSLRLSC AASGFNIKDTYIHWVRQAPGKGLEWV ARIYPTNGYTRYADSVKGRFTISADTS KNTAYLQMNSLRAEDTAVYYCSRWG GDGFYAMDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALGAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1089)	DIVMTQTPLSLPVTLGE PASISCRSSQSLLHTNG YNYLDWYLQKPGQSPQ LLVYSASTRASGVPDRF SGSGSGTDFTLKISRVE AEDVGIYYCMQALQTP WTFGQGTKVEIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1090)
A47	B3	C1	DH3	DL2	BA-0102-050	QVQLVQSGGGVVQPGTSLRLSCAASG FTFSSSTMHWVRQAPGKGLEWVAGFS YDGDTQWYADSVKGRFTISRDNSRNT LYLQMNSLRSEDTAVYYCARENVAAD WFDAWGQGALITVSSPLGLSGRSDNE VQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA	QSALTQPASVSGSPGQS ITFSCTGTSSDFGGYNY VSWYQQHPGKAPKLMI YDVSKRPSGVSNHFSGS KSGNTASLTISGLQAED EADYYCSSFTGDSVIFG GGTKLTVLPLGLSGRSD NHDIQMTQSPSSLSASV GDRVTITCRASQDVNT AVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPED FATYYCQQHYTTPPTF GQGTKVEIKRSVAAPS

						GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1091)	VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQESV TEQDSKDSTYSLSSTLT LSKADYEKHKVYACEV THQGLSSPVTKSFNRGE C(SEQ ID NO:1092)
A49	B3	C1	DH3	DL2	BA-0102-051	QVQLVESGGGLVKPGGSLRLSCAASG FTFGDYYMNWIRQAPGKGLEWVAYIS SSSAYTRYADSVKGRFTISRDNTKNSL YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1093)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YYYLDWYLQKPGQSPQ VLIYLGSNRAPGVPDRF SGSGSGTDFTLKISRVE ADDVGIYYCMQGLMTP FTFGPGTKLDIKPLGLS GRSDNHDIQMTQSPSSL SASVGDRVTITCRASQD VNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSR FSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTP PTFGQGTKVEIKRSVAA PSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKV QWCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYACE VTHQGLSSPVTKSFNRG EC(SEQ ID NO:1094)
A50	B3	C1	DH3	DL2	BA-0102-052	QVQLVESGGVAVQPGGSLRLSCTASG FTLDDYSMHWVRQRPGKGLEWVSVIY TGGNTYYSESVKGRFNIARDNSKNSLY LQMNSLRAEDTAVYYCARDGNYYDS RGYYYDTFDLWGQGTMVTVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN	PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQALRT PYTFGQGTKVDIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF

						NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1095)	NRGEC(SEQ ID NO:1096)
A51	B3	C1	DH3	DL2	BA-0102-053	QVQLVQSGAEVKKPGASVKVSCKVSG YTLSELSIHWVRQAPGKGLEWMGRFD PEDGETSYAQKFQGRVTMTEDTSTDT AYMELSSLRSEDTAVYYCARDGNYYD SRGYYYDTFDMWGQGTLVTVSSPLGL SGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1097)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLDWYLQKPGQSPQ LLIYMGSNRASGVPDRF SGSGSGTDFTLKISRVE AEDVGVYYCMQGLQT PYTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1098)
A52	B3	C1	DH3	DL2	BA-0102-054	QVQLVESGGGLIQPGRSLRLSCVGSGF KFGDYAMSWVRQAPGKGLEWVGFIR SKAYGGTTEYAASVKGRFDISRDDSES IAYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1099)	DIQMTQSPSSVSASVGD RVTITCRASQEITTWLA WYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFAT YYCQQADSFPYTFGQG TKVEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1100)
A53	B3	C1	DH3	DL2	BA-0102-055	QVQLVQSGAEVKKPGASVKLSCKASG YTFSSYWMHWVRQAPGQRLEWMGEI NPGNGHTNYNEKFKSRVTITVDKSAST	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHSNG YNYLGWYRQKPGQSP

						AYMELSSLRSEDTAVYYCARDGNYYD SRGYYYDTFDMWGQGTLVTVSSPLGL SGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1101)	QLLIYLGSNRAFGVPDR FSGSGSGTDYTLKISRV EAEDVGVYYCMQALR TPYTFGQGAKLDIKPLG LSGRSDNHDIQMTQSPS SLSASVGDRVTITCRAS QDVNTAVAWYQQKPG KAPKLLIYSASFLYSGV PSRFSGSRSGTDFTLTIS SLQPEDFATYYCQQHY TTPPTFGQGTKVEIKRS VAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPRE AKVQWCVDNALQSGN SQESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1102)
A54	B3	C1	DH3	DL2	BA-0102-056	QMQLVESGGGFVQPGRSLRLSCTASGF TFGDYAMSWVRQAPGRGLEWLGFIRS KAYGGTTEYAASVKGRFTISRDDSKSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1103)	DIQMTQSPSSVSASVGD KVTIACRASQGIVSWLA WYQQKPGKAPRLLIYA ASNLQDGVPSRFSGSGS GTVFTLTISSLQPEDFAT YYCQQANSFPYTFGQG TKLEIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1104)
A56	B3	C1	DH3	DL2	BA-0102-057	QMQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLTWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDMWGQGTLITVSSPLGLS GRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEW VARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRW	DIQMTQSPSSVSASIGD RVTITCRASEDISRQLA WYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFAT YYCQQANSFPYTFGQG TKLDIKPLGLSGRSDNH DIQMTQSPSSLSASVGD RVTITCRASQDVNTAV

						GGDGFYAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1105)	AWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGQ GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVC LLNNFYPREAKVQWCV DNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSK ADYEKHKVYACEVTH QGLSSPVTKSFNRGEC(SEQ ID NO:1106)
A57	B3	C1	DH3	DL2	BA-0102-058	QVQLVESGGGLVQPGRSLRLSCTASGF TFGDYALNWVRQAPGKGLEWVGFIRS QTYGGTTEYAASVKGRFTISRDDSRSI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMVTVSSPLG LSGRSDNEVQLVESGGGLVQPGGSLRL SCAASGFNIKDTYIHWVRQAPGKGLE WVARIYPTNGYTRYADSVKGRFTISAD TSKNTAYLQMNSLRAEDTAVYYCSR WGGDGFYAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1107)	DIVMTQTPLSLPVTPGE PASISCRSSQSLLHTNG YNYLDWYLQKPGQSPQ LLVYSASTRASGVPDRF SGSGSGTDFTLKISRLE AEDVGVYYCMQALQT PWTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPSS LSASVGDRVTITCRASQ DVNTAVAWYQQKPGK APKLLIYSASFLYSGVP SRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYT TPPTFGQGTKVEIKRSV AAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSLS STLTLSKADYEKHKVY ACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1108)

As a result, as shown in Figure 4, the productivity of the multispecific fusion protein up to the first purification was about 1 to 163% compared to the productivity of the single antibody Trastuzumab (average 141 mg/L). In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 83% to about 100%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed when compared to the sizes of the heavy chain and the light chain of each single antibody control, MA-01-Y065, respectively. The composition of the single antibodies is shown in Table 46.

Example 2.3.2. a DVD-Ig type multispecific fusion protein comprising a ReleaDome

[anti-ANXA1-anti-CD47]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to CD47 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a DVD-Ig form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD47, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CD47, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 28. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 28]

Part Number					Protein code	HC	LC
A55	B3	C3	DH1	DL1	BA-0107-001	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLGLSGRSDNQV QLQQPGAELVKPGASLRVSCKAS GYTFTNYWMYWVRQRPGRGLEW IGWIDPNSGGTKYNEKFKSKATLT VDKPSSTAYMQLSSLTSEDSAVYN CARGGYTMDYWGQGTSVTVSSA STKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGP	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH DVVMTQTPLSLPVS LGDQASISCRASQSL VHSNGNTYLHWYL QKPGQSPKLLIYKVS NRFSGVPDRFSGSGS GTDFTLKISRVEAED LGVYFCSQSTHVPLT FGAGTKLELKRSVA

						SVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1109)	APSVFIFPPSDEQLKS GTASVVCLLNNFYP REAKVQWKVDNAL QSGNSQESVTEQDS KDSTYSLSSTLTLSK ADYEKHKVYACEVT HQGLSSPVTKSFNR GEC(SEQ ID NO:1110)
A55	B3	C5	DH1	DL1	BA-0107-002	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLGLSGRSDNQV QLVQSGAEVKKPGASVKVSCKAS GYTFTNYNMHWVRQAPGQRLEW MGTIYPGNDDTSYNQKFKDRVTIT ADTSASTAYMELSSLRSEDTAVYY CARGGYRAMDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1111)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH DIVMTQSPLSLPVTP GEPASISCRSSQSIVY SNGNTYLGWYLQKP GQSPQLLIYKVSNRF SGVPDRFSGSGSGTD FTLKISRVEAEDVGV YYCFQGSHVPYTFG QGTKLEIKRSVAAPS VFIFPPSDEQLKSGT ASVVCLLNNFYPRE AKVQWKVDNALQS GNSQESVTEQDSKD STYSLSSTLTLSKAD YEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO:1112)
A55	B3	C7	DH1	DL1	BA-0107-003	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLGLSGRSDNQM QLVQSGAEVKKTGSSVKVSCKAS GFNIKDYYLHWVRQAPGQALEW MGWIDPDQGDTEYAQKFQDRVTI TRDRSMSTAYMELSSLRSEDTAM YYCNAAYGSSSYPMDYWGQGTIV TVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPE	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH NIQMTQSPSAMSAS VGDRVTITCKASQDI HRYLSWFQQKPGKV PKHLIYRANRLVSG VPSRFSGSGSGTEFT LTISSLQPEDFATYY CLQYDEFPYTFGGG TKVEIKRSVAAPSVF

						LLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP GK(SEQ ID NO:1113)	IFPPSDEQLKSGTAS VVCLLNNFYPREAK VQWKVDNALQSGN SQESVTEQDSKDST YSLSSTLTLSKADYE KHKVYACEVTHQGL SSPVTKSFNRGEC(S EQ ID NO:1114)
A55	B1	C3	DH 1	DL 1	BA- 0107- 004	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLSAAAGSDNQV QLQQPGAELVKPGASLRVSCKAS GYTFTNYWMYWVRQRPGRGLEW IGWIDPNSGGTKYNEKFKSKATLT VDKPSSTAYMQLSSLTSEDSAVYN CARGGYTMDYWGQGTSVTVSSA STKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1115)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLSAAAGSDNH DVVMTQTPLSLPVS LGDQASISCRASQSL VHSNGNTYLHWYL QKPGQSPKLLIYKVS NRFSGVPDRFSGSGS GTDFTLKISRVEAED LGVYFCSQSTHVPLT FGAGTKLELKRSVA APSVFIFPPSDEQLKS GTASVVCLLNNFYP REAKVQWKVDNAL QSGNSQESVTEQDS KDSTYSLSSTLTLSK ADYEKHKVYACEVT HQGLSSPVTKSFNR GEC(SEQ ID NO:1116)
A55	B2	C3	DH 1	DL 1	BA- 0107- 005	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQVQLQ QPGAELVKPGASLRVSCKASGYTF TNYWMYWVRQRPGRGLEWIGWI DPNSGGTKYNEKFKSKATLTVDK PSSTAYMQLSSLTSEDSAVYNCAR GGYTMDYWGQGTSVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVF	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKLSGRSDNHDV VMTQTPLSLPVSLG DQASISCRASQSLVH SNGNTYLHWYLQKP GQSPKLLIYKVSNRF SGVPDRFSGSGSGTD FTLKISRVEAEDLGV YFCSQSTHVPLTFGA GTKLELKRSVAAPS

						LFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1117)	VFIFPPSDEQLKSGT ASVVCLLNNFYPRE AKVQWKVDNALQS GNSQESVTEQDSKD STYSLSSTLTLSKAD YEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO:1118)
A55	B4	C3	DH1	DL1	BA-0107-006	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQVQLQ QPGAELVKPGASLRVSCKASGYTF TNYWMYWVRQRPGRGLEWIGWI DPNSGGTKYNEKFKSKATLTVDK PSSTAYMQLSSLTSEDSAVYNCAR GGYTMDYWGQGTSVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1119)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKLSGRSANPAGL YDVVMTQTPLSLPV SLGDQASISCRASQS LVHSNGNTYLHWYL QKPGQSPKLLIYKVS NRFSGVPDRFSGSGS GTDFTLKISRVEAED LGVYFCSQSTHVPLT FGAGTKLELKRSVA APSVFIFPPSDEQLKS GTASVVCLLNNFYP REAKVQWKVDNAL QSGNSQESVTEQDS KDSTYSLSSTLTLSK ADYEKHKVYACEVT HQGLSSPVTKSFNR GEC(SEQ ID NO:1120)
A55	B1	C5	DH1	DL1	BA-0107-007	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLSAAAGSDNQV QLVQSGAEVKKPGASVKVSCKAS GYTFTNYNMHWVRQAPGQRLEW MGTIYPGNDDTSYNQKFKDRVTIT ADTSASTAYMELSSLRSEDTAVYY CARGGYRAMDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGG	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLSAAAGSDNH DIVMTQSPLSLPVTP GEPASISCRSSQSIVY SNGNTYLGWYLQKP GQSPQLLIYKVSNRF SGVPDRFSGSGSGTD FTLKISRVEAEDVGV YYCFQGSHVPYTFG QGTKLEIKRSVAAPS

						PSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1121)	VFIFPPSDEQLKSGT ASVVCLLNNFYPRE AKVQWKVDNALQS GNSQESVTEQDSKD STYSLSSTLTLSKAD YEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO:1122)
A55	B2	C5	DH 1	DL 1	BA- 0107- 008	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQVQLV QSGAEVKKPGASVKVSCKASGYT FTNYNMHWVRQAPGQRLEWMGT IYPGNDDTSYNQKFKDRVTITADT SASTAYMELSSLRSEDTAVYYCAR GGYRAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1123)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKLSGRSDNHDIV MTQSPLSLPVTPGEP ASISCRSSQSIVYSNG NTYLGWYLQKPGQS PQLLIYKVSNRFSGV PDRFSGSGSGTDFTL KISRVEAEDVGVYY CFQGSHVPYTFGQG TKLEIKRSVAAPSVF IFPPSDEQLKSGTAS VVCLLNNFYPREAK VQWKVDNALQSGN SQESVTEQDSKDST YSLSSTLTLSKADYE KHKVYACEVTHQGL SSPVTKSFNRGEC(S EQ ID NO:1124)
A55	B4	C5	DH 1	DL 1	BA- 0107- 009	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSANPAGLQ VQLVQSGAEVKKPGASVKVSCKA SGYTFTNYNMHWVRQAPGQRLE WMGTIYPGNDDTSYNQKFKDRVT ITADTSASTAYMELSSLRSEDTAV YYCARGGYRAMDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELL	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKLSGRSANPAGL YDIVMTQSPLSLPVT PGEPASISCRSSQSIV YSNGNTYLGWYLQ KPGQSPQLLIYKVSN RFSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQGSHVPYT FGQGTKLEIKRSVAA

						GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1125)	PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1126)
A55	B5	C5	DH1	DL1	BA-0107-010	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLSGRSDNQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWVRQAPGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTSASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1127)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLSGRSDNHDIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKLEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1128)
A55	B6	C5	DH1	DL1	BA-0107-011	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYNMHWVRQAPGQRLEWMGTIYPGNDDTSYNQKFKDRVTITADTSASTAYMELSSLRSEDTAVYYCARGGYRAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLYDIVMTQSPLSLPVTPGEPASISCRSSQSIVYSNGNTYLGWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGQGTKL EIKRSVAAPSVFIFPP

						PPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK(SEQ ID NO:1129)	SDEQLKSGTASVVC LLNNFYPREAKVQW KVDNALQSGNSQES VTEQDSKDSTYSLSS TLTLSKADYEKHKV YACEVTHQGLSSPV TKSFNRGEC(SEQ ID NO:1130)
A55	B7	C5	DH1	DL1	BA-0107-012	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSASTKGQVQLVQS GAEVKKPGASVKVSCKASGYTFT NYNMHWVRQAPGQRLEWMGTIY PGNDDTSYNQKFKDRVTITADTSA STAYMELSSLRSEDTAVYYCARG GYRAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1131)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKASTKGPDIVMT QSPLSLPVTPGEPASI SCRSSQSIVYSNGNT YLGWYLQKPGQSPQ LLIYKVSNRFSGVPD RFSGSGSGTDFTLKI SRVEAEDVGVYYCF QGSHVPYTFGQGTK LEIKRSVAAPSVFIFP PSDEQLKSGTASVV CLLNNFYPREAKVQ WKVDNALQSGNSQ ESVTEQDSKDSTYSL SSTLTLSKADYEKH KVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1132)
A55	B8	C5	DH1	DL1	BA-0107-013	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLSAAAQVQLVQ SGAEVKKPGASVKVSCKASGYTF TNYNMHWVRQAPGQRLEWMGTI YPGNDDTSYNQKFKDRVTITADTS ASTAYMELSSLRSEDTAVYYCAR GGYRAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPS	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLSAAAHDIVM TQSPLSLPVTPGEPA SISCRSSQSIVYSNGN TYLGWYLQKPGQSP QLLIYKVSNRFSGVP DRFSGSGSGTDFTLK ISRVEAEDVGVYYC FQGSHVPYTFGQGT KLEIKRSVAAPSVFIF

						VFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1133)	PPSDEQLKSGTASVV CLLNNFYPREAKVQ WKVDNALQSGNSQ ESVTEQDSKDSTYSL SSTLTLSKADYEKH KVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1134)
A55	B6	C3	DH1	DL1	BA-0107-014	QVQLVQSGGGLVQPGRSLRISCKA SGFNFGDYPLSWVRQAPGKGLEW IGFIRSKSFGGTTEYAASVKGRFTI SRDDSRDIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDL WGQGTMITVSSPLGLQVQLQQPG AELVKPGASLRVSCKASGYTFTNY WMYWVRQRPGRGLEWIGWIDPN SGGTKYNEKFKSKATLTVDKPSST AYMQLSSLTSEDSAVYNCARGGY TMDYWGQGTSVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK(SEQ ID NO:1135)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLYDVVMT QTPLSLPVSLGDQAS ISCRASQSLVHSNGN TYLHWYLQKPGQSP KLLIYKVSNRFSGVP DRFSGSGSGTDFTLK ISRVEAEDLGVYFCS QSTHVPLTFGAGTK LELKRSVAAPSVFIF PPSDEQLKSGTASVV CLLNNFYPREAKVQ WKVDNALQSGNSQ ESVTEQDSKDSTYSL SSTLTLSKADYEKH KVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1136)

As a result, as shown in Figure 5, the productivity of the multispecific fusion protein up to the first purification was about 7% to about 129% compared to the productivity of the single antibody (MA-07-001, average 118 mg/L; MA-07-002, average 48 mg/L). In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 84% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed when compared to the sizes of the heavy chain and the light chain of each single antibody control, MA-01-Y829, MA-07-001, MA-07-002 or MA-07-003, respectively. The composition of the single antibodies is shown in Table 46.

Example 2.3.3. DVD-Ig type multispecific fusion protein comprising a ReleaDome

[anti-ANXA1-anti-EGFR]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to EGFR are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a DVD-Ig form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector. In this case, the C-terminus of some light chains was produced to comprise a first non-cleavable linker and a peptide motif. The amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 29. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 29]

Part Number					Protein code	HC	LC
A55	B3	C9	DH3	DL2	BA-0109-001	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL KQSGPGLVQPSQSLSITCTVSGFSLTNYGV HWVRQSPGKGLEWLGVIWSGGNTDYNT PFTSRLSINKDNSKSQVFFKMNSLQSNDT AIYYCARALTYYDYEFAYWGQGTLVTVS AASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCV	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHDILLTQSPVI LSVSPGERVSFSCRAS QSIGTNIHWYQQRTNG SPRLLIKYASESISGIPS RFSGSGSGTDFTLSINS VESEDIADYYCQQNN NWPTTFGAGTKLELK

						VVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALGAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1137)	RSVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFY PREAKVQWCVDNALQ SGNSQESVTEQDSKDS TYSLSSTLTLSKADYE KHKVYACEVTHQGLS SPVTKSFNRGEC(SEQ ID NO:1138)
A5 5	B 3	C 11	DH 3	DL 2	BA- 0109- 002	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKGLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1139)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPS SLSASVGDRVTITCQA SQDISNYLNWYQQKP GKAPKLLIYDASNLET GVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQ HFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPS DEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1140)
A5 5	B 3	C 13	DH 3	DL 2	BA- 0109- 003	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSQTLSLTCTVSGGSISSGDY YWSWIRQPPGKGLEWIGYIYYSGSTDYNP SLKSRVTMSVDTSKNQFSLKVNSVTAAD TAVYYCARVSIFGVGTFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALGAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1141)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHEIVMTQSPA TLSLSPGERATLSCRA SQSVSSYLAWYQQKP GQAPRLLIYDASNRAT GIPARFSGSGSGTDFTL TISSLEPEDFAVYYCH QYGSTPLTFGGGTKAE IKRSVAAPSVFIFPPSD EQLKSGTASVVCLLN NFYPREAKVQWCVDN ALQSGNSQESVTEQDS KDSTYSLSSTLTLSKA DYEKHKVYACEVTHQ GLSSPVTKSFNRGEC(S EQ ID NO:1142)

A55	B1	C13	DH2	DL2	BA-0109-004	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLSAAAGSDNQVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1143)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLSAAAGSDNHEIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAAEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1144)
A55	B2	C13	DH2	DL2	BA-0109-005	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1145)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGRSDNHEIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1146)
A55	B3	C13	DH2	DL2	BA-0109-006	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLSGRSDNQVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1147)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLSGRSDNHEIVMTQSPA

						TAVYYCARVSIFGVGTFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1147)	TLSLSPGERATLSCRA SQSVSSYLAWYQQKP GQAPRLLIYDASNRAT GIPARFSGSGSGTDFTL TISSLEPEDFAVYYCH QYGSTPLTFGGGTKAE IKRSVAAPSVFIFPPSD EQLKSGTASVVCLLN NFYPREAKVQWCVDN ALQSGNSQESVTEQDS KDSTYSLSSTLTLSKA DYEKHKVYACEVTHQ GLSSPVTKSFNRGEC(S EQ ID NO:1148)
A55	B4	C13	DH2	DL2	BA-0109-007	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSLSGRSANPAGLQVQ LQESGPGLVKPSQTLSLTCTVSGGSISSGD YYWSWIRQPPGKGLEWIGYIYYSGSTDY NPSLKSRVTMSVDTSKNQFSLKVNSVTA ADTAVYYCARVSIFGVGTFDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK(SEQ ID NO:1149)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SANPAGLYEIVMTQSP ATLSLSPGERATLSCR ASQSVSSYLAWYQQK PGQAPRLLIYDASNRA TGIPARFSGSGSGTDFT LTISSLEPEDFAVYYC HQYGSTPLTFGGGTK AEIKRSVAAPSVFIFPP SDEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1150)
A33	B4	C13	DH2	DL2	BA-0109-008	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSLSGRSANPAGLQVQLQESGP GLVKPSQTLSLTCTVSGGSISSGDYYWSW IRQPPGKGLEWIGYIYYSGSTDYNPSLKSR VTMSVDTSKNQFSLKVNSVTAADTAVYY CARVSIFGVGTFDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEY	DIQMTQSPSTLSASVG DRVTITCRASQNVDK WLAWYQQKPGKAPK LLIYKASGLESGVPSRF SGSGSGTEFTLTISSLQ PDDFATYYCQQYDSY PLTFGGGTKVEIKLSG RSANPAGLYEIVMTQS PATLSLSPGERATLSC RASQSVSSYLAWYQQ KPGQAPRLLIYDASNR ATGIPARFSGSGSGTD FTLTISSLEPEDFAVYY CHQYGSTPLTFGGGTK AEIKRSVAAPSVFIFPP SDEQLKSGTASVVCLL

						KCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1151)	NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1152)
A55	B5	C13	DH2	DL2	BA-0109-009	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLSGRSDNQVQLQES GPGLVKPSQTLSLTCTVSGGSISSGDYYW SWIRQPPGKGLEWIGYIYYSGSTDYNPSL KSRVTMSVDTSKNQFSLKVNSVTAADTA VYYCARVSIFGVGTFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1153)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLSG RSDNHEIVMTQSPATL SLSPGERATLSCRASQ SVSSYLAWYQQKPGQ APRLLIYDASNRATGIP ARFSGSGSGTDFTLTIS SLEPEDFAVYYCHQY GSTPLTFGGGTKAEIK RSVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFY PREAKVQWCVDNALQ SGNSQESVTEQDSKDS TYSLSSTLTLSKADYE KHKVYACEVTHQGLS SPVTKSFNRGEC(SEQ ID NO:1154)
A55	B6	C13	DH2	DL2	BA-0109-010	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLQVQLQESGPGL VKPSQTLSLTCTVSGGSISSGDYYWSWIR QPPGKGLEWIGYIYYSGSTDYNPSLKSRV TMSVDTSKNQFSLKVNSVTAADTAVYYC ARVSIFGVGTFDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1155)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YEIVMTQSPATLSLSP GERATLSCRASQSVSS YLAWYQQKPGQAPRL LIYDASNRATGIPARFS GSGSGTDFTLTISSLEP EDFAVYYCHQYGSTP LTFGGGTKAEIKRSVA APSVFIFPPSDEQLKSG TASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1156)
A55	B1	C11	DH2	DL2	BA-0109-	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW

					011	TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLSAAAGSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKGLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1157)	LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLSA AAGSDNHDIQMTQSPS SLSASVGDRVTITCQA SQDISNYLNWYQQKP GKAPKLLIYDASNLET GVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQ HFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPS DEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1158)
A55	B2	C11	DH2	DL2	BA-0109-012	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSLSGRSDNQVQLQES GPGLVKPSETLSLTCTVSGGSVSSGDYYW TWIRQSPGKGLEWIGHIYYSGNTNYNPSL KSRLTISIDTSKTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGTMVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1159)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1160)
A55	B3	C11	DH2	DL2	BA-0109-013	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKGLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVK	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPS SLSASVGDRVTITCQA SQDISNYLNWYQQKP

						DYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1161)	GKAPKLLIYDASNLET GVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQ HFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPS DEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1162)
A55	B4	C11	DH2	DL2	BA-0109-014	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSLSGRSANPAGLQVQ LQESGPGLVKPSETLSLTCTVSGGSVSSG DYYWTWIRQSPGKGLEWIGHIYYSGNTN YNPSLKSRLTISIDTSKTQFSLKLSSVTAA DTAIYYCVRDRVTGAFDIWGQGTMVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1163)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SANPAGLYDIQMTQSP SSLSASVGDRVTITCQ ASQDISNYLNWYQQK PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLQPEDIATYFC QHFDHLPLAFGGGTK VEIKRSVAAPSVFIFPP SDEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1164)
A55	B5	C11	DH2	DL2	BA-0109-015	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLSGRSDNQVQLQES GPGLVKPSETLSLTCTVSGGSVSSGDYYW TWIRQSPGKGLEWIGHIYYSGNTNYNPSL KSRLTISIDTSKTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGTMVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAV	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLSG RSDNHDIQMTQSPSSL SASVGDRVTITCQASQ DISNYLNWYQQKPGK APKLLIYDASNLETGV PSRFSGSGSGTDFTFTI SSLQPEDIATYFCQHF DHLPLAFGGGTKVEIK RSVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFY PREAKVQWCVDNALQ SGNSQESVTEQDSKDS

						EWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1165)	TYSLSSTLTLSKADYE KHKVYACEVTHQGLS SPVTKSFNRGEC(SEQ ID NO:1166)
A5 5	B 6	C 11	DH 2	DL 2	BA- 0109- 016	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLQVQLQESGPGL VKPSETLSLTCTVSGGSVSSGDYYWTWIR QSPGKGLEWIGHIYYSGNTNYNPSLKSRL TISIDTSKTQFSLKLSSVTAADTAIYYCVR DRVTGAFDIWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK(SEQ ID NO:1167)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YDIQMTQSPSSLSASV GDRVTITCQASQDISN YLNWYQQKPGKAPKL LIYDASNLETGVPSRFS GSGSGTDFTFTISSLQP EDIATYFCQHFDHLPL AFGGGTKVEIKRSVAA PSVFIFPPSDEQLKSGT ASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1168)
A5 5	B 7	C 11	DH 2	DL 2	BA- 0109- 017	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSASTKGQVQLQESGP GLVKPSETLSLTCTVSGGSVSSGDYYWT WIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYC VRDRVTGAFDIWGQGTMVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1169)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKASTK GPDIQMTQSPSSLSAS VGDRVTITCQASQDIS NYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1170)
A5 5	B 8	C 11	DH 2	DL 2	BA- 0109- 018	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS

						FDLWGQGTMITVSSPLSAAAQVQLQESG PGLVKPSETLSLTCTVSGGSVSSGDYYWT WIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYC VRDRVTGAFDIWGQGTMVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1171)	GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLSA AAHDIQMTQSPSSLSA SVGDRVTITCQASQDI SNYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1172)
A55	B3	C12	DH2	DL2	BA-0109-019	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKCLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1173)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPS SLSASVGDRVTITCQA SQDISNYLNWYQQKP GKAPKLLIYDASNLET GVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQ HFDHLPLAFGCGTKVE IKRSVAAPSVFIFPPSD EQLKSGTASVVCLLN NFYPREAKVQWCVDN ALQSGNSQESVTEQDS KDSTYSLSSTLTLSKA DYEKHKVYACEVTHQ GLSSPVTKSFNRGEC(SEQ ID NO:1174)
A55	B3/B7	C11	DH2	DL2	BA-0109-020	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKGLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKP	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKASTK GPDIQMTQSPSSLSAS VGDRVTITCQASQDIS NYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS

						SNTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1175)	LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1176)
A55	B7/B3	C11	DH2	DL2	BA-0109-021	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSASTKGQVQLQESGP GLVKPSETLSLTCTVSGGSVSSGDYYWT WIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYC VRDRVTGAFDIWGQGTMVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1177)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL SGRSDNHDIQMTQSPS SLSASVGDRVTITCQA SQDISNYLNWYQQKP GKAPKLLIYDASNLET GVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQ HFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPS DEQLKSGTASVVCLL NNFYPREAKVQWCVD NALQSGNSQESVTEQ DSKDSTYSLSSTLTLS KADYEKHKVYACEVT HQGLSSPVTKSFNRGE C(SEQ ID NO:1178)
A33	B6	C11	DH2	DL2	BA-0109-024	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLQVQLQESGPGLVKPSE TLSLTCTVSGGSVSSGDYYWTWIRQSPGK GLEWIGHIYYSGNTNYNPSLKSRLTISIDT SKTQFSLKLSSVTAADTAIYYCVRDRVTG AFDIWGQGTMVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG	DIQMTQSPSTLSASVG DRVTITCRASQNVDK WLAWYQQKPGKAPK LLIYKASGLESGVPSRF SGSGSGTEFTLTISSLQ PDDFATYYCQQYDSY PLTFGGGTKVEIKPLG LYDIQMTQSPSSLSAS VGDRVTITCQASQDIS NYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS

						K(SEQ ID NO:1179)	PVTKSFNRGEC(SEQ ID NO:1180)
A33	B7	C11	DH2	DL2	BA-0109-025	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSASTKGQVQLQESGPGLVKPS ETLSLTCTVSGGSVSSGDYYWTWIRQSPG KGLEWIGHIYYSGNTNYNPSLKSRLTISID TSKTQFSLKLSSVTAADTAIYYCVRDRVT GAFDIWGQGTMVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPEAAGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PGK(SEQ ID NO:1181)	DIQMTQSPSTLSASVG DRVTITCRASQNVDK WLAWYQQKPGKAPK LLIYKASGLESGVPSRF SGSGSGTEFTLTISSLQ PDDFATYYCQQYDSY PLTFGGGTKVEIKAST KGPDIQMTQSPSSLSA SVGDRVTITCQASQDI SNYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1182)
A58	B6	C11	DH2	DL2	BA-0109-026	EVQLLESGGGLVQPGGSLRLSCAASGFTF SGYYMSWVRQAPGKGLEWVSSISPSGSSI YYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCAKGSPGFDYWGQGTLVT VSSPLGLQVQLQESGPGLVKPSETLSLTCT VSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYNPSLKSRLTISIDTSKTQFSL KLSSVTAADTAIYYCVRDRVTGAFDIWG QGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1183)	QSVLTQPPSASGAPGQ RVTISCSGSSFNIGSND VSWYQQLPGTAPKLLI YSDSHRPSGVPDRFSG SKSGTSASLAISGLQSE DEADYYCGSWDYSLS AYVFGGGTKLTVLPL GLYDIQMTQSPSSLSA SVGDRVTITCQASQDI SNYLNWYQQKPGKAP KLLIYDASNLETGVPS RFSGSGSGTDFTFTISS LQPEDIATYFCQHFDH LPLAFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1184)
A58	B7	C11	DH2	DL2	BA-0109-027	EVQLLESGGGLVQPGGSLRLSCAASGFTF SGYYMSWVRQAPGKGLEWVSSISPSGSSI YYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCAKGSPGFDYWGQGTLVT VSSASTKGQVQLQESGPGLVKPSETLSLT CTVSGGSVSSGDYYWTWIRQSPGKGLEW	QSVLTQPPSASGAPGQ RVTISCSGSSFNIGSND VSWYQQLPGTAPKLLI YSDSHRPSGVPDRFSG SKSGTSASLAISGLQSE DEADYYCGSWDYSLS

						IGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1185)	AYVFGGGTKLTVLASTKGPDIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1186)
A55	B9	C11	DH2	DL2	BA-0109-028	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSEADQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1187)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKEADHDIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1188)
A55	B2	C11	DH2	DL4	BA-0109-029	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGRSDNHDIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKR

						HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1159)	SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGECGGGG GGGCVIM(SEQ ID NO:1189)
A55	B6	C11	DH2	DL4	BA-0109-030	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLQVQLQESGPGL VKPSETLSLTCTVSGGSVSSGDYYWTWIR QSPGKGLEWIGHIYYSGNTNYNPSLKSRL TISIDTSKTQFSLKLSSVTAADTAIYYCVR DRVTGAFDIWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK(SEQ ID NO:1167)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YDIQMTQSPSSLSASV GDRVTITCQASQDISN YLNWYQQKPGKAPKL LIYDASNLETGVPSRFS GSGSGTDFTFTISSLQP EDIATYFCQHFDHLPL AFGGGTKVEIKRSVAA PSVFIFPPSDEQLKSGT ASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGECGGGGGGC VIM(SEQ ID NO:1190)
A59	B2	C11	DH2	DL2	BA-0109-031	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSLSGRSDNQVQLQES GPGLVKPSETLSLTCTVSGGSVSSGDYYW TWIRQSPGKGLEWIGHIYYSGNTNYNPSL KSRLTISIDTSKTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGTMVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1191)	DIVMTQTPLSLPVTPG EPASISCRSSQSLLHSN GYNYLDWYLQKPGQS PQLLIYMGSNRASGVP DRFSGSGSGTDFTLKIS RVEAEDVGVYYCMQ ALQTQLTFGGGTKVEI KLSGRSDNHDIQMTQS PSSLSASVGDRVTITC QASQDISNYLNWYQQ KPGKAPKLLIYDASNL ETGVPSRFSGSGSGTD FTFTISSLQPEDIATYF CQHFDHLPLAFGGGT KVEIKRSVAAPSVFIFP PSDEQLKSGTASVVCL LNNFYPREAKVQWCV DNALQSGNSQESVTE QDSKDSTYSLSSTLTL SKADYEKHKVYACEV THQGLSSPVTKSFNRG

							EC(SEQ ID NO:1192)
A62	B2	C11	DH2	DL2	BA-0109-032	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKRIGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1193)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGRSDNHDIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1194)
A63	B2	C11	DH2	DL2	BA-0109-033	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKRYGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1195)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGRSDNHDIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1196)
A65	B2	C11	DH2	DL2	BA-0109-034	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRDKTVGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYN	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGR

						PSLKSRLTISIDTSKTQFSLKLSSVTAADTA IYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1197)	SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1198)
A66	B2	C11	DH2	DL2	BA-0109-035	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRDKTY GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSLSGRSDNQVQLQ ESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYN PSLKSRLTISIDTSKTQFSLKLSSVTAADTA IYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1199)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1200)
A68	B2	C11	DH2	DL2	BA-0109-036	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRPKWL GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSLSGRSDNQVQLQ ESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYN PSLKSRLTISIDTSKTQFSLKLSSVTAADTA IYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL

						REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1201)	KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1202)
A62	B2	C11	DH2	DL2	BA-0109-037	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRDKRIG GTTEYAASVKGRFTISRDDSRDIAYLQMN SLRAEDTAVYYCARDGNYYDSRGYYYD TFDLWGQGTMITVSSLSGRSDNQVQLQE SGPGLVKPSETLSLTCTVSGGSVSSGDYY WTWIRQSPGKGLEWIGHIYYSGNTNYNP SLKSRLTISIDTSKTQFSLKLSSVTAADTAI YYCVRDRVTGAFDIWGQGTMVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1193)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1194)
A65	B2	C11	DH2	DL2	BA-0109-038	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRDKTV GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSLSGRSDNQVQLQ ESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYN PSLKSRLTISIDTSKTQFSLKLSSVTAADTA IYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1197)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1198)
A6	B	C	DH	DL	BA-	QVQLVQSGGGLVQPGRSLRLSCKASGFN	DIQMTQSPSSVSASVG

8	2	11	2	2	0109-039	FGDYPLSWVRQAPGKGLEWIGFIRPKWL GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSLSGRSDNQVQLQ ESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYN PSLKSRLTISIDTSKTQFSLKLSSVTAADTA IYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1201)	DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKLSGR SDNHDIQMTQSPSSLS ASVGDRVTITCQASQD ISNYLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTIS SLQPEDIATYFCQHFD HLPLAFGGGTKVEIKR SVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYP REAKVQWCVDNALQS GNSQESVTEQDSKDST YSLSSTLTLSKADYEK HKVYACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1202)
A62	B6	C11	DH2	DL2	BA-0109-040	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRDKRIG GTTEYAASVKGRFTISRDDSRDIAYLQMN SLRAEDTAVYYCARDGNYYDSRGYYYD TFDLWGQGTMITVSSPLGLQVQLQESGPG LVKPSETLSLTCTVSGGSVSSGDYYWTWI RQSPGKGLEWIGHIYYSGNTNYNPSLKSR LTISIDTSKTQFSLKLSSVTAADTAIYYCV RDRVTGAFDIWGQGTMVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1203)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YDIQMTQSPSSLSASV GDRVTITCQASQDISN YLNWYQQKPGKAPKL LIYDASNLETGVPSRFS GSGSGTDFTFTISSLQP EDIATYFCQHFDHLPL AFGGGTKVEIKRSVAA PSVFIFPPSDEQLKSGT ASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1204)
A65	B6	C11	DH2	DL2	BA-0109-041	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRDKTV GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSPLGLQVQLQESGP GLVKPSETLSLTCTVSGGSVSSGDYYWT WIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYC VRDRVTGAFDIWGQGTMVTVSSASTKGP	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YDIQMTQSPSSLSASV GDRVTITCQASQDISN

						SVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1205)	YLNWYQQKPGKAPKL LIYDASNLETGVPSRFS GSGSGTDFTFTISSLQP EDIATYFCQHFDHLPL AFGGGTKVEIKRSVAA PSVFIFPPSDEQLKSGT ASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1206)
A68	B6	C11	DH2	DL2	BA-0109-042	QVQLVQSGGGLVQPGRSLRLSCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRPKWL GGTTEYAASVKGRFTISRDDSRDIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSPLGLQVQLQESGP GLVKPSETLSLTCTVSGGSVSSGDYYWT WIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYC VRDRVTGAFDIWGQGTMVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1207)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLL IYAASNLQSGVPSRFS GSGSGTDFILTINSLQP DDFATYYCQQANSFP YTFGQGTKVEIKPLGL YDIQMTQSPSSLSASV GDRVTITCQASQDISN YLNWYQQKPGKAPKL LIYDASNLETGVPSRFS GSGSGTDFTFTISSLQP EDIATYFCQHFDHLPL AFGGGTKVEIKRSVAA PSVFIFPPSDEQLKSGT ASVVCLLNNFYPREA KVQWCVDNALQSGNS QESVTEQDSKDSTYSL SSTLTLSKADYEKHKV YACEVTHQGLSSPVTK SFNRGEC(SEQ ID NO:1208)

As a result, as shown in Figure 6, the productivity of the multispecific fusion protein of the multispecific fusion protein up to the first purification was about 1% to about 90% compared to the productivity (average 40 mg/L, 201 mg/L, 80 mg/L) of the single antibody (MA-09-001, MA-09-002, MA-09-003). In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 71% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed when compared to the sizes of the heavy chain and the light chain of each single antibody control, MA-01-Y065, respectively. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 83% to about 100%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed when compared to the sizes of

the heavy chain and the light chain of each single antibody control, MA-09-001, MA-09-002, or MA-09-003, respectively. The composition of the single antibodies is shown in Table 46.

Example 2.3.4. DVD-Ig type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-DLK1]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to DLK1 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a DVD-Ig form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to DLK1, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to DLK1, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector. In this case, the C-terminus of some light chains was produced to comprise a first non-cleavable linker and a peptide motif. The amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 30. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 30]

Part Number					Protein code	HC	LC
A55	B1	C20	DH2	DL2	BA-0113-001	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLSAAAGSDNQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGP	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLSAAAGSDNHDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAP

						SVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSL SPGK(SEQ ID NO:1209)	KLLIYGAASLQSAVAS RFSGSGSGTEFTLTISSL QPEDFANYYCQQIYTT PLTFGGGTKVEIKRSV AAPSVFIFPPSDEQLKS GTASVVCLLNNFYPRE AKVQWCVDNALQSGN SQESVTEQDSKDSTYS LSSTLTLSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC (SEQ ID NO:1210)
A55	B2	C202	DH2	DL2	BA-0113-002	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSLSGR SDNQVQLVQSGGAVVQPGHSLRLSCE ASGFKFKDYGMHWVRQAPGKGLEWL AVISHDGRNKNYADSVKGRLTISRDNS KNTLSFQMNSLRAEDTAVYYCVRDWS YAFDIWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1211)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKLSGRSD NHDIQMTQSPSFLSASV GDRVNITCRASQDISRR LAWYQQKPGKAPKLLI YGAASLQSAVASRFSG SGSGTEFTLTISSLQPED FANYYCQQIYTTPLTF GGGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGEC(SEQ ID NO:1212)
A55	B3	C202	DH2	DL2	BA-0113-003	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLGLS GRSDNQVQLVQSGGAVVQPGHSLRLS CEASGFKFKDYGMHWVRQAPGKGLE WLAVISHDGRNKNYADSVKGRLTISR DNSKNTLSFQMNSLRAEDTAVYYCVR DWSYAFDIWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHN	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKPLGLSG RSDNHDIQMTQSPSFLS ASVGDRVNITCRASQD ISRRLAWYQQKPGKAP KLLIYGAASLQSAVAS RFSGSGSGTEFTLTISSL QPEDFANYYCQQIYTT PLTFGGGTKVEIKRSV AAPSVFIFPPSDEQLKS GTASVVCLLNNFYPRE

						AKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSP GK(SEQ ID NO:1213)	AKVQWCVDNALQSGN SQESVTEQDSKDSTYS LSSTLTLSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1214)
A5 5	B 4	C20	DH 2	DL 2	BA- 0113- 004	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSLSGR SANPAGLQVQLVQSGGAVVQPGHSLR LSCEASGFKFKDYGMHWVRQAPGKG LEWLAVISHDGRNKNYADSVKGRLTIS RDNSKNTLSFQMNSLRAEDTAVYYCV RDWSYAFDIWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSL SPGK(SEQ ID NO:1215)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKLSGRSA NPAGLYDIQMTQSPSF LSASVGDRVNITCRAS QDISRRLAWYQQKPGK APKLLIYGAASLQSAV ASRFSGSGSGTEFTLTIS SLQPEDFANYYCQQIY TTPLTFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWCVDNALQSG NSQESVTEQDSKDSTY SLSSTLTLSKADYEKH KVYACEVTHQGLSSPV TKSFNRGEC(SEQ ID NO:1216)
A5 5	B 5	C20	DH 2	DL 2	BA- 0113- 005	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLSG RSDNQVQLVQSGGAVVQPGHSLRLSC EASGFKFKDYGMHWVRQAPGKGLEW LAVISHDGRNKNYADSVKGRLTISRDN SKNTLSFQMNSLRAEDTAVYYCVRDW SYAFDIWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKPLSGRSD NHDIQMTQSPSFLSASV GDRVNITCRASQDISRR LAWYQQKPGKAPKLLI YGAASLQSAVASRFSG SGSGTEFTLTISSLQPED FANYYCQQIYTTPLTF GGGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGEC(SEQ ID NO:1218)

						SEQ ID NO:1217)	
A55	B6	C20	DH2	DL2	BA-0113-006	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1219)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLYDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1220)
A55	B7	C20	DH2	DL2	BA-0113-007	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSASTKGQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1221)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKASTKGPDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1222)
A55	B8	C20	DH2	DL2	BA-0113-008	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLSA	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPD

						AAQVQLVQSGGAVVQPGHSLRLSCEA SGFKFKDYGMHWVRQAPGKGLEWLA VISHDGRNKNYADSVKGRLTISRDNSK NTLSFQMNSLRAEDTAVYYCVRDWSY AFDIWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1223)	DFATYYCQQANSFPYT FGQGTKVEIKPLSAAA HDIQMTQSPSFLSASVG DRVNITCRASQDISRRL AWYQQKPGKAPKLLIY GAASLQSAVASRFSGS GSGTEFTLTISSLQPEDF ANYYCQQIYTTPLTFG GGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASV VCLLNNFYPREAKVQ WCVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGEC(SEQ ID NO:1224)
A55	B9	C20	DH2	DL2	BA-0113-009	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSEADQ VQLVQSGGAVVQPGHSLRLSCEASGF KFKDYGMHWVRQAPGKGLEWLAVIS HDGRNKNYADSVKGRLTISRDNSKNT LSFQMNSLRAEDTAVYYCVRDWSYAF DIWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1225)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKEADHDI QMTQSPSFLSASVGDR VNITCRASQDISRRLA WYQQKPGKAPKLLIYG AASLQSAVASRFSGSG SGTEFTLTISSLQPEDFA NYYCQQIYTTPLTFGG GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVV CLLNNFYPREAKVQW CVDNALQSGNSQESVT EQDSKDSTYSLSSTLTL SKADYEKHKVYACEV THQGLSSPVTKSFNRG EC(SEQ ID NO:1226)
A55	B1	C20	DH2	DL4	BA-0113-010	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLSA AAGSDNQVQLVQSGGAVVQPGHSLRL SCEASGFKFKDYGMHWVRQAPGKGL EWLAVISHDGRNKNYADSVKGRLTIS RDNSKNTLSFQMNSLRAEDTAVYYCV RDWSYAFDIWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYF	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKPLSAAA GSDNHDIQMTQSPSFLS ASVGDRVNITCRASQD ISRRLAWYQQKPGKAP KLLIYGAASLQSAVAS

						PEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSL SPGK(SEQ ID NO:1209)	RFSGSGSGTEFTLTISSL QPEDFANYYCQQIYTT PLTFGGGTKVEIKRSV AAPSVFIFPPSDEQLKS GTASVVCLLNNFYPRE AKVQWKVDNALQSGN SQESVTEQDSKDSTYS LSSTLTLSKADYEKHK VYACEVTHQGLSSPVT KSFNRGECGGGGGGG CVIM(SEQ ID NO:1227)
A55	B2	C20	DH2	DL4	BA-0113-011	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSLSGR SDNQVQLVQSGGAVVQPGHSLRLSCE ASGFKFKDYGMHWVRQAPGKGLEWL AVISHDGRNKNYADSVKGRLTISRDNS KNTLSFQMNSLRAEDTAVYYCVRDWS YAFDIWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1211)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKLSGRSD NHDIQMTQSPSFLSASV GDRVNITCRASQDISRR LAWYQQKPGKAPKLLI YGAASLQSAVASRFSG SGSGTEFTLTISSLQPED FANYYCQQIYTTPLTF GGGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WKVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGECGGGGGGGCVIM(SEQ ID NO:1228)
A55	B3	C20	DH2	DL4	BA-0113-012	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLGLS GRSDNQVQLVQSGGAVVQPGHSLRLS CEASGFKFKDYGMHWVRQAPGKGLE WLAVISHDGRNKNYADSVKGRLTISR DNSKNTLSFQMNSLRAEDTAVYYCVR DWSYAFDIWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQD	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKPLGLSG RSDNHDIQMTQSPSFLS ASVGDRVNITCRASQD ISRRLAWYQQKPGKAP KLLIYGAASLQSAVAS RFSGSGSGTEFTLTISSL QPEDFANYYCQQIYTT PLTFGGGTKVEIKRSV AAPSVFIFPPSDEQLKS GTASVVCLLNNFYPRE AKVQWKVDNALQSGN

						WLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSP GK(SEQ ID NO:1213)	SQESVTEQDSKDSTYS LSSTLTLSKADYEKHK VYACEVTHQGLSSPVT KSFNRGECGGGGGGG CVIM(SEQ ID NO:1229)
A55	B4	C20	DH2	DL4	BA-0113-013	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSLSGR SANPAGLQVQLVQSGGAVVQPGHSLR LSCEASGFKFKDYGMHWVRQAPGKG LEWLAVISHDGRNKNYADSVKGRLTIS RDNSKNTLSFQMNSLRAEDTAVYYCV RDWSYAFDIWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSL SPGK(SEQ ID NO:1215)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKLSGRSA NPAGLYDIQMTQSPSF LSASVGDRVNITCRAS QDISRRLAWYQQKPGK APKLLIYGAASLQSAV ASRFSGSGSGTEFTLTIS SLQPEDFANYYCQQIY TTPLTFGGGTKVEIKRS VAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPR EAKVQWKVDNALQSG NSQESVTEQDSKDSTY SLSSTLTLSKADYEKH KVYACEVTHQGLSSPV TKSFNRGECGGGGGG GCVIM(SEQ ID NO:1230)
A55	B5	C20	DH2	DL4	BA-0113-014	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSPLSG RSDNQVQLVQSGGAVVQPGHSLRLSC EASGFKFKDYGMHWVRQAPGKGLEW LAVISHDGRNKNYADSVKGRLTISRDN SKNTLSFQMNSLRAEDTAVYYCVRDW SYAFDIWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1217)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKPLSGRSD NHDIQMTQSPSFLSASV GDRVNITCRASQDISRR LAWYQQKPGKAPKLLI YGAASLQSAVASRFSG SGSGTEFTLTISSLQPED FANYYCQQIYTTPLTF GGGTKVEIKRSVAAPS VFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQ WKVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGECGGGGGGCVIM(SEQ ID NO:1231)

A55	B6	C20	DH2	DL4	BA-0113-015	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1219)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLYDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGCVIM(SEQ ID NO:1232)
A55	B7	C20	DH2	DL4	BA-0113-016	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSASTKGQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1221)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKASTKGPDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGCVIM(SEQ ID NO:1233)
A55	B8	C20	DH2	DL4	BA-0113-017	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLSAAAQVQLVQSGGAVVQPGHSLRLSCEA	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYT

						SGFKFKDYGMHWVRQAPGKGLEWLA VISHDGRNKNYADSVKGRLTISRDNSK NTLSFQMNSLRAEDTAVYYCVRDWSY AFDIWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1223)	FGQGTKVEIKPLSAAA HDIQMTQSPSFLSASVG DRVNITCRASQDISRRL AWYQQKPGKAPKLLIY GAASLQSAVASRFSGS GSGTEFTLTISSLQPEDF ANYYCQQIYTTPLTFG GGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASV VCLLNNFYPREAKVQ WKVDNALQSGNSQES VTEQDSKDSTYSLSSTL TLSKADYEKHKVYAC EVTHQGLSSPVTKSFN RGECGGGGGGGCVIM(SEQ ID NO:1234)
A55	B9	C20	DH2	DL4	BA-0113-018	QVQLVQSGGGLVQPGRSLRISCKASGF NFGDYPLSWVRQAPGKGLEWIGFIRSK SFGGTTEYAASVKGRFTISRDDSRDIA YLQMNSLRAEDTAVYYCARDGNYYD SRGYYYDTFDLWGQGTMITVSSEADQ VQLVQSGGAVVQPGHSLRLSCEASGF KFKDYGMHWVRQAPGKGLEWLAVIS HDGRNKNYADSVKGRLTISRDNSKNT LSFQMNSLRAEDTAVYYCVRDWSYAF DIWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1225)	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKEADHDI QMTQSPSFLSASVGDR VNITCRASQDISRRLA WYQQKPGKAPKLLIYG AASLQSAVASRFSGSG SGTEFTLTISSLQPEDFA NYYCQQIYTTPLTFGG GTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVV CLLNNFYPREAKVQW KVDNALQSGNSQESVT EQDSKDSTYSLSSTLTL SKADYEKHKVYACEV THQGLSSPVTKSFNRG ECGGGGGGGCVIM(SE Q ID NO:1235)
A69	B2	C20	DH2	DL4	BA-0113-019	QVQLVQSGGGLVQPGRSLRLSCKASG FNFGDYPLSWVRQAPGKGLEWIGFIRS KSFGGTTEYAASVKGRFTISRDDSRDI AYLQMNSLRAEDTAVYYCARDGNYY DSRGYYYDTFDLWGQGTMITVSSLSG RSDNQVQLVQSGGAVVQPGHSLRLSC EASGFKFKDYGMHWVRQAPGKGLEW LAVISHDGRNKNYADSVKGRLTISRDN SKNTLSFQMNSLRAEDTAVYYCVRDW SYAFDIWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYS	DIQMTQSPSSVSASVG DRVTLTCRASQGIRSW LAWYQQKPGKAPKLLI YAASNLQSGVPSRFSG SGSGTDFILTINSLQPD DFATYYCQQANSFPYT FGQGTKVEIKLSGRSD NHDIQMTQSPSFLSASV GDRVNITCRASQDISRR LAWYQQKPGKAPKLLI YGAASLQSAVASRFSG SGSGTEFTLTISSLQPED

						LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1236)	FANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGCVIM(SEQ ID NO:1237)
A69	B6	C20	DH2	DL4	BA-0113-020	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLQVQLVQSGGAVVQPGHSLRLSCEASGFKFKDYGMHWVRQAPGKGLEWLAVISHDGRNKNYADSVKGRLTISRDNSKNTLSFQMNSLRAEDTAVYYCVRDWSYAFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1238)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLYDIQMTQSPSFLSASVGDRVNITCRASQDISRRLAWYQQKPGKAPKLLIYGAASLQSAVASRFSGSGSGTEFTLTISSLQPEDFANYYCQQIYTTPLTFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGCVIM(SEQ ID NO:1239)

As a result, as shown in Figure 7, the productivity of the multispecific fusion protein up to the first purification was about 5 mg/L to about 96 mg/L. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 81% to about 98%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed. The composition of the single antibodies is shown in Table 46.

Example 2.3.5. DVD-Ig type multispecific fusion protein comprising a ReleaDome targeting various disease-related proteins

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first

domain (first component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to Annexin A1 (ANXA1), and a second domain (third component) comprising a heavy chain variable region and a light chain variable region of an antibody that binds to various disease site-specific overexpressed proteins (e.g., CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, or Amyloid-beta (Aβ) protofibrils) are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a DVD-Ig form or a structure modified therefrom (Table 31).

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, or Aβ protofibrils, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, or Aβ protofibrils, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 32. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 31]

Part Number					Structure code	Structure type	Target of first component	Target of third component	Molecular weight (LC/MS)	PI
A55	B2	C22	DH2	DL2	ST-001	DVD-IgG LALA	ANXA1	CLDN18.2	201694	8.6
A55	B2	C23	DH2	DL2	ST-002	DVD-IgG LALA	ANXA1	CLDN18.2	199113	8.6
A55	B2	C24	DH2	DL2	ST-003	DVD-IgG LALA	ANXA1	TEM8	199962	8.1
A55	B2	C25	DH2	DL2	ST-004	DVD-IgG LALA	ANXA1	FAPα	198959	8.7
A55	B2	C26	DH	DL	ST-005	DVD-IgG	ANXA	EpCAM	200691	8.5

			2	2		LALA	1			
A55	B2	C27	DH2	DL1	ST-006	DVD-IgG LALA	ANXA1	PD-1	198688	8.7
A55	B2	C28	DH2	DL2	ST-007	DVD-IgG LALA	ANXA1	PD-L1	199341	8.5
A55	B2	C33	DH2	DL1	ST-008	DVD-IgG LALA	ANXA1	Amyloid-beta (Aβ) protofibrils	201818	8.7

[Table 32]

Part Number					Structure code	UNIT 1	UNIT 2	HC	LC
A55	B2	C22	DH2	DL2	ST-001	Y829	Zobeluximab	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSLSGRSDNQVQLQQPGAELVRPGASVKLSCKASGYTFTSYWINWVKQRPGQGLEWIGNIYPSDSYTNYNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTRSWRGNSFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1240)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKLSGRSDNHDIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPFTFGSGTKLEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWCVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:1241)
A55	B2	C23	DH2	DL2	ST-002	Y829	PR002726	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYC	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNL

								ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNE VQLLESGGGLVQPGGSLRLS CAASGFTFSSFVMSWVRQA PGKGLEWVSTISGSGRSTYY ADSVKGRFTISRDNSKNTLH LQMNSLRAEDTAVYYCAKD AAAAGTKFDYWGQGTLVT VSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK(SEQ ID NO:1242)	QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHEIVLTQ SPATLSLSPGER ATLSCRASQSV SSYLAWYQQK PGQAPRLLIYD ASNRATGIPAR FSGSGSGTDFT LTISSLEPEDFA VYYCQQRSNW PLTFGGGTKVE IKRSVAAPSVFI FPPSDEQLKSG TASVVCLLNNF YPREAKVQWC VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1243)
A55	B2	C24	DH2	DL2	ST-003	Y829	m825	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQ VQLVQSGAEVKKPGTSVKV SCKVPGYTFSSYAISWVRQA PGQGLEWMGGIIPIFGTTNY AQKFQGRVTITGEESTSTVY MELSSLRSEDTAVYYCARD TDYMFDYWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPS	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHSSELTQ DPVVSVALGET VSITCQGDNLR DFYASWYQQK PGQAPLLVMY GKNRRPSGIPD RFSGSTSGNTLS LTITGAQAEDE ADYYCSSRDNS KHVVFGGGTK VTVLRSVAAPS VFIFPPSDEQLK SGTASVVCLLN NFYPREAKVQ WCVDNALQSG NSQESVTEQDS

								DIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1244)	KDSTYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFNR GEC(SEQ ID NO:1245)
A55	B2	C25	DH2	DL2	ST-004	Y829	humanized MFP5	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQ VQLVQSGAEVKKPGASVKV SCKASGYTFTNNGINWLRQ APGQGLEWMGEIYPRSTNT LYAQKFQGRVTITADRSSNT AYMELSSLRSEDTAVYFCA RTLTAPFAFWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK(SEQ ID NO:1246)	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHQIVLTQ SPATLSLSPGER ATLSCSASSGV NFMHWYQQKP GQAPRRLIFDTS KLASGIPARFSG SGSGTDYTLTIS SLEPEDFAVYY CQQWSFNPPTF GQGTKVEIKRS VAAPSVFIFPPS DEQLKSGTASV VCLLNNFYPRE AKVQWCVDNA LQSGNSQESVT EQDSKDSTYSL SSTLTLSKADY EKHKVYACEV THQGLSSPVTK SFNRGEC(SEQ ID NO:1247)
A55	B2	C26	DH2	DL2	ST-005	Y829	ING-1	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQI QLVQSGPEVKKPGESVKISC KASGYTFTKYGMNWVKQA PGQGLKWMGWINTYTEEPT YGDDFKGRFTFTLDTSTSTA YLEISSLRSEDTATYFCARFG SAVDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWN	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHQIVLTQ SPATLSLSPGER ATLSCSASSGV NFMHWYQQKP GQAPRRLIFDTS

								SGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHN HYTQKSLSLSPGK(SEQ ID NO:1248)	KLASGIPARFSG SGSGTDYTLTIS SLEPEDFAVYY CQQWSFNPPTF GQGTKVEIKRS VAAPSVFIFPPS DEQLKSGTASV VCLLNNFYPRE AKVQWCVDNA LQSGNSQESVT EQDSKDSTYSL SSTLTLSKADY EKHKVYACEV THQGLSSPVTK SFNRGEC(SEQ ID NO:1249)
A55	B2	C27	DH2	DL1	ST-006	Y829	Nivolumab	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNQ VQLVESGGGVVQPGRSLRL DCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKR YYADSVKGRFTISRDNSKNT LFLQMNSLRAEDTAVYYCA TNDDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHN HYTQKSLSLSPGK(SEQ ID NO:1250)	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHEIVLTQ SPATLSLSPGER ATLSCRASQSV SSYLAWYQQK PGQAPRLLIYD ASNRATGIPAR FSGSGSGTDFT LTISSLEPEDFA VYYCQQSSNW PRTFGQGTKVE IKRSVAAPSVFI FPPSDEQLKSG TASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1251)
A55	B2	C28	DH2	DL2	ST-007	Y829	Atezolizumab	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA

								IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNE VQLVESGGGLVQPGGSLRLS CAASGFTFSDSWIHWVRQA PGKGLEWVAWISPYGGSTY YADSVKGRFTISADTSKNTA YLQMNSLRAEDTAVYYCAR RHWPGGFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK(SEQ ID NO:1252)	PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHDIQMTQ SPSSLSASVGD RVTITCRASQD VSTAVAWYQQ KPGKAPKLLIY SASFLYSGVPS RFSGSGSGTDF TLTISSLQPEDF ATYYCQQYLY HPATFGQGTKV EIKRSVAAPSVF IFPPSDEQLKSG TASVVCLLNNF YPREAKVQWC VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1253)
A55	B2	C33	DH2	DL1	ST-008	Y829	Lecanemab	QVQLVQSGGGLVQPGRSLRI SCKASGFNFGDYPLSWVRQ APGKGLEWIGFIRSKSFGGT TEYAASVKGRFTISRDDSRD IAYLQMNSLRAEDTAVYYC ARDGNYYDSRGYYYDTFDL WGQGTMITVSSLSGRSDNE VQLVESGGGLVQPGGSLRLS CSASGFTFSSFGMHWVRQA PGKGLEWVAYISSGSSTIYY GDTVKGRFTISRDNAKNSLF LQMSSLRAEDTAVYYCARE GGYYYGRSYYTMDYWGQG TTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQV	DIQMTQSPSSV SASVGDRVTLT CRASQGIRSWL AWYQQKPGKA PKLLIYAASNL QSGVPSRFSGS GSGTDFILTINS LQPDDFATYYC QQANSFPYTFG QGTKVEIKLSG RSDNHDVVMT QSPLSLPVTPG APASISCRSSQS IVHSNGNTYLE WYLQKPGQSP KLLIYKVSNRF SGVPDRFSGSG SGTDFTLRISRV EAEDVGIYYCF QGSHVPPTFGP GTKLEIKRSVA APSVFIFPPSDE QLKSGTASVVC LLNNFYPREAK VQWKVDNALQ

								YTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG K(SEQ ID NO:1254)	SGNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC(SEQ ID NO:1255)

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to CLDN18.2, TEM8, albumin, VEGFR2, PSMA, ICAM, FAPα, or B7H3, and a second domain (third component) comprising a heavy chain variable region (VH2), a heavy chain constant region (CH1), a light chain variable region (VL2), and a light chain constant region (CL) of an antibody that binds to ANXA1 or EGFR are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that forms a DVD-Ig form or a structure modified therefrom (Table 33).

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, or Aβ protofibrils, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) of an antibody that binds to CLDN18.2, TEM8, FAPα, EpCAM, PD-1, PD-L1, or Aβ protofibrils, a first non-cleavable linker, and a light chain constant region (CL) into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 34. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 33]

Part Number					Structure code	Structure type	Target of first target component	Target of third component	Molecular weight (LC/MS)	PI
A70	B2	C11	DH	DL2	ST-009	DVD-IgG	TEM8	EGFR	197305	6.7

			2			LALA				
A70	B2	C19	DH2	DL2	ST-010	DVD-IgG LALA	TEM8	ANXA1	199788	8.1
A71	B2	C11	DH2	DL2	ST-011	DVD-IgG LALA	Albumin	EGFR	197291	7.6
A72	B2	C11	DH2	DL2	ST-012	DVD-IgG LALA	KDR (VEGFR2)	EGFR	195793	8.0
A73	B2	C11	DH2	DL2	ST-013	DVD-IgG LALA	PSMA	EGFR	196418	6.7
A74	B2	C11	DH2	DL2	ST-014	DVD-IgG LALA	ICAM1	EGFR	197373	7.3
A75	B2	C11	DH2	DL2	ST-015	DVD-IgG LALA	FAPα	EGFR	196302	8.2
A76	B2	C11	DH2	DL2	ST-016	DVD-IgG LALA	B7H3	EGFR	196775	8.1

[Table 34]

Part Number					Structure code	UNIT1	UNIT2	HC	LC
A70	B2	C11	DH2	DL2	ST-009	m825	Panitumumab	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSYAISWVRQAPGQGLEWMGGIIPIFGTTNYAQKFQGRVTITGEESTSTVYMELSSLRSEDTAVYYCARDTDYMFDYWGQGTLVTVSSLSGRSDNQVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVLPAPIEKTISKAKGQPREPQV	SSELTQDPVVSVALGETVSITCQGDNLRDFYASWYQQKPGQAPLLVMYGKNRRPSGIPDRFSGSTSGNTLSLTITGAQAEDEADYYCSSRDNSKHVVFGGGTKVTVLLSGRVTITCQASQDRVTITCQPSQSPSSLSASVGDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIKRSVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWC

								YTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG K(SEQ ID NO:1256)	VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1257)
A70	B2	C19	DH2	DL2	ST-010	m825	Y829	QVQLVQSGAEVKKPGTSVK VSCKVPGYTFSSYAISWVRQ APGQGLEWMGGIIPIFGTTN YAQKFQGRVTITGEESTSTV YMELSSLRSEDTAVYYCAR DTDYMFDYWGQGTLVTVSS LSGRSDNQVQLVQSGGGLV QPGRSLRICKASGFNFGDYP LSWVRQAPGKGLEWIGFIRS KSFGGTTEYAASVKGRFTIS RDDSRDIAYLQMNSLRAED TAVYYCARDGNYYDSRGY YYDTFDLWGQGTMITVSSA STKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHN HYTQKSLSLSPGK(SEQ ID NO:1258)	SSELTQDPVVS VALGETVSITC QGDNLRDFYAS WYQQKPGQAP LLVMYGKNRR PSGIPDRFSGST SGNTLSLTITGA QAEDEADYYC SSRDNSKHVVF GGGTKVTVLLS GRSDNHDIQMT QSPSSVSASVG DRVTLTCRASQ GIRSWLAWYQ QKPGKAPKLLI YAASNLQSGVP SRFSGSGSGTD FILTINSLQPDD FATYYCQQANS FPYTFGQGTKV EIKRSVAAPSVF IFPPSDEQLKSG TASVVCLLNNF YPREAKVQWC VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1259)
A71	B2	C11	DH2	DL2	ST-011	anti-Albumin	Panitumumab	EVQLLESGGGLVQPGGSLRL SCAVSGIDLSNYAINWVRQA PGKGLEWIGIIWASGTTFYA TWAKGRFTISRDNSKNTVYL QMNSLRAEDTAVYYCARTV PGYSTAPYFDLWGQGTLVT VSSLSGRSDNQVQLQESGPG LVKPSETLSLTCTVSGGSVSS GDYYWTWIRQSPGKGLEWI GHIYYSGNTNYNPSLKSRLTI SIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQ GTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDY	DIQMTQSPSSV SASVGDRVTIT CQSSPSVWSNF LSWYQQKPGK APKLLIYEASK LTSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC GGGYSSISDTTF GGGTKVEIKLS GRSDNHDIQMT QSPSSLSASVG DRVTITCQASQ DISNYLNWYQ

								FPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG K(SEQ ID NO:1260)	QKPGKAPKLLI YDASNLETGVP SRFSGSGSGTD FTFTISSLQPEDI ATYFCQHFDHL PLAFGGGTKVE IKRSVAAPSVFI FPPSDEQLKSG TASVVCLLNNF YPREAKVQWC VDNALQSGNS QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1261)
A72	B2	C11	DH2	DL2	ST-012	Ramucirumab	Panitumumab	EVQLVQSGGGLVKPGGSLR LSCAASGFTFSSYSMNWVR QAPGKGLEWVSSISSSSSYIY YADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCAR VTDAFDIWGQGTMVTVSSL SGRSDNQVQLQESGPGLVKP SETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIY YSGNTNYNPSLKSRLTISIDT SKTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGTM VTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK(S EQ ID NO:1262)	DIQMTQSPSSV SASIGDRVTITC RASQGIDNWLG WYQQKPGKAP KLLIYDASNLD TGVPSRFSGSG SGTYFTLTISSL QAEDFAVYFCQ QAKAFPPTFGG GTKVDIKLSGR SDNHDIQMTQS PSSLSASVGDR VTITCQASQDIS NYLNWYQQKP GKAPKLLIYDA SNLETGVPSRFS GSGSGTDFTFTI SSLQPEDIATYF CQHFDHLPLAF GGGTKVEIKRS VAAPSVFIFPPS DEQLKSGTASV VCLLNNFYPRE AKVQWCVDNA LQSGNSQESVT EQDSKDSTYSL SSTLTLSKADY EKHKVYACEV THQGLSSPVTK SFNRGEC(SEQ ID NO:1263)
A73	B2	C11	DH2	DL2	ST-013	MEDI3726	Panitumumab	EVQLVQSGPEVKKPGATVKI SCKTSGYTFTEYTIHWVKQA PGKGLEWIGNINPNNGGTTY NQKFEDKATLTVDKSTDTA	DIQMTQSPSSLS TSVGDRVTLTC KASQDVGTAV DWYQQKPGPS

								YMELSSLRSEDTAVYYCAA GWNFDYWGQGTLLTVSSLS GRSDNQVQLQESGPGLVKPS ETLSLTCTVSGGSVSSGDYY WTWIRQSPGKGLEWIGHIYY SGNTNYNPSLKSRLTISIDTS KTQFSLKLSSVTAADTAIYY CVRDRVTGAFDIWGQGTMV TVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK(SEQ ID NO:1264)	PKLLIYWASTR HTGIPSRFSGSG SGTDFTLTISSL QPEDFADYYCQ QYNSYPLTFGP GTKVDIKLSGR SDNHDIQMTQS PSSLSASVGDR VTITCQASQDIS NYLNWYQQKP GKAPKLLIYDA SNLETGVPSRFS GSGSGTDFTFTI SSLQPEDIATYF CQHFDHLPLAF GGGTKVEIKRS VAAPSVFIFPPS DEQLKSGTASV VCLLNNFYPRE AKVQWCVDNA LQSGNSQESVT EQDSKDSTYSL SSTLTLSKADY EKHKVYACEV THQGLSSPVTK SFNRGEC(SEQ ID NO:1265)
A74	B2	C11	DH2	DL2	ST-014	Icmo0191fgi	Panitumumab	QVQLQESGPGLVKPSETLSL TCAVSGYPISSGYFWGWIRQ PPGKGLEWIGSIYQSGSTYY NPSLKRRVTMSLDTSKNQFS LKLSSVTAADTAVYYCARD GYCSGGSCYPFDYWGQGTL VTVSSLSGRSDNQVQLQESG PGLVKPSETLSLTCTVSGGS VSSGDYYWTWIRQSPGKGL EWIGHIYYSGNTNYNPSLKS RLTISIDTSKTQFSLKLSSVT AADTAIYYCVRDRVTGAFDI WGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTH TCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQV	QSVLTQPPSVS GTPGQRVTISCS GSSSNIGGSTV NWYQQLPGTA PKLLIYNNDQR PSGVPDRFSGS KSGTSGSLAISG LQSEDEADYYC ESWDDSLSGRV FGGGTKLTVLL SGRSDNHDIQM TQSPSSLSASVG DRVTITCQASQ DISNYLNWYQ QKPGKAPKLLI YDASNLETGVP SRFSGSGSGTD FTFTISSLQPEDI ATYFCQHFDHL PLAFGGGTKVE IKRSVAAPSVFI FPPSDEQLKSG TASVVCLLNNF YPREAKVQWC VDNALQSGNS

								SLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSL SLSPGK(SEQ ID NO:1266)	QESVTEQDSKD STYSLSSTLTLS KADYEKHKVY ACEVTHQGLSS PVTKSFNRGEC(SEQ ID NO:1267)
A75	B2	C11	DH2	DL2	ST-015	humanized MFP5	Panitumumab	QVQLVQSGAEVKKPGASVK VSCKASGYTFTNNGINWLR QAPGQGLEWMGEIYPRSTN TLYAQKFQGRVTITADRSSN TAYMELSSLRSEDTAVYFCA RTLTAPFAFWGQGTLVTVSS LSGRSDNQVQLQESGPGLV KPSETLSLTCTVSGGSVSSG DYYWTWIRQSPGKGLEWIG HIYYSGNTNYNPSLKSRLTIS IDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQ GTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG K(SEQ ID NO:1268)	QIVLTQSPATLS LSPGERATLSCS ASSGVNFMHW YQQKPGQAPR RLIFDTSKLASG IPARFSGSGSGT DYTLTISSLEPE DFAVYYCQQW SFNPPTFGQGT KVEIKLSGRSD NHDIQMTQSPS SLSASVGDRVT ITCQASQDISNY LNWYQQKPGK APKLLIYDASN LETGVPSRFSGS GSGTDFTFTISS LQPEDIATYFC QHFDHLPLAFG GGTKVEIKRSV AAPSVFIFPPSD EQLKSGTASVV CLLNNFYPREA KVQWCVDNAL QSGNSQESVTE QDSKDSTYSLS STLTLSKADYE KHKVYACEVT HQGLSSPVTKS FNRGEC(SEQ ID NO:1269)
A76	B2	C11	DH2	DL2	ST-016	m8524	Panitumumab	QVQLQQSGAEVKKPGSSVK VSCKASGGTFSSYAISWVRQ APGQGLEWMGGIIPILGIAN YAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCAR GGSGSYHMDVWGKGTTVT VSSLSGRSDNQVQLQESGPG LVKPSETLSLTCTVSGGSVSS GDYYWTWIRQSPGKGLEWI GHIYYSGNTNYNPSLKSRLTI SIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQ GTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHT	EIVLTQSPATLS LSPGERATLSC RASQSVSSYLA WYQQKPGQAP RLLIYDASNRA TGIPARFSGSGS GTDFTLTISSLE PEDFAVYYCQQ RSNWPPRITFG QGTRLEIKLSG RSDNHDIQMTQ SPSSLSASVGD RVTITCQASQDI SNYLNWYQQK PGKAPKLLIYD

								FPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG K(SEQ ID NO:1270)	ASNLETGVPSR FSGSGSGTDFTF TISSLQPEDIAT YFCQHFDHLPL AFGGGTKVEIK RSVAAPSVFIFP PSDEQLKSGTA SVVCLLNNFYP REAKVQWCVD NALQSGNSQES VTEQDSKDSTY SLSSTLTLSKAD YEKHKVYACE VTHQGLSSPVT KSFNRGEC(SEQ ID NO:1271)

Example 2.4 ReleaBody type multispecific fusion protein comprising a ReleaDome

Example 2.4.1. ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-HER2]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to HER2 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a ReleaBody form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to HER2, a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to HER2 into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 35. The amino acid sequences of the above fusion proteins are

described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 35]

Part Number; '-', Not associated					Protein code	HC	LC
A58	B2	C2	DH7	-	BA-0102-R001	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGYYMSWVRQAPGKGLEWVSSISPSGSSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSPGFDYWGQGTLVTVSSLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1272)	QSVLTQPPSASGAPGQRVTISCSGSSFNIGSNDVSWYQQLPGTAPKLLIYSDSHRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCGSWDYSLSAYVFGGGTKLTVLLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1273)
A13	B3	C2	DH7	-	BA-0102-R002	QMQLVQSGAEVQKPGASVKVSCKASGNTFNGYYIHWVRQAPGQGLEWMGIINPSGSSTFYAQKFRGRVTMTKDTSTSTVYMKLSSLRSEDTAVYYCAQEGWTEQHPYAEYLQNWGQGTLVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1274)	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYDASTLQPGVPSRFSGGGSGTDFTLTIRSVQPEDYATYFCQQSYITPFAFGQGTKLEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1275)
A13	B3	C2	DH9	-	BA-0102-R003	QMQLVQSGAEVQKPGASVKVSCKASGNTFNGYYIHWVRQAPGQGLEWMGIINPSGSSTFYAQKFRGRVTMTKDTSTSTVYMKLSSLRSEDTAVYYCAQEGWTEQHPYAEYLQNWGQGTLVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYL	DIQMTQSPSFLSASVGDRVTITCRASQYIGTYLAWYQQQPGKAPKLLIYDASTLQPGVPSRFSGGGSGTDFTLTIRSVQPEDFATYFCQQSYITPFAFGQGTKLEIKPL

						QMNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1276)	GLSGRSDNHDIQM TQSPSSLSASVGDR VTITCRASQDVNT AVAWYQQKPGKA PKLLIYSASFLYSG VPSRFSGSRSGTDF TLTISSLQPEDFAT YYCQQHYTTPPTF GCGTKVEIK(SEQ ID NO:1277)
A55	B3	C2	DH9	-	BA-0102-R004	QVQLVQSGGGLVQPGRSLRISCKASGFN FGDYPLSWVRQAPGKGLEWIGFIRSKSF GGTTEYAASVKGRFTISRDDSRDIAYLQ MNSLRAEDTAVYYCARDGNYYDSRGY YYDTFDLWGQGTMITVSSPLGLSGRSD NEVQLVESGGGLVQPGGSLRLSCAASG FNIKDTYIHWVRQAPGKCLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1278)	DIQMTQSPSSVSAS VGDRVTLTCRASQ GIRSWLAWYQQKP GKAPKLLIYAASN LQSGVPSRFSGSGS GTDFILTINSLQPD DFATYYCQQANSF PYTFGQGTKVEIKP LGLSGRSDNHDIQ MTQSPSSLSASVG DRVTITCRASQDV NTAVAWYQQKPG KAPKLLIYSASFLY SGVPSRFSGSRSGT DFTLTISSLQPEDF ATYYCQQHYTTPP TFGCGTKVEIK(SE Q ID NO:1279)
A9	B3	C2	DH6	-	BA-0102-R005	QMQLVESGGGLVQPGGSLRLSCAASGF TFSDFAMTWVRQAPGKGLEWVSSISGT SGRTYYADSVKGRSTVSTDNSKNTVYL RMNSLRAEDTAVYYCARGSPSGSADY WGQGTLVTVSSPLGLSGRSDNEVQLVE SGGGLVQPGGSLRLSCAASGFNIKDTYI HWVRQAPGKCLEWVARIYPTNGYTRY ADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCSRWGGDGFYAMDYWGQ GTLVTVSSDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK(SEQ ID NO:1280)	QLVLTQPHSVSESP GKTVTISCTRSSGSI ASKYVQWYQQRP GSAPTTVIYEDNQR PSGVPDRFSGSIDIS SNSASLTISGLKTE DEADYYCQSYDSS TVVFGGGTKLTVL PLGLSGRSDNHDIQ MTQSPSSLSASVG DRVTITCRASQDV NTAVAWYQQKPG KAPKLLIYSASFLY SGVPSRFSGSRSGT DFTLTISSLQPEDF ATYYCQQHYTTPP TFGCGTKVEIK(SE Q ID NO:1281)
A13	B3	C2	DH6	-	BA-0102-R006	QMQLVQSGAEVQKPGASVKVSCKASG NTFNGYYIHWVRQAPGQGLEWMGIINP SGSSTFYAQKFRGRVTMTKDTSTSTVY MKLSSLRSEDTAVYYCAQEGWTEQHPY	DIQMTQSPSFLSAS VGDRVTITCRASQ YIGTYLAWYQQQP GKAPKLLIYDASTL

						AEYLQNWGQGTLVTVSSPLGLSGRSDN EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKCLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK(SEQ ID NO:1282)	QPGVPSRFSGGGS GTDFTLTIRSVQPE DYATYFCQQSYITP FAFGQGTKLEIKPL GLSGRSDNHDIQM TQSPSSLSASVGDR VTITCRASQDVNT AVAWYQQKPGKA PKLLIYSASFLYSG VPSRFSGSRSGTDF TLTISSLQPEDFAT YYCQQHYTTPPTF GCGTKVEIK(SEQ ID NO:1277)
A28	B3	C2	DH6	-	BA-0102-R007	QVQLVESGGGLVPPGGSLRLSCAASGFS FSDHYMDWVRQAPGKGLEWVGFIRSA AYGGTTEYAASVKGRFTISRDDSKSIAY LQMNSLRAEDTAVYYCARDGNYYDSR GYYYDTFDLWGQGTMVTVSSPLGLSGR SDNEVQLVESGGGLVQPGGSLRLSCAA SGFNIKDTYIHWVRQAPGKCLEWVARI YPTNGYTRYADSVKGRFTISADTSKNTA YLQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLVTVSSDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1283)	DIQMTQSPSSLSAS VGDKVTITCRASQ GISSYLAWYQQKP GKAPKLLIYVASSL QTGVPSRFSGSRSG TDFTLTISSLQSEDF GTYYCQQSYRTPY TFGQGTKLEIKPLG LSGRSDNHDIQMT QSPSSLSASVGDRV TITCRASQDVNTA VAWYQQKPGKAP KLLIYSASFLYSGV PSRFSGSRSGTDFT LTISSLQPEDFATY YCQQHYTTPPTFG CGTKVEIK(SEQ ID NO:1284)
A33	B3	C2	DH6	-	BA-0102-R008	QVQLVESGGGVVQPGRSLRLSCAASGF TFSSYAMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCARDQTRLGPTT FDYWGQGSLVTVSSPLGLSGRSDNEVQ LVESGGGLVQPGGSLRLSCAASGFNIKD TYIHWVRQAPGKCLEWVARIYPTNGYT RYADSVKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCSRWGGDGFYAMDYW GQGTLVTVSSDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK(SEQ ID	DIQMTQSPSTLSAS VGDRVTITCRASQ NVDKWLAWYQQK PGKAPKLLIYKASG LESGVPSRFSGSGS GTEFTLTISSLQPD DFATYYCQQYDSY PLTFGGGTKVEIKP LGLSGRSDNHDIQ MTQSPSSLSASVG DRVTITCRASQDV NTAVAWYQQKPG KAPKLLIYSASFLY SGVPSRFSGSRSGT DFTLTISSLQPEDF ATYYCQQHYTTPP TFGCGTKVEIK(SE Q ID NO:1286)

						NO:1285)	
A55	B3	C2	DH6	-	BA-0102-R009	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1287)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1279)
A9	B3	C2	DH9	-	BA-0102-R010	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDFAMTWVRQAPGKGLEWVSSISGTSGRTYYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYCARGSPSGSADYWGQGTLVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1288)	QLVLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYCQSYDSSTVVFGGGTKLTVLPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1281)
A28	B3	C2	DH9	-	BA-0102-R011	QVQLVESGGGLVPPGGSLRLSCAASGFSFSDHYMDWVRQAPGKGLEWVGFIRSAAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL	DIQMTQSPSSLSASVGDKVTITCRASQGISSYLAWYQQKPGKAPKLLIYVASSLQTGVPSRFSGSRSGTDFTLTISSLQSEDFGTYYCQQSYRTPYTFGQGTKLEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGV

						HQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1289)	PSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1284)
A33	B3	C2	DH9	-	BA-0102-R012	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQTRLGPTTFDYWGQGSLVTVSSPLGLSGRSDNEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1290)	DIQMTQSPSTLSASVGDRVTITCRASQNVDKWLAWYQQKPGKAPKLLIYKASGLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDSYPLTFGGGTKVEIKPLGLSGRSDNHDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGCGTKVEIK(SEQ ID NO:1286)

As a result, as shown in Figure 8, the productivity of the multispecific fusion protein up to the first purification was about 7 mg/L to about 291 mg/L. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 44% to about 98%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed.

Example 2.4.2. ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CTLA4]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CTLA4 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a ReleaBody form or a structure modified

therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CTLA4, a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CTLA4 into each expression vector.

In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 36. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 36]

Part Number '-', Not associated					Protein code	HC	LC
A58	B2	C15	DH7	-	BA-0104-R001	EVQLLESGGGLVQPGGSLRLSCAASGFTF SGYYMSWVRQAPGKGLEWVSSISPSGSSI YYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCAKGSPGFDYWGQGTLVT VSSLSGRSDNQVQLVESGGGVVQPGRSL RLSCAASGFTFSSYTMHWVRQAPGKCLE WVTFISYDGNNKYYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAIYYCARTGWLG PFDYWGQGTLVTVSSDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1291)	QSVLTQPPSASGAPG QRVTISCSGSSFNIGS NDVSWYQQLPGTAP KLLIYSDSHRPSGVP DRFSGSKSGTSASLA ISGLQSEDEADYYCG SWDYSLSAYVFGGG TKLTVLLSGRSDNH EIVLTQSPGTLSLSPG ERATLSCRASQSVGS SYLAWYQQKPGQAP RLLIYGAFSRATGIP DRFSGSGSGTDFTLT ISRLEPEDFAVYYCQ QYGSSPWTFGCGTK VEIK(SEQ ID NO:1292)
A9	B3	C15	DH8	-	BA-0104-R002	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT LVTVSSPLGLSGRSDNQVQLVESGGGVV QPGRSLRLSCAASGFTFSSYTMHWVRQA PGKCLEWVTFISYDGNNKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAIYYCA RTGWLGPFDYWGQGTLVTVSSEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSL	QLVLTQPHSVSESPG KTVTISCTRSSGSIAS KYVQWYQQRPGSA PTTVIYEDNQRPSGV PDRFSGSIDISSNSAS LTISGLKTEDEADYY CQSYDSSTVVFGGG TKLTVLPLGLSGRSD NHEIVLTQSPGTLSL SPGERATLSCRASQS VGSSYLAWYQQKPG QAPRLLIYGAFSRAT GIPDRFSGSGSGTDF TLTISRLEPEDFAVY

						TCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1293)	YCQQYGSSPWTFGC GTKVEIK(SEQ ID NO:1294)
A2 8	B 3	C15	DH 8	-	BA- 0104- R003	QVQLVESGGGLVPPGGSLRLSCAASGFSF SDHYMDWVRQAPGKGLEWVGFIRSAAY GGTTEYAASVKGRFTISRDDSKSIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMVTVSSPLGLSGRSDNQV QLVESGGGVVQPGRSLRLSCAASGFTFSS YTMHWVRQAPGKCLEWVTFISYDGNNK YYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAIYYCARTGWLGPFDYWGQGTL VTVSSEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1295)	DIQMTQSPSSLSASV GDKVTITCRASQGIS SYLAWYQQKPGKAP KLLIYVASSLQTGVP SRFSGSRSGTDFTLTI SSLQSEDFGTYYCQ QSYRTPYTFGQGTK LEIKPLGLSGRSDNH EIVLTQSPGTLSLSPG ERATLSCRASQSVGS SYLAWYQQKPGQAP RLLIYGAFSRATGIP DRFSGSGSGTDFTLT ISRLEPEDFAVYYCQ QYGSSPWTFGCGTK VEIK(SEQ ID NO:1296)
A5 5	B 3	C15	DH 8	-	BA- 0104- R005	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL VESGGGVVQPGRSLRLSCAASGFTFSSYT MHWVRQAPGKCLEWVTFISYDGNNKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAIYYCARTGWLGPFDYWGQGTLVTVS SEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK(SEQ ID NO:1297)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH EIVLTQSPGTLSLSPG ERATLSCRASQSVGS SYLAWYQQKPGQAP RLLIYGAFSRATGIP DRFSGSGSGTDFTLT ISRLEPEDFAVYYCQ QYGSSPWTFGCGTK VEIK(SEQ ID NO:1298)
A9	B 3	C16	DH 8	-	BA- 0104- R006	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT LVTVSSPLGLSGRSDNQVQLVESGGGVV QPGRSLRLSCAASGFTFSSYGMHWVRQA PGKCLEWVAVIWYDGSNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYY CARDPRGATLYYYYYGMDVWGQGTTVT VSSEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNS	QLVLTQPHSVSESPG KTVTISCTRSSGSIAS KYVQWYQQRPGSA PTTVIYEDNQRPSGV PDRFSGSIDISSNSAS LTISGLKTEDEADYY CQSYDSSTVVFGGG TKLTVLPLGLSGRSD NHDIQMTQSPSSLSA SVGDRVTITCRASQS INSYLDWYQQKPGK APKLLIYAASSLQSG

						TYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1299)	VPSRFSGSGSGTDFT LTISSLQPEDFATYY CQQYYSTPFTFGCGT KVEIK(SEQ ID NO:1300)
A28	B3	C16	DH8	-	BA-0104-R007	QVQLVESGGGLVPPGGSLRLSCAASGFSF SDHYMDWVRQAPGKGLEWVGFIRSAAY GGTTEYAASVKGRFTISRDDSKSIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMVTVSSPLGLSGRSDNQV QLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKCLEWVAVIWYDGSN KYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCARDPRGATLYYYYYGM DVWGQGTTVTVSSEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK(SEQ ID NO:1301)	DIQMTQSPSSLSASV GDKVTITCRASQGIS SYLAWYQQKPGKAP KLLIYVASSLQTGVP SRFSGSRSGTDFTLTI SSLQSEDFGTYYCQ QSYRTPYTFGQGTK LEIKPLGLSGRSDNH DIQMTQSPSSLSASV GDRVTITCRASQSIN SYLDWYQQKPGKAP KLLIYAASSLQSGVP SRFSGSGSGTDFTLTI SSLQPEDFATYYCQ QYYSTPFTFGCGTK VEIK(SEQ ID NO:1302)
A33	B3	C16	DH8	-	BA-0104-R008	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLVESGGG VVQPGRSLRLSCAASGFTFSSYGMHWVR QAPGKCLEWVAVIWYDGSNKYYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDPRGATLYYYYYGMDVWGQGT TVTVSSEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1303)	DIQMTQSPSTLSASV GDRVTITCRASQNV DKWLAWYQQKPGK APKLLIYKASGLESG VPSRFSGSGSGTEFT LTISSLQPDDFATYY CQQYDSYPLTFGGG TKVEIKPLGLSGRSD NHDIQMTQSPSSLSA SVGDRVTITCRASQS INSYLDWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYY CQQYYSTPFTFGCGT KVEIK(SEQ ID NO:1304)
A55	B3	C16	DH8	-	BA-0104-R009	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL VESGGGVVQPGRSLRLSCAASGFTFSSYG MHWVRQAPGKCLEWVAVIWYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLR AEDTAVYYCARDPRGATLYYYYYGMDV WGQGTTVTVSSEPKSCDKTHTCPPCPAPE	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH DIQMTQSPSSLSASV GDRVTITCRASQSIN

						LLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1305)	SYLDWYQQKPGKAP KLLIYAASSLQSGVP SRFSGSGSGTDFTLTI SSLQPEDFATYYCQ QYYSTPFTFGCGTK VEIK(SEQ ID NO:1306)

As a result, as shown in Figure 9, the productivity of the multispecific fusion protein up to the first purification was about 4 mg/L to about 112 mg/L. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 48% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed.

Example 2.4.3. ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-CD47]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to CD47 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a ReleaBody form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to CD47, a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to CD47 into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 37. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 37]

Part Number; '-', Not associated					Protein code	HC	LC
A55	B3	C4	DH8	-	BA-0107-R001	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDYPLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAASVKGRFTISRDDSRDIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMITVSSPLGLSGRSDNQVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRCLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARGGYTMDYWGQGTSVTVSSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1307)	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTINSLQPDDFATYYCQQANSFPYTFGQGTKVEIKPLGLSGRSDNHDVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGCGTKLELK(SEQ ID NO:1308)
A9	B3	C4	DH8	-	BA-0107-R002	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDFAMTWVRQAPGKGLEWVSSISGTSGRTYYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYCARGSPSGSADYWGQGTLVTVSSPLGLSGRSDNQVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRCLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARGGYTMDYWGQGTSVTVSSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1309)	QLVLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYCQSYDSSTVVFGGGTKLTVLPLGLSGRSDNHDVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGCGTKLELK(SEQ ID NO:1310)
A28	B3	C4	DH8	-	BA-0107-R003	QVQLVESGGGLVPPGGSLRLSCAASGFSFSDHYMDWVRQAPGKGLEWVGFIRSAAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNQVQLQQPGAELVKPGASLRVSCKASGYTFTNYWMYWVRQRPGRCLEWIGWIDPNSGGTKYNEKFKSKATLTVDKPSSTAYMQLSSLTSEDSAVYNCARGGYTMDYWGQGTSVTVSSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS	DIQMTQSPSSLSASVGDKVTITCRASQGISSYLAWYQQKPGKAPKLLIYVASSLQTGVPSRFSGSRSGTDFTLTISSLQSEDFGTYYCQQSYRTPYTFGQGTKLEIKPLGLSGRSDNHDVVMTQTPLSLPVSLGDQASISCRASQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFS

						TYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1311)	GVPDRFSGSGSGTDF TLKISRVEAEDLGVY FCSQSTHVPLTFGCG TKLELK(SEQ ID NO:1312)
A33	B3	C4	DH8	-	BA-0107-R004	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLQQPGAE LVKPGASLRVSCKASGYTFTNYWMYWV RQRPGRCLEWIGWIDPNSGGTKYNEKFK SKATLTVDKPSSTAYMQLSSLTSEDSAVY NCARGGYTMDYWGQGTSVTVSSEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1313)	DIQMTQSPSTLSASV GDRVTITCRASQNV DKWLAWYQQKPGK APKLLIYKASGLESG VPSRFSGSGSGTEFT LTISSLQPDDFATYY CQQYDSYPLTFGGG TKVEIKPLGLSGRSD NHDVVMTQTPLSLP VSLGDQASISCRASQ SLVHSNGNTYLHWY LQKPGQSPKLLIYKV SNRFSGVPDRFSGSG SGTDFTLKISRVEAE DLGVYFCSQSTHVPL TFGCGTKLELK(SEQ ID NO:1314)
A9	B3	C6	DH8	-	BA-0107-R005	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT LVTVSSPLGLSGRSDNQVQLVQSGAEVK KPGASVKVSCKASGYTFTNYNMHWVRQ APGQCLEWMGTIYPGNDDTSYNQKFKDR VTITADTSASTAYMELSSLRSEDTAVYYC ARGGYRAMDYWGQGTLVTVSSEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1315)	QLVLTQPHSVSESPG KTVTISCTRSSGSIAS KYVQWYQQRPGSAP TTVIYEDNQRPSGVP DRFSGSIDISSNSASL TISGLKTEDEADYYC QSYDSSTVVFGGGT KLTVLPLGLSGRSDN HDIVMTQSPLSLPVT PGEPASISCRSSQSIV YSNGNTYLGWYLQK PGQSPQLLIYKVSNR FSGVPDRFSGSGSGT DFTLKISRVEAEDVG VYYCFQGSHVPYTF GCGTKLEIK(SEQ ID NO:1316)
A28	B3	C6	DH8	-	BA-0107-R006	QVQLVESGGGLVPPGGSLRLSCAASGFSF SDHYMDWVRQAPGKGLEWVGFIRSAAY GGTTEYAASVKGRFTISRDDSKSIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMVTVSSPLGLSGRSDNQV QLVQSGAEVKKPGASVKVSCKASGYTFT NYNMHWVRQAPGQCLEWMGTIYPGND DTSYNQKFKDRVTITADTSASTAYMELSS LRSEDTAVYYCARGGYRAMDYWGQGTL VTVSSEPKSCDKTHTCPPCPAPELLGGPSV	DIQMTQSPSSLSASV GDKVTITCRASQGIS SYLAWYQQKPGKAP KLLIYVASSLQTGVP SRFSGSRSGTDFTLTI SSLQSEDFGTYYCQQ SYRTPYTFGQGTKLE IKPLGLSGRSDNHDI VMTQSPLSLPVTPGE PASISCRSSQSIVYSN

						FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1317)	GNTYLGWYLQKPGQ SPQLLIYKVSNRFSG VPDRFSGSGSGTDFT LKISRVEAEDVGVY YCFQGSHVPYTFGC GTKLEIK(SEQ ID NO:1318)
A3 3	B 3	C 6	DH 8	-	BA- 0107- R007	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLVQSGAE VKKPGASVKVSCKASGYTFTNYNMHWV RQAPGQCLEWMGTIYPGNDDTSYNQKFK DRVTITADTSASTAYMELSSLRSEDTAVY YCARGGYRAMDYWGQGTLVTVSSEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1319)	DIQMTQSPSTLSASV GDRVTITCRASQNV DKWLAWYQQKPGK APKLLIYKASGLESG VPSRFSGSGSGTEFT LTISSLQPDDFATYY CQQYDSYPLTFGGG TKVEIKPLGLSGRSD NHDIVMTQSPLSLPV TPGEPASISCRSSQSI VYSNGNTYLGWYLQ KPGQSPQLLIYKVSN RFSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQGSHVPYT FGCGTKLEIK(SEQ ID NO:1320)
A5 5	B 3	C 6	DH 8	-	BA- 0107- R008	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL VQSGAEVKKPGASVKVSCKASGYTFTNY NMHWVRQAPGQCLEWMGTIYPGNDDTS YNQKFKDRVTITADTSASTAYMELSSLRS EDTAVYYCARGGYRAMDYWGQGTLVT VSSEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1321)	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ QANSFPYTFGQGTK VEIKPLGLSGRSDNH DIVMTQSPLSLPVTP GEPASISCRSSQSIVY SNGNTYLGWYLQKP GQSPQLLIYKVSNRF SGVPDRFSGSGSGTD FTLKISRVEAEDVGV YYCFQGSHVPYTFG CGTKLEIK(SEQ ID NO:1322)
A9	B 3	C 8	DH 8	-	BA- 0107- R009	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT LVTVSSPLGLSGRSDNQMQLVQSGAEVK KTGSSVKVSCKASGFNIKDYYLHWVRQA PGQCLEWMGWIDPDQGDTEYAQKFQDR VTITRDRSMSTAYMELSSLRSEDTAMYY	QLVLTQPHSVSESPG KTVTISCTRSSGSIAS KYVQWYQQRPGSAP TTVIYEDNQRPSGVP DRFSGSIDISSNSASL TISGLKTEDEADYYC QSYDSSTVVFGGGT KLTVLPLGLSGRSDN

						CNAAYGSSSYPMDYWGQGTIVTVSSEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG K(SEQ ID NO:1323)	HNIQMTQSPSAMSAS VGDRVTITCKASQDI HRYLSWFQQKPGKV PKHLIYRANRLVSGV PSRFSGSGSGTEFTLT ISSLQPEDFATYYCL QYDEFPYTFGCGTK VEIK(SEQ ID NO:1324)
A28	B3	C8	DH8	-	BA-0107-R010	QVQLVESGGGLVPPGGSLRLSCAASGFSF SDHYMDWVRQAPGKGLEWVGFIRSAAY GGTTEYAASVKGRFTISRDDSKSIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMVTVSSPLGLSGRSDNQM QLVQSGAEVKKTGSSVKVSCKASGFNIK DYYLHWVRQAPGQCLEWMGWIDPDQG DTEYAQKFQDRVTITRDRSMSTAYMELS SLRSEDTAMYYCNAAYGSSSYPMDYWG QGTIVTVSSEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1325)	DIQMTQSPSSLSASV GDKVTITCRASQGIS SYLAWYQQKPGKAP KLLIYVASSLQTGVP SRFSGSRSGTDFTLTI SSLQSEDFGTYYCQQ SYRTPYTFGQGTKLE IKPLGLSGRSDNHNI QMTQSPSAMSASVG DRVTITCKASQDIHR YLSWFQQKPGKVPK HLIYRANRLVSGVPS RFSGSGSGTEFTLTIS SLQPEDFATYYCLQY DEFPYTFGCGTKVEI K(SEQ ID NO:1326)
A33	B3	C8	DH8	-	BA-0107-R011	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQMQLVQSGA EVKKTGSSVKVSCKASGFNIKDYYLHWV RQAPGQCLEWMGWIDPDQGDTEYAQKF QDRVTITRDRSMSTAYMELSSLRSEDTA MYYCNAAYGSSSYPMDYWGQGTIVTVS SEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK(SEQ ID NO:1327)	DIQMTQSPSTLSASV GDRVTITCRASQNV DKWLAWYQQKPGK APKLLIYKASGLESG VPSRFSGSGSGTEFT LTISSLQPDDFATYY CQQYDSYPLTFGGG TKVEIKPLGLSGRSD NHNIQMTQSPSAMS ASVGDRVTITCKASQ DIHRYLSWFQQKPG KVPKHLIYRANRLVS GVPSRFSGSGSGTEF TLTISSLQPEDFATYY CLQYDEFPYTFGCGT KVEIK(SEQ ID NO:1328)
A55	B3	C8	DH8	-	BA-0107-R012	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQMQL VQSGAEVKKTGSSVKVSCKASGFNIKDY	DIQMTQSPSSVSASV GDRVTLTCRASQGIR SWLAWYQQKPGKA PKLLIYAASNLQSGV PSRFSGSGSGTDFILT INSLQPDDFATYYCQ

						YLHWVRQAPGQCLEWMGWIDPDQGDTE YAQKFQDRVTITRDRSMSTAYMELSSLRS EDTAMYYCNAAYGSSSYPMDYWGQGTI VTVSSEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1329)	QANSFPYTFGQGTK VEIKPLGLSGRSDNH NIQMTQSPSAMSASV GDRVTITCKASQDIH RYLSWFQQKPGKVP KHLIYRANRLVSGVP SRFSGSGSGTEFTLTI SSLQPEDFATYYCLQ YDEFPYTFGCGTKVE IK(SEQ ID NO:1330)

As a result, as shown in Figure 10, the productivity of the multispecific fusion protein up to the first purification was about 0.1 mg/L to about 72.8 mg/L. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 51% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed.

Example 2.4.4. ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to EGFR are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a ReleaBody form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to EGFR into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion

proteins are shown in Table 38. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 38]

Part Number; '-', Not associated					Protein code	HC	LC
A9	B3	C10	DH9	-	BA-0109-R001	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDFAMTWVRQAPGKGLEWVSSISGTSGRTYYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYCARGSPSGSADYWGQGTLVTVSSPLGLSGRSDNQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKCLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1331)	QLVLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYCQSYDSSTVVFGGGTKLTVLPLGLSGRSDNHDILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGCGTKLELK(SEQ ID NO:1332)
A28	B3	C10	DH9	-	BA-0109-R002	QVQLVESGGGLVPPGGSLRLSCAASGFSFSDHYMDWVRQAPGKGLEWVGFIRSAAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKCLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1333)	DIQMTQSPSSLSASVGDKVTITCRASQGISSYLAWYQQKPGKAPKLLIYVASSLQTGVPSRFSGSRSGTDFTLTISSLQSEDFGTYYCQQSYRTPYTFGQGTKLEIKPLGLSGRSDNHDILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGCGTKLELK(SEQ ID NO:1334)
A33	B3	C10	DH9	-	BA-0109-R003	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQTRLGPTTFDYWGQGSLVTVSSPLGLSGRSDNQVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKCLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCAR	DIQMTQSPSTLSASVGDRVTITCRASQNVDKWLAWYQQKPGKAPKLLIYKASGLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDSYPLTFGGGTKVEIKPLG

						ALTYYDYEFAYWGQGTLVTVSAEPKSCD KTHTCPPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1335)	LSGRSDNHDILLTQ SPVILSVSPGERVSF SCRASQSIGTNIHW YQQRTNGSPRLLIK YASESISGIPSRFSG SGSGTDFTLSINSVE SEDIADYYCQQNN NWPTTFGCGTKLE LK(SEQ ID NO:1336)
A 55	B 3	C10	DH 9	-	BA- 0109- R004	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL KQSGPGLVQPSQSLSITCTVSGFSLTNYGV HWVRQSPGKCLEWLGVIWSGGNTDYNT PFTSRLSINKDNSKSQVFFKMNSLQSNDT AIYYCARALTYYDYEFAYWGQGTLVTVS AEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK(SEQ ID NO:1337)	DIQMTQSPSSVSAS VGDRVTLTCRASQ GIRSWLAWYQQKP GKAPKLLIYAASNL QSGVPSRFSGSGSG TDFILTINSLQPDDF ATYYCQQANSFPY TFGQGTKVEIKPLG LSGRSDNHDILLTQ SPVILSVSPGERVSF SCRASQSIGTNIHW YQQRTNGSPRLLIK YASESISGIPSRFSG SGSGTDFTLSINSVE SEDIADYYCQQNN NWPTTFGCGTKLE LK(SEQ ID NO:1338)
A 9	B 3	C12	DH 9	-	BA- 0109- R005	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT LVTVSSPLGLSGRSDNQVQLQESGPGLVK PSETLSLTCTVSGGSVSSGDYYWTWIRQS PGKCLEWIGHIYYSGNTNYNPSLKSRLTIS IDTSKTQFSLKLSSVTAADTAIYYCVRDR VTGAFDIWGQGTMVTVSSEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALGAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1339)	QLVLTQPHSVSESP GKTVTISCTRSSGSI ASKYVQWYQQRP GSAPTTVIYEDNQR PSGVPDRFSGSIDIS SNSASLTISGLKTE DEADYYCQSYDSS TVVFGGGTKLTVL PLGLSGRSDNHDIQ MTQSPSSLSASVGD RVTITCQASQDISN YLNWYQQKPGKAP KLLIYDASNLETGV PSRFSGSGSGTDFT FTISSLQPEDIATYF CQHFDHLPLAFGC GTKVEIK(SEQ ID NO:1340)
A 33	B 3	C14	DH 9	-	BA- 0109- R011	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLQESGPG LVKPSQTLSLTCTVSGGSISSGDYYWSWI	DIQMTQSPSTLSAS VGDRVTITCRASQN VDKWLAWYQQKP GKAPKLLIYKASGL ESGVPSRFSGSGSG TEFTLTISSLQPDDF

						RQPPGKCLEWIGYIYYSGSTDYNPSLKSR VTMSVDTSKNQFSLKVNSVTAADTAVYY CARVSIFGVGTFDYWGQGTLVTVSSEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALGA PIEKTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSP GK(SEQ ID NO:1341)	ATYYCQQYDSYPL TFGGGTKVEIKPLG LSGRSDNHEIVMTQ SPATLSLSPGERAT LSCRASQSVSSYLA WYQQKPGQAPRLL IYDASNRATGIPAR FSGSGSGTDFTLTIS SLEPEDFAVYYCH QYGSTPLTFGCGTK AEIK(SEQ ID NO:1342)
A33	B3	C12	DH8	-	BA-0109-R015	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLQESGPG LVKPSETLSLTCTVSGGSVSSGDYYWTWI RQSPGKCLEWIGHIYYSGNTNYNPSLKSR LTISIDTSKTQFSLKLSSVTAADTAIYYCV RDRVTGAFDIWGQGTMVTVSSEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1343)	DIQMTQSPSTLSAS VGDRVTITCRASQN VDKWLAWYQQKP GKAPKLLIYKASGL ESGVPSRFSGSGSG TEFTLTISSLQPDDF ATYYCQQYDSYPL TFGGGTKVEIKPLG LSGRSDNHDIQMT QSPSSLSASVGDRV TITCQASQDISNYL NWYQQKPGKAPKL LIYDASNLETGVPS RFSGSGSGTDFTFTI SSLQPEDIATYFCQ HFDHLPLAFGCGT KVEIK(SEQ ID NO:1344)
A55	B3	C12	DH8	-	BA-0109-R016	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QESGPGLVKPSETLSLTCTVSGGSVSSGD YYWTWIRQSPGKCLEWIGHIYYSGNTNY NPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSE PKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PGK(SEQ ID NO:1345)	DIQMTQSPSSVSAS VGDRVTLTCRASQ GIRSWLAWYQQKP GKAPKLLIYAASNL QSGVPSRFSGSGSG TDFILTINSLQPDDF ATYYCQQANSFPY TFGQGTKVEIKPLG LSGRSDNHDIQMT QSPSSLSASVGDRV TITCQASQDISNYL NWYQQKPGKAPKL LIYDASNLETGVPS RFSGSGSGTDFTFTI SSLQPEDIATYFCQ HFDHLPLAFGCGT KVEIK(SEQ ID NO:1346)
A9	B3	C14	DH8	-	BA-0109-R017	QMQLVESGGGLVQPGGSLRLSCAASGFT FSDFAMTWVRQAPGKGLEWVSSISGTSG RTYYADSVKGRSTVSTDNSKNTVYLRMN SLRAEDTAVYYCARGSPSGSADYWGQGT	QLVLTQPHSVSESP GKTVTISCTRSSGSI ASKYVQWYQQRP GSAPTTVIYEDNQR

						LVTVSSPLGLSGRSDNQVQLQESGPGLVK PSQTLSLTCTVSGGSISSGDYYWSWIRQPP GKCLEWIGYIYYSGSTDYNPSLKSRVTMS VDTSKNQFSLKVNSVTAADTAVYYCARV SIFGVGTFDYWGQGTLVTVSSEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SE Q ID NO:1347)	PSGVPDRFSGSIDIS SNSASLTISGLKTE DEADYYCQSYDSS TVVFGGGTKLTVL PLGLSGRSDNHEIV MTQSPATLSLSPGE RATLSCRASQSVSS YLAWYQQKPGQAP RLLIYDASNRATGI PARFSGSGSGTDFT LTISSLEPEDFAVY YCHQYGSTPLTFGC GTKAEIK(SEQ ID NO:1348)
A 28	B 3	C14	DH 8	-	BA- 0109- R018	QVQLVESGGGLVPPGGSLRLSCAASGFSF SDHYMDWVRQAPGKGLEWVGFIRSAAY GGTTEYAASVKGRFTISRDDSKSIAYLQM NSLRAEDTAVYYCARDGNYYDSRGYYY DTFDLWGQGTMVTVSSPLGLSGRSDNQV QLQESGPGLVKPSQTLSLTCTVSGGSISSG DYYWSWIRQPPGKCLEWIGYIYYSGSTD YNPSLKSRVTMSVDTSKNQFSLKVNSVT AADTAVYYCARVSIFGVGTFDYWGQGTL VTVSSEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK(SEQ ID NO:1349)	DIQMTQSPSSLSAS VGDKVTITCRASQ GISSYLAWYQQKP GKAPKLLIYVASSL QTGVPSRFSGSRSG TDFTLTISSLQSEDF GTYYCQQSYRTPY TFGQGTKLEIKPLG LSGRSDNHEIVMTQ SPATLSLSPGERAT LSCRASQSVSSYLA WYQQKPGQAPRLL IYDASNRATGIPAR FSGSGSGTDFTLTIS SLEPEDFAVYYCH QYGSTPLTFGCGTK AEIK(SEQ ID NO:1350)

As a result, as shown in Figure 11, the productivity of the multispecific fusion protein up to the first purification was about 0.1 mg/L to about 55.6 mg/L. In addition, SEC-UPLC analysis results showed that each multispecific fusion protein had a purity of about 52% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed.

Example 2.4.5. ReleaBody type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-B7H3]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein was produced by linking a ReleaDome, in which a first domain (first component) comprising a heavy chain variable region (VH1) and a light chain

variable region (VL1) of an antibody that binds to ANXA1, and a second domain (third component) comprising a heavy chain variable region (VH2) and a light chain variable region (VL2) of an antibody that binds to B7H3 are serially linked via a first linker (second component), to an Fc region or a variant thereof (fourth component) via a third linker to produce a multispecific fusion protein that comprises a ReleaBody form or a structure modified therefrom.

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to B7H3, a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, and a light chain variable region (VL2) of an antibody that binds to B7H3 into each expression vector. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 39. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 39]

Part Number					Protein code	HC	LC
A9	B3	C18	DH9	-	BA-0111-R001	QMQLVESGGGLVQPGGSLRLSCAASGFTFSDFAMTWVRQAPGKGLEWVSSISGTSGRTYYADSVKGRSTVSTDNSKNTVYLRMNSLRAEDTAVYYCARGSPSGSADYWGQGTLVTVSSPLGLSGRSDNQVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQCLEWMGGIIPILGIANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1351)	QLVLTQPHSVSESPGKTVTISCTRSSGSIASKYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDISSNSASLTISGLKTEDEADYYCQSYDSSTVVFGGGTKLTVLPLGLSGRSDNHEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGCGTRLEIK(SEQ ID NO:1352)
A28	B3	C18	DH9	-	BA-0111-R002	QVQLVESGGGLVPPGGSLRLSCAASGFSFSDHYMDWVRQAPGKGLEWVGFIRSAAYGGTTEYAASVKGRFTISRDDSKSIAYLQMNSLRAEDTAVYYCARDGNYYDSRGYYYDTFDLWGQGTMVTVSSPLGLSGRSDNQVQLQQSGAEVKKPGSSVKVSCKASGGTFSS	DIQMTQSPSSLSASVGDKVTITCRASQGISSYLAWYQQKPGKAPKLLIYVASSLQTGVPSRFSGSRSGTDFTLTISSLQSEDF

						YAISWVRQAPGQCLEWMGGIIPILGIANY AQKFQGRVTITADESTSTAYMELSSLRSE DTAVYYCARGGSGSYHMDVWGKGTTVT VSSEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK(SEQ ID NO:1353)	GTYYCQQSYRTPY TFGQGTKLEIKPLG LSGRSDNHEIVLTQ SPATLSLSPGERAT LSCRASQSVSSYLA WYQQKPGQAPRLL IYDASNRATGIPAR FSGSGSGTDFTLTIS SLEPEDFAVYYCQ QRSNWPPRITFGCG TRLEIK(SEQ ID NO:1354)
A33	B3	C18	DH9	-	BA-0111-R003	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYAMHWVRQAPGKGLEWVAVISYDGS NKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDQTRLGPTTFDYWG QGSLVTVSSPLGLSGRSDNQVQLQQSGAE VKKPGSSVKVSCKASGGTFSSYAISWVRQ APGQCLEWMGGIIPILGIANYAQKFQGRV TITADESTSTAYMELSSLRSEDTAVYYCA RGGSGSYHMDVWGKGTTVTVSSEPKSCD KTHTCPPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1355)	DIQMTQSPSTLSAS VGDRVTITCRASQN VDKWLAWYQQKP GKAPKLLIYKASGL ESGVPSRFSGSGSG TEFTLTISSLQPDDF ATYYCQQYDSYPL TFGGGTKVEIKPLG LSGRSDNHEIVLTQ SPATLSLSPGERAT LSCRASQSVSSYLA WYQQKPGQAPRLL IYDASNRATGIPAR FSGSGSGTDFTLTIS SLEPEDFAVYYCQ QRSNWPPRITFGCG TRLEIK(SEQ ID NO:1356)
A55	B3	C18	DH9	-	BA-0111-R004	QVQLVQSGGGLVQPGRSLRISCKASGFNF GDYPLSWVRQAPGKGLEWIGFIRSKSFGG TTEYAASVKGRFTISRDDSRDIAYLQMNS LRAEDTAVYYCARDGNYYDSRGYYYDT FDLWGQGTMITVSSPLGLSGRSDNQVQL QQSGAEVKKPGSSVKVSCKASGGTFSSY AISWVRQAPGQCLEWMGGIIPILGIANYA QKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARGGSGSYHMDVWGKGTTVTV SSEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK(SEQ ID NO:1357)	DIQMTQSPSSVSAS VGDRVTLTCRASQ GIRSWLAWYQQKP GKAPKLLIYAASNL QSGVPSRFSGSGSG TDFILTINSLQPDDF ATYYCQQANSFPY TFGQGTKVEIKPLG LSGRSDNHEIVLTQ SPATLSLSPGERAT LSCRASQSVSSYLA WYQQKPGQAPRLL IYDASNRATGIPAR FSGSGSGTDFTLTIS SLEPEDFAVYYCQ QRSNWPPRITFGCG TRLEIK(SEQ ID NO:1358)

As a result, as shown in Figure 12, the productivity of the multispecific fusion protein up to the first purification was about 14 mg/L to about 40.6 mg/L. In addition, SEC-UPLC analysis

results showed that each multispecific fusion protein had a purity of about 69% to about 99%. Regarding the size of the fusion protein, the heavy and light chain bands with increased size were observed.

Example 2.5. DVD-Ig variant type multispecific fusion protein comprising a ReleaDome

Example 2.5.1. DVD-Ig variant [DVD-Ig CrossMab, KIH, single arm-cleavable] type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

A [DVD-Ig CrossMab, KIH, single arm-cleavable] variant was produced in which the CH1 of one heavy chain and the CL of one light chain in the structure of the multispecific fusion protein of Example 2.3.3 are CrossMabbed with each other, the first linker comprises a non-cleavable substrate sequence or a cleavable substrate sequence, and the Fc region is modified to comprise a LALAPG sequence variant and a knob into hole sequence (Figure 13a).

Specifically, the multispecific fusion protein constituting the multispecific fusion protein dimer was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first cleavable linker, a light chain variable region (VL2) that binds to EGFR, a first non-cleavable linker, and a light chain constant region into each expression vector.

In addition, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH2) of an antibody that binds to ANXA1, a first non-cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a light chain constant region (CL), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first non-cleavable linker, a light chain variable region (VL2) that binds to EGFR, a first non-cleavable linker, and a heavy chain constant region (CH1) into each expression vector. In this case, the Fc variant may comprise the amino acid L234A/L235A substitution in CH2 of the Fc region (human IgG1) and the amino acid P329G substitution (LALAPG) in CH3. In addition, the CH3 may comprise a 'knob' structure or a 'hole' structure. In this case, the amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the multispecific fusion proteins are shown in Table 40. The amino acid sequences of the above fusion proteins are described

sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a dimer.

[Table 40]

Part Number					Protein code	HC(1)	LC(1)	HC(2)*; * Cross CL-CH in HC(2)	LC(2)**; ** Cross CH in LC(2)
A55/A55	B3/B7	C11/C11	DH4/DH5	DL2/DL3	BA-0109-022	QVQLVQSGGGL VQPGRSLRISCK ASGFNFGDYPLS WVRQAPGKGLE WIGFIRSKSFGGT TEYAASVKGRFT ISRDDSRDIAYLQ MNSLRAEDTAV YYCARDGNYYD SRGYYYDTFDL WGQGTMITVSSP LGLSGRSDNQVQ LQESGPGLVKPS ETLSLTCTVSGG SVSSGDYYWTWI RQSPGKGLEWIG HIYYSGNTNYNP SLKSRLTISIDTS KTQFSLKLSSVT AADTAIYYCVRD RVTGAFDIWGQ GTMVTVSSASTK GPSVFPLAPSSKS TSGGTAALGCLV EDYFPEPVTVSW NSGALTSGVHTF PAVLQSSGLYSL SSVVTVPSSSLGT QTYICNVNHKPS NTKVDEKVEPKS CDKTHTCPPCPA PEAAGGPSVFLF PPKPKDTLMISRT PEVTCVVVDVSH EDPEVKFNWYV DGVEVHNAKTK PREEQYNSTYRV VSVLTVLHQDW LNGKEYKCKVS NKALGAPIEKTIS KAKGQPREPQVC TLPPSRDELTKN QVSLSCAVKGFY PSDIAVEWESNG	DIQMTQS PSSVSAS VGDRVTL TCRASQG IRSWLAW YQQKPGK APKLLIY AASNLQS GVPSRFS GSGSGTD FILTINSL QPDDFAT YYCQQA NSFPYTF GQGTKVE IKPLGLSG RSDNHDI QMTQSPS SLSASVG DRVTITC QASQDIS NYLNWY QQKPGKA PKLLIYD ASNLETG VPSRFSGS GSGTDFT FTISSLQP EDIATYF CQHFDHL PLAFGGG TKVEIKR SVAAPSV FIFPPSDE QLKSGTA SVVCLLN NFYPREA KVQWCV DNALQSG NSQESVT EQDSKDS TYSLSSTL TLSKADY EKHKVY	QVQLVQSGG GLVQPGRSLR ISCKASGFNF GDYPLSWVR QAPGKGLEWI GFIRSKSFGGT TEYAASVKGR FTISRDDSRDI AYLQMNSLR AEDTAVYYC ARDGNYYDS RGYYYDTFDL WGQGTMITV SSASTKGQVQ LQESGPGLVK PSETLSLTCTV SGGSVSSGDY YWTWIRQSPG KGLEWIGHIY YSGNTNYNPS LKSRLTISIDT SKTQFSLKLSS VTAADTAIYY CVRDRVTGAF DIWGQGTMV TVSSRSVAAP SVFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSKA DYEKHKVYA CEVTHQGLSS PVTKSFNRGE CDKTHTCPPC PAPEAAGGPS VFLFPPKPKD TLMISRTPEVT CVVVDVSHE DPEVKFNWY VDGVEVHNA KTKPREEQYN	DIQMTQSPS SVSASVGDR VTLTCRASQ GIRSWLAW YQQKPGKAP KLLIYAASN LQSGVPSRF SGSGSGTDFI LTINSLQPDD FATYYCQQA NSFPYTFGQ GTKVEIKAS TKGPDIQMT QSPSSLSASV GDRVTITCQ ASQDISNYL NWYQQKPG KAPKLLIYD ASNLETGVP SRFSGSGSG TDFTFTISSL QPEDIATYF CQHFDHLPL AFGGGTKVE IKASTKGPS VFPLAPSSKS TSGGTAALG CLVKDYFPE PVTVSWNSG ALTSGVHTF PAVLQSSGL YSLSSVVTV PSSSLGTQT YICNVNHKP SNTKVDKK VEPKSC(SEQ ID NO:1362)

						QPENNYKTTPPV LDSDGSFFLVSK LTVDKSRWQQG NVFSCSVMHEAL HNHYTQKSLSLS PGK(SEQ ID NO:1359)	ACEVTHQ GLSSPVT KSFNRGE C(SEQ ID NO:1360)	STYRVVSVLT VLHQDWLNG KEYKCKVSN KALGAPIEKTI SKAKGQPREP QVYTLPPCRD ELTKNQVSL WCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFS CSVMHEALH NHYTQKSLSL SPGK(SEQ ID NO:1361)	

As a result, as shown in Figures 13b to 13d, the productivity of the multispecific fusion protein up to the first purification was 15.63 mg/L. In addition, SEC-UPLC analysis results showed that the multispecific fusion protein had a purity of about 72.71%. Furthermore, the sizes of the heavy chain and the light chain of the fusion protein could be confirmed through SDS-PAGE.

Example 2.5.2. DVD-Ig variant [DVD-Ig asymmetric] type multispecific fusion protein comprising a ReleaDome [anti-ANXA1-anti-EGFR]

In the present invention, a fusion protein comprising the ReleaDome and the following component, which is one embodiment of a multispecific fusion protein, was produced by the method of Example 2.1 and Example 2.2 above.

The multispecific fusion protein dimer was produced by linking a dual functional domain structure (ReleaDome), in which a first domain (first component) that binds to ANXA1 and a second domain (third component) that binds to EGFR are serially linked via a first linker (second component); or a structure comprising only a structure in which VH2 and VL2 of the second domain are CrossMabbed with CL and CH1, to an Fc region or a variant thereof (fourth component) to produce a multispecific fusion protein dimer that comprises a DVD-Ig form or a structure modified therefrom. In this case, the Fc region of the multispecific fusion protein was produced to comprise a LALAPG sequence variant and a knob into hole structure (Figure 14a).

Specifically, the multispecific fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH1) of an antibody that binds to ANXA1, a first cleavable linker, a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a heavy chain constant region (CH1), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL1) of an antibody that binds to ANXA1, a first

cleavable linker, a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a light chain constant region into each vector.

In addition, the fusion protein was expressed by loading a polynucleotide encoding a heavy chain (HC) comprising a heavy chain variable region (VH2) of an antibody that binds to EGFR, a first non-cleavable linker, a light chain constant region (CL), a third linker, and an Fc region or a variant thereof; and a polynucleotide encoding a light chain (LC) comprising a light chain variable region (VL2) of an antibody that binds to EGFR, a first non-cleavable linker, and a heavy chain constant region (CH1) into each vector. The amino acid sequences of the heavy chain (HC) and the light chain (LC) of each of the fusion proteins are shown in Table 41. The amino acid sequences of the above fusion proteins are described sequentially from the N-terminus to the C-terminus.

The multispecific fusion protein produced as described above formed a heterodimer.

[Table 41]

Part Number; '-', Not associated					Protein code	HC(1)	LC(1)	HC(2)*; * Cross CL-CH in HC(2)	LC(2)**; ** Cross CH in LC(2)
A55/-	B3/-	C11/C11	DH4/DH5	DL2/DL3	BA-0109-023	QVQLVQSGGGLVQ	DIQMTQSPS	QVQLQESGPGLV	DIQMTQ
						PGRSLRISCKASGFN	SVSASVGDR	KPSETLSLTCTVS	SPSSLSA
						FGDYPLSWVRQAP	VTLTCRASQ	GGSVSSGDYYW	SVGDRV
						GKGLEWIGFIRSKSF	GIRSWLAW	TWIRQSPGKGLE	TITCQAS
						GGTTEYAASVKGRF	YQQKPGKAP	WIGHIYYSGNTN	QDISNY
						TISRDDSRDIAYLQ	KLLIYAASN	YNPSLKSRLTISI	LNWYQ
						MNSLRAEDTAVYY	LQSGVPSRF	DTSKTQFSLKLSS	QKPGKA
						CARDGNYYDSRGY	SGSGSGTDFI	VTAADTAIYYCV	PKLLIY
						YYDTFDLWGQGTM	LTINSLQPDD	RDRVTGAFDIWG	DASNLE
						ITVSSPLGLSGRSDN	FATYYCQQA	QGTMVTVSSRSV	TGVPSR
						QVQLQESGPGLVKP	NSFPYTFGQ	AAPSVFIFPPSDE	FSGSGS
						SETLSLTCTVSGGS	GTKVEIKPL	QLKSGTASVVCL	GTDFTF
						VSSGDYYWTWIRQ	GLSGRSDNH	LNNFYPREAKVQ	TISSLQP
						SPGKGLEWIGHIYY	DIQMTQSPS	WKVDNALQSGN	EDIATY
						SGNTNYNPSLKSRL	SLSASVGDR	SQESVTEQDSKD	FCQHFD
						TISIDTSKTQFSLKLS	VTITCQASQ	STYSLSSTLTLSK	HLPLAF
						SVTAADTAIYYCVR	DISNYLNWY	ADYEKHKVYAC	GGGTKV
						DRVTGAFDIWGQG	QQKPGKAPK	EVTHQGLSSPVT	EIKAST
						TMVTVSSASTKGPS	LLIYDASNL	KSFNRGECDKTH	KGPSVF
						VFPLAPSSKSTSGGT	ETGVPSRFS	TCPPCPAPEAAG	PLAPSS
						AALGCLVEDYFPEP	GSGSGTDFT	GPSVFLFPPKPKD	KSTSGG
						VTVSWNSGALTSG	FTISSLQPEDI	TLMISRTPEVTC	TAALGC
						VHTFPAVLQSSGLY	ATYFCQHFD	VVVDVSHEDPEV	LVKDYF
						SLSSVVTVPSSSLGT	HLPLAFGGG	KFNWYVDGVEV	PEPVTV
						QTYICNVNHKPSNT	TKVEIKRSV	HNAKTKPREEQY	SWNSGA
						KVDEKVEPKSCDKT	AAPSVFIFPP	NSTYRVVSVLTV	LTSGVH
						HTCPPCPAPEAAGG	SDEQLKSGT	LHQDWLNGKEY	TFPAVL
						PSVFLFPPKPKDTL	ASVVCLLNN	KCKVSNKALGA	QSSGLY
						MISRTPEVTCVVVD	FYPREAKVQ	PIEKTISKAKGQP	SLSSVV

						VSHEDPEVKFNWY VDGVEVHNAKTKP REEQYNSTYRVVSV LTVLHQDWLNGKE YKCKVSNKALGAPI EKTISKAKGQPREP QVCTLPPSRDELTK NQVSLSCAVKGFYP SDIAVEWESNGQPE NNYKTTPPVLDSDG SFFLVSKLTVDKSR WQQGNVFSCSVMH EALHNHYTQKSLSL SPGK(SEQ ID NO:1363)	WCVDNALQ SGNSQESVT EQDSKDSTY SLSSTLTLSK ADYEKHKV YACEVTHQ GLSSPVTKSF NRGEC(SEQ ID NO:1364)	REPQVYTLPPCR DELTKNQVSLW CLVKGFYPSDIA VEWESNGQPEN NYKTTPPVLDSD GSFFLYSKLTVD KSRWQQGNVFS CSVMHEALHNH YTQKSLSLSPGK(SEQ ID NO:1365)	TVPSSSL GTQTYI CNVNH KPSNTK VDKKVE PKSC(SE Q ID NO:1366)

As a result, as shown in Figures 14b to 14d, the productivity of the multispecific fusion protein up to the first purification was 24.65 mg/L. In addition, SEC-UPLC analysis results showed that the multispecific fusion protein had a purity of about 37.79%. Furthermore, the sizes of the heavy chain and the light chain of the fusion protein could be confirmed through SDS-PAGE.

Example 2.6. Various types of multispecific fusion protein variants comprising a ReleaDome

In one embodiment of the present invention, various types of multispecific fusion protein variants comprising a dual functional domain structure can be produced, using a ReleaDome as a specific example of a molecule of a multispecific fusion protein. The types of the fusion proteins, their schematic diagrams, and amino acid sequences are described in Figures 3a to 3c, Table 42, and Table 43.

[Table 42]

Part Number ('-' or N/A, Not associated; N/D, Not determined)							Structure code	Structure type	Target of first component	Target of third component	Part F Target	Molecular weight(LC/MS)	PI
A77	B2	C11	DH2	DL2	-	-	ST-017	scFv-IgG LALA	ANXA1	EGFR	N/A	199635	8.23
A78	B2	C11	DH2	DL2	-	-	ST-018	VHH-IgG LALA	ANXA1	EGFR	N/A	174291	8.03
A79	B2	C11	DH2	DL2	-	-	ST-019	Fab-IgG LALA	ANXA1	EGFR	N/A	244009	8.28
A80	B2	C11	DH2	DL2	-	-	ST-020	Peptide-IgG LALA	ANXA1	EGFR	N/A	244009	7.64
A81	B2	C11	DH2	DL2	-	-	ST-021	Fab-IgG LALA	TEM8	EGFR	N/A	240964	7.09
A79	B2	C2	DH7	-	-	-	ST-022	Fab-RC LALA-	ANXA1	HER2	N/A	200028	8.56

								PG					
A81	B2	C2	DH7	-	-	-	ST-023	Fab-RC LALA-PG	TEM8	HER2	N/A	196983	7.79
A55	B2	C21	DH4	DL1	-	-	ST-024	DVD-IgG TriAb LALA-PG	ANXA1	CD3	N/A	200340	8.62
		C28	DH5	DL3						PD-L1			
A55	B2	C29	DH9	-	E2	F2	ST-025	RC-scFv TriAb LALA-PG	ANXA1	CD3	PD-L1	210279	8.77
A55	B2	C30	DH9	-	-	-	ST-026	RC VL-VH LALA-PG	ANXA1	EGFR	N/A	156139	8.08
A82	B2	C11	DH9	-	-	-	ST-027	RC VH-VL LALA-PG	ANXA1	EGFR	N/A	156139	8.08
A55	B2	C29	DH10	-	-	-	ST-028	RC TriAb LALA-PG	ANXA1	CD3	N/A	156888	8.66
		C31	DH11	-						PD-L1			
A55	B2	C29	DH10	-	-	-	ST-029	RC+scFv TriAb LALA-PG	ANXA1	CD3	N/A	130357	8.58
-	-	C32	DH11	-						PD-L1			
A55	B2	C21	DH4	DL1	-	-	ST-030	DVD-IgG asymmetric TriAb LALA-PG	ANXA1	CD3	N/A	172885	8.53
-	-	C28	DH5	DL3						PD-L1			
A55	B2	C21	DH4	DL1	-	-	ST-031	DVD-IgG+scFv TriAb LALA-PG	ANXA1	CD3	N/A	152084	8.48
-	-	C32	DH11	-						PD-L1			
A79	B2	C29	DH10	-	-	-	ST-032	Fab-RC-IgG asymmetric TriAb LALA-PG	ANXA1	CD3	N/A	161691	8.65
-	-	C28	DH12	DL1						PD-L1			
A79	B2	C29	DH10	-	-	-	ST-033	Fab-RC+scFv TriAb LALA-PG	ANXA1	CD3	N/A	152623	8.56
-	-	C32	DH11	-						PD-L1			
A55	B2	C21	DH13	DL1	-	-	ST-034	ALiCE	ANXA1	CD3	PD-L1	180094	8.91

			DH14										
A55	B2	C12	DH15	-	-	-	ST-035	MiniBody	ANXA1	EGFR	N/A	135597	8.41
A55	B2	C29	DH16	-	-	-	ST-036	MiniBody TriAb	ANXA1	CD3	N/A	133657	8.61
		C31	DH17	-						PD-L1	N/A		
A55	B2	C11	DH18	DL2	-	-	ST-038	DVD-IgG Minibody	ANXA1	EGFR	N/A	176335	8.04
A79	B2	C12	DH15	-	-	-	ST-039	Fab Minibody	ANXA1	EGFR	N/A	177440	7.99
A77/-	B2/-	C12	DH9	-	-	-	ST-040	scFv-RC LALA-PG	ANXA1	EGFR	N/A	156297	8.08
A77/-	B2/-	C11	DH18	DL2	-	-	ST-041	scFv-Fab Minibody	ANXA1	EGFR	N/A	176493	8.04
A77/-	B2/-	C12	DH15	-	-	-	ST-042	scFv Minibody	ANXA1	EGFR	N/A	129086	7.93
A77/-	B2/-	C21	DH13	DL1	-	-	ST-043	scFv ALiCE	ANXA1	CD3	PD-L1	165714	8.89
			DH14										

[Table 43]

Structure code	HC	LC
ST-017	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS GGGGSGGGGSGGGGSDIQMTQSPSSVSASVGD RVTLTCRASQGIRSWLAWYQQKPGKAPKLLIY AASNLQSGVPSRFSGSGSGTDFILTINSLQPDDF ATYYCQQANSFPYTFGQGTKVEIKLSGRSDNQ VQLQESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRD RVTGAFDIWGQGTMVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1367)	DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGGGTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVCLL NNFYPREAKVQWCVDNAL QSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNR GE(SEQ ID NO:1368)
ST-018	QVQLVQSGGGSVKAGRSLRLSCTASGFTFGDY	DIQMTQSPSSLSASVGDRV

	AMSWVRQAPGKEREFVAFIRSKAYGGTTEYA ASVKGRFTISRDDSKSIAYLQMNSLRAEDTAV YYCARDGNYYDSRGYYYDTFDLWGQGTTVT VSSLSGRSDNQVQLQESGPGLVKPSETLSLTCT VSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYY SGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTA ADTAIYYCVRDRVTGAFDIWGQGTMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK(SEQ ID NO:1369)	TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGGGTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVCLL NNFYPREAKVQWCVDNAL QSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNR GE(SEQ ID NO:1370)
ST-019	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNQVQLQESGPGLVKPSETLSLT CTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHI YYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSV TAADTAIYYCVRDRVTGAFDIWGQGTMVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1371)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWCVDNA LQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFN RGECLSGRSDNHDIQMTQS PSSLSASVGDRVTITCQASQ DISNYLNWYQQKPGKAPK LLIYDASNLETGVPSRFSGS GSGTDFTFTISSLQPEDIAT YFCQHFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREA KVQWCVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQG LSSPVTKSFNRGEC(SEQ ID NO:1372)
ST-020	IFLLWQRLSGRSDNQVQLQESGPGLVKPSETLS LTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLS SVTAADTAIYYCVRDRVTGAFDIWGQGTMVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTV	DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGGGTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVCLL NNFYPREAKVQWCVDNAL QSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVY

	LHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK(SEQ ID NO:1373)	ACEVTHQGLSSPVTKSFNR GEC(SEQ ID NO:1374)
ST-021	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSY AISWVRQAPGQGLEWMGGIIPIFGTTNYAQKF QGRVTITGEESTSTVYMELSSLRSEDTAVYYCA RDTDYMFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCLSGRSD NQVQLQESGPGLVKPSETLSLTCTVSGGSVSSG DYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPS LKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCV RDRVTGAFDIWGQGTMVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK(S EQ ID NO:1375)	SSELTQDPVVSVALGETVSI TCQGDNLRDFYASWYQQK PGQAPLLVMYGKNRRPSGI PDRFSGSTSGNTLSLTITGA QAEDEADYYCSSRDNSKH VVFGGGTKVTVLRSVAAPS VFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWCVDN ALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSF NRGECLSGRSDNHDIQMTQ SPSSLSASVGDRVTITCQAS QDISNYLNWYQQKPGKAP KLLIYDASNLETGVPSRFSG SGSGTDFTFTISSLQPEDIAT YFCQHFDHLPLAFGGGTKV EIKRSVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREA KVQWCVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQG LSSPVTKSFNRGEC(SEQ ID NO:1376)
ST-022	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKCLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCSRWGGDGFYAMDYWGQGTL VTVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALGAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK(SEQ ID NO:1377)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWCVDNA LQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFN RGECLSGRSDNHDIQMTQS PSSLSASVGDRVTITCRASQ DVNTAVAWYQQKPGKAP KLLIYSASFLYSGVPSRFSG SRSGTDFTLTISSLQPEDFA TYYCQQHYTTPPTFGCGTK VEIK(SEQ ID NO:1378)
ST-023	QVQLVQSGAEVKKPGTSVKVSCKVPGYTFSSY AISWVRQAPGQGLEWMGGIIPIFGTTNYAQKF QGRVTITGEESTSTVYMELSSLRSEDTAVYYCA RDTDYMFDYWGQGTLVTVSSASTKGPSVFPLA	SSELTQDPVVSVALGETVSI TCQGDNLRDFYASWYQQK PGQAPLLVMYGKNRRPSGI PDRFSGSTSGNTLSLTITGA

	PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCLSGRSD NEVQLVESGGGLVQPGGSLRLSCAASGFNIKD TYIHWVRQAPGKCLEWVARIYPTNGYTRYAD SVKGRFTISADTSKNTAYLQMNSLRAEDTAVY YCSRWGGDGFYAMDYWGQGTLVTVSSDKTH TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALGAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1379)	QAEDEADYYCSSRDNSKH VVFGGGTKVTVLRSVAAPS VFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWCVDN ALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSF NRGECLSGRSDNHDIQMTQ SPSSLSASVGDRVTITCRAS QDVNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSRFS GSRSGTDFTLTISSLQPEDF ATYYCQQHYTTPPTFGCGT KVEIK(SEQ ID NO:1380)
ST-024	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVEDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDEKVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTIS KAKGQPREPQVCTLPPSRDELTKNQVSLSCAV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1381)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1382)
	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRA EDTAVYYCARRHWPGGFDYWGQGTLVTVSSR SVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALGAPIEKTISKA KGQPREPQVYTLPPCRDELTKNQVSLWCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNH	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRASQDVSTAVAWYQ QKPGKAPKLLIYSASFLYS GVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYLYHP ATFGQGTKVEIKASTKGPS VFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPK SC(SEQ ID NO:1384)

	YTQKSLSLSPGK(SEQ ID NO:1383)	
ST-025	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKCLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGKGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFSDSWIHWVRQA PGKGLEWVAWISPYGGSTYYADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCARRHWPG GFDYWGQGTLVTVSSGGGGSGGGGSGGGGSD IQMTQSPSSLSASVGDRVTITCRASQDVSTAVA WYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQYLYHPATFGQ GTKVEIK(SEQ ID NO:1385)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGCGTKVEIK(SEQ ID NO:1386)
ST-026	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNDIQMTQSPSSLSASVGDRVTITCQAS QDISNYLNWYQQKPGKAPKLLIYDASNLETGV PSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFD HLPLAFGCGTKVEIKEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1387)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH QVQLQESGPGLVKPSETLS LTCTVSGGSVSSGDYYWT WIRQSPGKCLEWIGHIYYS GNTNYNPSLKSRLTISIDTS KTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGT MVTVSS(SEQ ID NO:1388)
ST-027	DIQMTQSPSSVSASVGDRVTLTCRASQGIRSWL AWYQQKPGKAPKLLIYAASNLQSGVPSRFSGS GSGTDFILTINSLQPDDFATYYCQQANSFPYTF GQGTKVEIKLSGRSDNQVQLQESGPGLVKPSE TLSLTCTVSGGSVSSGDYYWTWIRQSPGKCLE WIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSL KLSSVTAADTAIYYCVRDRVTGAFDIWGQGT MVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALGAPIEKTISK	QVQLVQSGGGLVQPGRSL RISCKASGFNFGDYPLSWV RQAPGKGLEWIGFIRSKSF GGTTEYAASVKGRFTISRD DSRDIAYLQMNSLRAEDTA VYYCARDGNYYDSRGYYY DTFDLWGQGTMITVSSLSG RSDNHDIQMTQSPSSLSAS VGDRVTITCQASQDISNYL NWYQQKPGKAPKLLIYDA SNLETGVPSRFSGSGSGTDF

	AKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1389)	TFTISSLQPEDIATYFCQHF DHLPLAFGCGTKVEIK(SEQ ID NO:1390)
ST-028	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKCLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1391)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGCGTKVEIK(SEQ ID NO:1386)
	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNDIQMTQSPSSLSASVGDRVTITCRAS QDVSTAVAWYQQKPGKAPKLLIYSASFLYSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL YHPATFGCGTKVEIKEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPCRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1392)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH EVQLVESGGGLVQPGGSLR LSCAASGFTFSDSWIHWVR QAPGKCLEWVAWISPYGG STYYADSVKGRFTISADTS KNTAYLQMNSLRAEDTAV YYCARRHWPGGFDYWGQ GTLVTVSS(SEQ ID NO:1393)
ST-029	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKCLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK(SEQ ID NO:1391)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGCGTKVEIK(SEQ ID NO:1386)

	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDS WIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CARRHWPGGFDYWGQGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQY LYHPATFGQGTKVEIKEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LGAPIEKTISKAKGQPREPQVYTLPPCRDELTK NQVSLWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1394)	N/A
ST-030	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVEDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDEKVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTIS KAKGQPREPQVCTLPPSRDELTKNQVSLSCAV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1381)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1382)
	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDS WIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CARRHWPGGFDYWGQGTLVTVSSRSVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGE CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPCRDELTKNQVSLWCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK(SEQ ID NO:1395)	DIQMTQSPSSLSASVGDRV TITCRASQDVSTAVAWYQ QKPGKAPKLLIYSASFLYS GVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYLYHP ATFGQGTKVEIKASTKGPS VFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPK SC(SEQ ID NO:1396)
ST-031	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ

	VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVEDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDEKVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTIS KAKGQPREPQVCTLPPSRDELTKNQVSLSCAV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK(SEQ ID NO:1381)	QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1382)
	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDS WIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CARRHWPGGFDYWGQGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQY LYHPATFGQGTKVEIKEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LGAPIEKTISKAKGQPREPQVYTLPPCRDELTK NQVSLWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1394)	N/A
ST-032	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFTFSTYAMNWVRQAPGKCLEWVGRIR SKYNNYATYYADSVKDRFTISRDDSKNSLYLQ MNSLKTEDTAVYYCARHGNFGNSYVSYFAYW GQGTLVTVSSEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVCTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK(SEQ ID NO:1397)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWCVDNA LQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFN RGECLSGRSDNHDIQMTQS PSSLSASVGDRVTITCRSST GAVTTSNYANWVQQKPGK APKALIGGTNKRAPGVPSR FSGSLIGDKATLTISSLQPE DFATYYCALWYSNLWVFG CGTKVEIK(SEQ ID NO:1398)

	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDS WIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CARRHWPGGFDYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PPCRDELTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K(SEQ ID NO:1399)	DIQMTQSPSSLSASVGDRV TITCRASQDVSTAVAWYQ QKPGKAPKLLIYSASFLYS GVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYLYHP ATFGQGTKVEIKRSVAAPS VFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSF NRGEC(SEQ ID NO:1400)
ST-033	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFTFSTYAMNWVRQAPGKCLEWVGRIR SKYNNYATYYADSVKDRFTISRDDSKNSLYLQ MNSLKTEDTAVYYCARHGNFGNSYVSYFAYW GQGTLVTVSSEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALGAPIE KTISKAKGQPREPQVCTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK(SEQ ID NO:1397)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWCVDNA LQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFN RGECLSGRSDNHDIQMTQS PSSLSASVGDRVTITCRSST GAVTTSNYANWVQQKPGK APKALIGGTNKRAPGVPSR FSGSLIGDKATLTISSLQPE DFATYYCALWYSNLWVFG CGTKVEIK(SEQ ID NO:1398)
	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDS WIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CARRHWPGGFDYWGQGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQY LYHPATFGQGTKVEIKEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LGAPIEKTISKAKGQPREPQVYTLPPCRDELTK NQVSLWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1394)	N/A
ST-034	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ

	VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPPCPAPELLGGPG GGGSEVQLVESGGGLVQPGGSLRLSCAASGFT FSDSWIHWVRQAPGKGLEWVAWISPYGGSTY YADSVKGRFTISADTSKNTAYLQMNSLRAEDT AVYYCARRHWPGGFDYWGQGTLVTVSS(SEQ ID NO:1401)	QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1382)
	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPPCPAPELLGGPG GGGSDIQMTQSPSSLSASVGDRVTITCRASQDV STAVAWYQQKPGKAPKLLIYSASFLYSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQYLYH PATFGQGTKVEIK(SEQ ID NO:1402)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1382)
ST-035	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNQVQLQESGPGLVKPSETLSLTCTVSG GSVSSGDYYWTWIRQSPGKCLEWIGHIYYSGN TNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSEPKSC DKTHTCPPCPAPEAAGGPGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1403)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH QVQLQESGPGLVKPSETLS LTCTVSGGSVSSGDYYWT WIRQSPGKCLEWIGHIYYS GNTNYNPSLKSRLTISIDTS KTQFSLKLSSVTAADTAIY YCVRDRVTGAFDIWGQGT MVTVSS(SEQ ID NO:1404)
ST-036	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS

	CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKCLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSEPKSCDKTHTCPPCPAPEAAGGPGQPR EPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLVSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK(SEQ ID NO:1405)	GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGCGTKVEIK(SEQ ID NO:1386)
	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNDIQMTQSPSSLSASVGDRVTITCRAS QDVSTAVAWYQQKPGKAPKLLIYSASFLYSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYL YHPATFGCGTKVEIKEPKSCDKTHTCPPCPAPE AAGGPGQPREPQVYTLPPCRDELTKNQVSLWC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK(SEQ ID NO:1406)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH EVQLVESGGGLVQPGGSLR LSCAASGFTFSDSWIHWVR QAPGKCLEWVAWISPYGG STYYADSVKGRFTISADTS KNTAYLQMNSLRAEDTAV YYCARRHWPGGFDYWGQ GTLVTVSS(SEQ ID NO:1393)
ST-038	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNQVQLQESGPGLVKPSETLSLTCTVSG GSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGN TNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADT AIYYCVRDRVTGAFDIWGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1407)	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKLSGRSDNH DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGGGTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVCLL NNFYPREAKVQWCVDNAL QSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNR GEC(SEQ ID NO:1160)
ST-039	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNQVQLQESGPGLVKPSETLSLT CTVSGGSVSSGDYYWTWIRQSPGKCLEWIGHI YYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSV	DIQMTQSPSSVSASVGDRV TLTCRASQGIRSWLAWYQ QKPGKAPKLLIYAASNLQS GVPSRFSGSGSGTDFILTINS LQPDDFATYYCQQANSFPY TFGQGTKVEIKRSVAAPSV FIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWCVDNA LQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKV

	TAADTAIYYCVRDRVTGAFDIWGQGTMVTVS SEPKSCDKTHTCPPCPAPEAAGGPGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K(SEQ ID NO:1408)	YACEVTHQGLSSPVTKSFN RGECLSGRSDNHDIQMTQS PSSLSASVGDRVTITCQASQ DISNYLNWYQQKPGKAPK LLIYDASNLETGVPSRFSGS GSGTDFTFTISSLQPEDIAT YFCQHFDHLPLAFGCGTKV EIK(SEQ ID NO:1409)
ST-040	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS GGGGSGGGGSGGGGSDIQMTQSPSSVSASVGD RVTLTCRASQGIRSWLAWYQQKPGKAPKLLIY AASNLQSGVPSRFSGSGSGTDFILTINSLQPDDF ATYYCQQANSFPYTFGQGTKVEIKLSGRSDNQ VQLQESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKCLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRD RVTGAFDIWGQGTMVTVSSEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALGAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1410)	DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGCGTKVEIK(SEQ ID NO:207)
ST-041	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS GGGGSGGGGSGGGGSDIQMTQSPSSVSASVGD RVTLTCRASQGIRSWLAWYQQKPGKAPKLLIY AASNLQSGVPSRFSGSGSGTDFILTINSLQPDDF ATYYCQQANSFPYTFGQGTKVEIKLSGRSDNQ VQLQESGPGLVKPSETLSLTCTVSGGSVSSGDY YWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLK SRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRD RVTGAFDIWGQGTMVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK(SEQ ID NO:1411)	DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL QPEDIATYFCQHFDHLPLA FGGGTKVEIKRSVAAPSVFI FPPSDEQLKSGTASVVCLL NNFYPREAKVQWCVDNAL QSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNR GEC(SEQ ID NO:1412)
ST-042	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS	DIQMTQSPSSLSASVGDRV TITCQASQDISNYLNWYQQ KPGKAPKLLIYDASNLETG VPSRFSGSGSGTDFTFTISSL

	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNQVQLQESGPGLVKPSETLSLT CTVSGGSVSSGDYYWTWIRQSPGKCLEWIGHI YYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSV TAADTAIYYCVRDRVTGAFDIWGQGTMVTVS SEPKSCDKTHTCPPCPAPEAAGGPGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K(SEQ ID NO:1413)	QPEDIATYFCQHFDHLPLA FGCGTKVEIK(SEQ ID NO:207)
ST-043	QVQLVQSGGGLVQPGRSLRLSCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCLSGRSDNEVQLVESGGGLVQPGGSLRLS CAASGFTFSTYAMNWVRQAPGKGLEWVGRIR SKYNNYATYYADSVKDRFTISRDDSKNSLYLQ MNSLKTEDTAVYYCARHGNFGNSYVSYFAYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPPCPAPELL GGPGGGGSEVQLVESGGGLVQPGGSLRLSCAA SGFTFSDSWIHWVRQAPGKGLEWVAWISPYG GSTYYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO:1414)	DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1415)
	QVQLVQSGGGLVQPGRSLRISCKASGFNFGDY PLSWVRQAPGKGLEWIGFIRSKSFGGTTEYAAS VKGRFTISRDDSRDIAYLQMNSLRAEDTAVYY CARDGNYYDSRGYYYDTFDLWGQGTMITVSS LSGRSDNEVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYAMNWVRQAPGKGLEWVGRIRSKYN NYATYYADSVKDRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSYFAYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPPCPAPELLGGPG GGGSDIQMTQSPSSLSASVGDRVTITCRASQDV STAVAWYQQKPGKAPKLLIYSASFLYSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQYLYH PATFGQGTKVEIK(SEQ ID NO:1416)	DIQMTQSPSSLSASVGDRV TITCRSSTGAVTTSNYANW VQQKPGKAPKALIGGTNKR APGVPSRFSGSLIGDKATLT ISSLQPEDFATYYCALWYS NLWVFGQGTKVEIKRSVA APSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVT KSFNRGEC(SEQ ID NO:1415)

Example 3. Preparation and analysis of multispecific fusion protein-drug conjugate

Multispecific fusion protein-drug conjugates or single antibody-drug conjugates were

produced by conjugating a maleimide linker-payload to a multispecific fusion protein or a single antibody using a known conjugation method (Nature Biotechnology 2008, Vol. 26, 925-932). In this case, an example of the components of the produced fusion protein-drug conjugates is described in Tables 44 and 45. In addition, an example of the components used in the single antibody-drug conjugates is described in Table 46.

Specifically, a multispecific fusion protein or a single antibody was diluted with sodium citrate (#40121004-3, Bioworld) buffer solution (25 mM, pH 6) or sodium phosphate (#BSPE-9680, T&I) buffer solution (20 mM, pH 8), and 2 mM to 5 mM of DTT (Dithithreitol; #43816-10 mL, Sigma) or a reducing agent was added to reduce the cysteine (Cys) residues at 37 °C for 3 hours. After removing residual DTT from the reaction mixture using a PD-10 column (#17-0851-01, Cytiva) (centrifugation conditions: 4,000 rpm, 18 min, RT) and Vivaspin-6 (#28-9323-17, Cytiva) (6 centrifugations), the reaction mixture was finally replaced with phosphate buffer solution (20 mM, pH 8). The reaction mixture with the replaced buffer solution was oxidized at 4 °C for 3 days to restore a disulfide bond. The oxidized multispecific fusion protein or single antibody was treated with a maleimide linker-payload to a molar concentration of about 3 to 6 times to bind the payload to the cysteine (Cys) residues of the multispecific fusion protein or single antibody (37 °C, 3 hours, rocking). After the reaction was completed, the reaction mixture was centrifuged using PD-10 and Vivaspin-6 to remove any remaining unbound substance, and the final multispecific fusion protein-drug conjugate product or single antibody-drug conjugate product was purified.

For the preparation analysis of the fusion protein-drug conjugate or the single antibody-drug conjugate, a PLRP-S column for biomolecules (#PL1912-3802, Agilent) was mounted to an ACQUITY H-Class PLUS Bio System (#176015105, Waters), and each sample (1 mg/mL, 10 uL) was loaded either directly (RP-UPLC) or after treatment with DTT at a concentration of 5 mM to 50 mM for 30 minutes (rRP-UPLC). The analysis was performed by mixing each sample at a flow rate of 1 mL/min to achieve a concentration of 30% to 50% of acetonitrile, and increasing or decreasing (gradient) at 80 °C for 20 minutes. The results were analyzed using the Waters Empower 3.6.1 version (Waters) program.

As a result, as shown in Figures 15a to 15g, various payloads were conjugated to multispecific fusion proteins or single antibody molecules. In this case, it was found that the average conjugation ratio (DAR, drug-antibody-ratio) of the drug-fusion protein or antibody ranged from about 1.3 to about 4.1.

[Table 44]

Part Number						Protein code	TODC code	Ave DAR	Linker-toxin Feature
A58	B2	C1	DH1	DL 2	G3	BA-0102-001	TD-0102-001.017	1.34	mal-VC-MMAF
A58	B3	C1	DH3	DL 2	G5	BA-0102-002	TD-0102-002.304	1.86	mal-TROSIG™-MMAF
A58	B3	C1	DH3	DL 2	G2	BA-0102-002	TD-0102-002-336	N/A	mal-FITC
A58	B3	C1	DH3	DL 2	G1	BA-0102-002	TD-0102-002-CW	N/A	mal-800CW
A4	B3	C1	DH3	DL 2	G5	BA-0102-003	TD-0102-003.304	2.00	mal-TROSIG™-MMAF
A9	B3	C1	DH3	DL 2	G5	BA-0102-005	TD-0102-005.304	1.84	mal-TROSIG™-MMAF
A9	B3	C1	DH3	DL 2	G1	BA-0102-005	TD-0102-005-CW	N/A	mal-800CW
A13	B3	C1	DH3	DL 2	G5	BA-0102-006	TD-0102-006.304	1.66	mal-TROSIG™-MMAF
A28	B3	C1	DH3	DL 2	G5	BA-0102-007	TD-0102-007.304	1.80	mal-TROSIG™-MMAF
A48	B3	C1	DH3	DL 2	G5	BA-0102-008	TD-0102-008.304	1.69	mal-TROSIG™-MMAF
A55	B3	C1	DH3	DL 2	G5	BA-0102-009	TD-0102-009.304	1.84	mal-TROSIG™-MMAF
A55	B3	C1	DH3	DL 2	G1	BA-0102-009	TD-0102-009-CW	N/A	mal-800CW
A55	B3	C1	DH3	DL 2	G6	BA-0102-009	TD-0102-009-317	N/D	mal-TROSIG™-MMAF2
A11	B3	C1	DH3	DL 2	G5	BA-0102-010	TD-0102-010.304	1.56	mal-TROSIG™-MMAF
A25	B3	C1	DH3	DL 2	G5	BA-0102-011	TD-0102-011.304	1.39	mal-TROSIG™-MMAF
A43	B3	C1	DH3	DL 2	G2	BA-0102-014	TD-0102-014-336	N/A	mal-FITC
A55	B1	C1	DH3	DL 2	G5	BA-0102-015	TD-0102-015.304	1.89	mal-TROSIG™-MMAF

A55	B1	C1	DH3	DL2	G2	BA-0102-015	TD-0102-015-336	N/A	mal-FITC
A55	B1	C1	DH3	DL2	G1	BA-0102-015	TD-0102-015-CW	N/A	mal-800CW
A33	B3	C1	DH3	DL2	G1	BA-0102-016	TD-0102-016-CW	N/A	mal-800CW
A33	B3	C1	DH3	DL2	G2	BA-0102-016	TD-0102-016-336	N/A	mal-FITC
A30	B3	C1	DH3	DL2	G5	BA-0102-012	TD-0102-012.304	N/D	mal-TROSIG™-MMAF
A42	B3	C1	DH3	DL2	G5	BA-0102-013	TD-0102-013.304	N/D	mal-TROSIG™-MMAF
A43	B3	C1	DH3	DL2	G5	BA-0102-014	TD-0102-014.304	N/D	mal-TROSIG™-MMAF
A55	B1	C1	DH3	DL2	G6	BA-0102-015	TD-0102-015.317	N/D	mal-TROSIG™-MMAF2
A55	B3	C2	DH9	-	G4	BA-0102-R004	TD-0102-R004.303	2.16	mal-TROSIG™-MMAF
A55	B3	C13	DH3	DL2	G1	BA-0109-003	TD-0109-003-CW	N/A	mal-800CW
A55	B1	C13	DH2	DL2	G7	BA-0109-004	TD-0109-004.327	3.63	mal-TROSIG™-MMAE2
A55	B2	C13	DH2	DL2	G7	BA-0109-005	TD-0109-005.327	3.79	mal-TROSIG™-MMAE2
A55	B3	C13	DH2	DL2	G7	BA-0109-006	TD-0109-006.327	3.91	mal-TROSIG™-MMAE2
A55	B4	C13	DH2	DL2	G7	BA-0109-007	TD-0109-007.327	4.10	mal-TROSIG™-MMAE2
A55	B5	C13	DH2	DL2	G7	BA-0109-009	TD-0109-009.327	4.07	mal-TROSIG™-MMAE2
A55	B6	C13	DH2	DL2	G7	BA-0109-010	TD-0109-010.327	3.78	mal-TROSIG™-MMAE2
A55	B1	C11	DH2	DL2	G2	BA-0109-011	TD-0109-011-336	N/A	mal-FITC
A55	B2	C11	DH2	DL2	G2	BA-0109-012	TD-0109-012-336	N/A	mal-FITC
A55	B3	C11	DH2	DL2	G2	BA-0109-013	TD-0109-013-336	N/A	mal-FITC

A55	B4	C11	DH2	DL2	G2	BA-0109-014	TD-0109-014-336	N/A	mal-FITC
A55	B5	C11	DH2	DL2	G2	BA-0109-015	TD-0109-015-336	N/A	mal-FITC
A55	B6	C11	DH2	DL2	G2	BA-0109-016	TD-0109-016-336	N/A	mal-FITC
A55	B7	C11	DH2	DL2	G2	BA-0109-017	TD-0109-017-336	N/A	mal-FITC
A55	B8	C11	DH2	DL2	G2	BA-0109-018	TD-0109-018-336	N/A	mal-FITC
A55	B1	C11	DH2	DL2	G8	BA-0109-011	TD-0109-011.348	3.51	mal-TROSIG™-MMAE2
A55	B2	C11	DH2	DL2	G8	BA-0109-012	TD-0109-012.348	3.58	mal-TROSIG™-MMAE2
A55	B4	C11	DH2	DL2	G8	BA-0109-014	TD-0109-014.348	3.51	mal-TROSIG™-MMAE2
A55	B5	C11	DH2	DL2	G8	BA-0109-015	TD-0109-015.348	3.58	mal-TROSIG™-MMAE2
A55	B6	C11	DH2	DL2	G8	BA-0109-016	TD-0109-016.348	3.49	mal-TROSIG™-MMAE2
A55	B8	C11	DH2	DL2	G8	BA-0109-018	TD-0109-018.348	3.55	mal-TROSIG™-MMAE2
A55	B8	C11	DH2	DL2	G8	BA-0109-028	TD-0109-028.348	3.62	mal-TROSIG™-MMAE2
A33	B6	C11	DH2	DL2	G8	BA-0109-024	TD-0109-024.348	3.55	mal-TROSIG™-MMAE2

[Table 45]

Part Number						Protein code	ADC code	Ave DAR	Linker-toxin Feature
-	-	C1	DH1	DL2	G5	MA-02-001	AD-02-006.304	1.82	mal-TROSIG™-MMAF
-	-	C1	DH1	DL2	G2,G3	MA-02-001	AD-02-001-FITC	N/D	mal-VC-MMAF(LT-017), mal-FITC(LT-336)
-	-	C1	DH1	DL2	G1	MA-02-001	AD-02-CW	N/A	mal-800CW
-	-	C19	DH3	DL2	G1	MA-01-Y829.1	AD-01-Y829.1-CW	N/A	mal-800CW
-	-	C19	DH3	DL2	G5	MA-01-Y829.1	AD-01-001.304	1.89	mal-TROSIG™-MMAF
-	-	C13	DH3	DL2	G1	MA-09-003	AD-09-003-CW	N/A	mal-800CW
-	-	C13	DH2	DL2	G7	MA-09-003.1	AD-09-003.327	3.96	mal-TROSIG™-MMAE2
-	-	C11	DH2	DL2	G2	MA-09-002.1	AD-09-002.1.336	N/A	mal-FITC
-	-	C1	DH1	DL2	G2	MA-02-001	MA-02-001-336	N/A	mal-FITC
-	-	C11	DH3	DL2	G2	MA-09-002	MA-09-002-336	N/A	mal-FITC
-	-	C23	DH2	DL2	G2	MA-06-006	MA-06-006-336	N/A	mal-FITC

[Table 46]

Part Number; '-', Not associated					Protein code
A58	-	-	DH1	DL1	MA-01-001
A1	-	-	DH1	DL1	MA-01-Y004
A4	-	-	DH1	DL1	MA-01-Y031
A5	-	-	DH1	DL1	MA-01-Y041
A9	-	-	DH1	DL1	MA-01-Y065
A11	-	-	DH1	DL1	MA-01-Y091
A12	-	-	DH1	DL1	MA-01-Y092
A13	-	-	DH1	DL1	MA-01-Y097
A14	-	-	DH1	DL1	MA-01-Y098
A28	-	-	DH1	DL1	MA-01-Y108
A22	-	-	DH1	DL1	MA-01-Y123
A23	-	-	DH1	DL1	MA-01-Y124
A25	-	-	DH1	DL1	MA-01-Y126
A26	-	-	DH1	DL1	MA-01-Y127
A29	-	-	DH1	DL1	MA-01-Y132

A30	-	-	DH1	DL1	MA-01-Y133
A33	-	-	DH1	DL1	MA-01-Y559
A37	-	-	DH1	DL1	MA-01-Y711
A38	-	-	DH1	DL1	MA-01-Y712
A39	-	-	DH1	DL1	MA-01-Y715
A40	-	-	DH1	DL1	MA-01-Y716
A42	-	-	DH1	DL1	MA-01-Y722
A43	-	-	DH1	DL1	MA-01-Y723
A44	-	-	DH1	DL1	MA-01-Y727
A45	-	-	DH1	DL1	MA-01-Y728
A46	-	-	DH1	DL1	MA-01-Y735
A48	-	-	DH1	DL1	MA-01-Y741
A49	-	-	DH1	DL1	MA-01-Y748
A50	-	-	DH1	DL1	MA-01-Y758
A53	-	-	DH1	DL1	MA-01-Y781
A55	-	-	DH1	DL1	MA-01-Y829
-	-	C19	DH3	DL2	MA-01-Y829.1
-	-	C1	DH1	DL2	MA-02-001
-	-	C3	DH1	DL1	MA-07-001
-	-	C5	DH1	DL1	MA-07-002
-	-	C7	DH1	DL1	MA-07-003
-	-	C9	DH3	DL2	MA-09-001
-	-	C11	DH3	DL2	MA-09-002
-	-	C11	DH2	DL2	MA-09-002.1
-	-	C13	DH3	DL2	MA-09-003
-	-	C13	DH2	DL2	MA-09-003.1
-	-	C11	DH2	DL4	MA-09-004

Example 4. Analysis of cleavage efficiency of a multispecific fusion protein by a proteolytic enzyme

The cleavage efficiency of a first cleavable linker (PRS, Protease recognition site) in a multispecific fusion protein by a proteolytic enzyme was confirmed. In this case, experiments were performed according to the manufacturer's instructions using Recombinant human matriptase/ST14 catalytic domain (MT-SP1; #3496-SEB-010, R&D systems), Recombinant human u-plasminogen activator/urokinase (uPA; #1310-SE-010, R&D systems), Recombinant human MMP-2 protein (hMMP-2; #902-MP-010, R&D systems), Recombinant human MMP-9

protein (hMMP-9; #911-MP-010, R&D systems), and Recombinant mouse MMP-9 protein (mMMP-9; #909-MM-010, R&D systems) as proteolytic enzymes. In this case, the size of each proteolytic enzyme was confirmed using SDS-PAGE (Figure 16).

Specifically, a multispecific fusion protein and MT-SP1 (mixing ratio = 1:0.02 to 1:0.10) or uPA (mixing ratio = 1:1) were added to a reaction solution (50 mM Tris, 50 mM NaCl, 0.01% (v/v) Tween 20, pH 8.5) and mixed. Thereafter, the mixture was reacted at 37 °C for 16 hours, and then SDS-PAGE was performed under reducing conditions. The cleavage efficiency of MT-SP1 is shown in Figures 17a to 17c and Table 47, and the cleavage efficiency of uPA is shown in Figure 18 and Table 48.

As a result, as shown in Figures 17a to 17c and Table 47, it was confirmed that various types of multispecific fusion proteins comprising a ReleaDome comprising the first cleavable linker of the present invention (including PRS and PRS variants), are cleaved by MT-SP1. In addition, it was confirmed that the cleavage efficiency varied depending on the amino acid sequence included in each first cleavable linker, the type of the first domain (UNIT1) or the second domain (UNIT2) of the ReleaDome, and the morphology of the multispecific fusion protein. In this test, a peptide comprising the substrate sequence of MT-SP1 was used as a positive control group.

In addition, as shown in Figure 18 and Table 48, it was confirmed that various types of multispecific fusion proteins comprising a ReleaDome comprising the first cleavable linker of the present invention (including PRS and PRS variants), are cleaved by uPA. In addition, it was confirmed that the cleavage efficiency varied depending on the amino acid sequence included in each first cleavable linker, the type of the first domain (UNIT1) or the second domain (UNIT2) of the ReleaDome, and the morphology of the multispecific fusion protein. In this test, a peptide comprising the substrate sequence of uPAwas used as a positive control group.

[Table 47]

Cut efficiency: No, no cut band; Low, <10%; Medium, 10~<50%; High, >50%; Partial, chain preference							
Part Number					Protein code	Sample : Protease	Cleavage by MT-SP1
A58	B2	C1	DH1	DL2	BA-0102-001	1 : 0.02	Medium
A58	B3	C1	DH3	DL2	BA-0102-002	1 : 0.02	High
A55	B3	C1	DH3	DL2	BA-0102-009	1 : 0.02	High
A55	B1	C1	DH3	DL2	BA-0102-015	1 : 0.02	No
A33	B3	C1	DH3	DL2	BA-0102-016	1 : 0.02	High
A58	B2	C2	DH7	-	BA-0102-R001	1 : 0.10	High

A55	B3	C2	DH9	-	BA-0102-R004	1 : 0.05	High
A55	B3	C3	DH1	DL1	BA-0107-001	1 : 0.02	High
A55	B3	C5	DH1	DL1	BA-0107-002	1 : 0.02	High
A55	B3	C5	DH1	DL1	BA-0107-002	1 : 0.02	High
A55	B3	C7	DH1	DL1	BA-0107-003	1 : 0.02	High
A55	B1	C3	DH1	DL1	BA-0107-004	1 : 0.02	No
A55	B2	C3	DH1	DL1	BA-0107-005	1 : 0.02	High
A55	B4	C3	DH1	DL1	BA-0107-006	1 : 0.02	High
A55	B1	C5	DH1	DL1	BA-0107-007	1 : 0.02	No
A55	B2	C5	DH1	DL1	BA-0107-008	1 : 0.02	High
A55	B4	C5	DH1	DL1	BA-0107-009	1 : 0.02	High
A55	B5	C5	DH1	DL1	BA-0107-010	1 : 0.02	High
A55	B6	C5	DH1	DL1	BA-0107-011	1 : 0.02	No
A55	B7	C5	DH1	DL1	BA-0107-012	1 : 0.02	No
A55	B8	C5	DH1	DL1	BA-0107-013	1 : 0.02	No
A55	B6	C3	DH1	DL1	BA-0107-014	1 : 0.02	No
A55	B3	C9	DH3	DL2	BA-0109-001	1 : 0.02	High
A55	B3	C11	DH3	DL2	BA-0109-002	1 : 0.02	High
A55	B3	C13	DH3	DL2	BA-0109-003	1 : 0.02	High
A55	B1	C13	DH2	DL2	BA-0109-004	1 : 0.02	No
A55	B2	C13	DH2	DL2	BA-0109-005	1 : 0.02	High
A55	B3	C13	DH2	DL2	BA-0109-006	1 : 0.02	High
A55	B4	C13	DH2	DL2	BA-0109-007	1 : 0.02	High
A55	B5	C13	DH2	DL2	BA-0109-009	1 : 0.02	High
A55	B6	C13	DH2	DL2	BA-0109-010	1 : 0.02	No
A55	B1	C11	DH2	DL2	BA-0109-011	1 : 0.02	No
A55	B2	C11	DH2	DL2	BA-0109-012	1 : 0.02	High
A55	B3	C11	DH2	DL2	BA-0109-013	1 : 0.02	High
A55	B4	C11	DH2	DL2	BA-0109-014	1 : 0.02	High
A55	B5	C11	DH2	DL2	BA-0109-015	1 : 0.02	High
A55	B6	C11	DH2	DL2	BA-0109-016	1 : 0.02	No
A55	B7	C11	DH2	DL2	BA-0109-017	1 : 0.02	No
A55	B8	C11	DH2	DL2	BA-0109-018	1 : 0.02	No
A55	B9	C11	DH2	DL2	BA-0109-028	1 : 0.02	No
A55	B2	C11	DH2	DL4	BA-0109-029	1 : 0.02	High

A59	B2	C11	DH2	DL2	BA-0109-031	1 : 0.02	High
A62	B2	C11	DH2	DL2	BA-0109-032	1 : 0.02	High
A65	B2	C11	DH2	DL2	BA-0109-034	1 : 0.02	High
A68	B2	C11	DH2	DL2	BA-0109-036	1 : 0.02	High
A55	B2	C20	DH2	DL4	BA-0113-011	1 : 0.02	High

[Table 48]

Cut efficiency: No, no cut band; Low, <10%; Medium, 10~<50%; High, >50%; Partial, chain preference							
Part Number					Protein code	Sample : Protease	Cleavage by uPA
A58	B2	C1	DH1	DL2	BA-0102-001	1 : 1	Medium
A58	B3	C1	DH3	DL2	BA-0102-002	1 : 1	HIgh
A55	B3	C1	DH3	DL2	BA-0102-009	1 : 1	High
A55	B1	C1	DH3	DL2	BA-0102-015	1 : 1	Low
A33	B3	C1	DH3	DL2	BA-0102-016	1 : 1	High
A55	B3	C5	DH1	DL1	BA-0107-002	1 : 1	High
A55	B1	C5	DH1	DL1	BA-0107-007	1 : 1	No
A55	B2	C5	DH1	DL1	BA-0107-008	1 : 1	High
A55	B4	C5	DH1	DL1	BA-0107-009	1 : 1	High
A55	B5	C5	DH1	DL1	BA-0107-010	1 : 1	High
A55	B6	C5	DH1	DL1	BA-0107-011	1 : 1	No
A55	B7	C5	DH1	DL1	BA-0107-012	1 : 1	No
A55	B8	C5	DH1	DL1	BA-0107-013	1 : 1	No
A55	B1	C11	DH2	DL2	BA-0109-011	1 : 1	No
A55	B2	C11	DH2	DL2	BA-0109-012	1 : 1	High, Partial
A55	B3	C11	DH2	DL2	BA-0109-013	1 : 1	High
A55	B4	C11	DH2	DL2	BA-0109-014	1 : 1	High
A55	B5	C11	DH2	DL2	BA-0109-015	1 : 1	High
A55	B6	C11	DH2	DL2	BA-0109-016	1 : 1	No
A55	B7	C11	DH2	DL2	BA-0109-017	1 : 1	No
A55	B8	C11	DH2	DL2	BA-0109-018	1 : 1	No
A55	B9	C11	DH2	DL2	BA-0109-028	1 : 1	No

In order to measure the cleavage efficiency of hMMP-2, hMMP-2 was first activated (37 °C, 2 hours) in a reaction solution (50 mM Tris, 10 mM $CaCl_2$, 150 mM NaCl, 0.05% Brij-

35 (w/v), pH 7.5) containing P-aminophenylmeruric acetate (APMA, final 1 mM). Thereafter, a multispecific fusion protein was added and mixed so that the mixing ratio of fusion protein to hMMP-2 was 1:0.02, and the reaction was carried out for more than 16 hours at 37 °C. The cleavage efficiency of hMMP-2 was confirmed by performing SDS-PAGE on the resulting product (Figure 19 and Table 49). In order to measure the cleavage efficiency of hMMP-9 or mMMP-9, hMMP-9 or mMMP-9 was added to the same reaction solution used for hMMP-2 and activated at 37 °C for 24 hours or for 2 hours, respectively. Thereafter, a multispecific fusion protein was added (fusion protein:hMMP-9 = 1:0.02 or 1:0.067 for hMMP-9; fusion protein:mMMP-9 = 1:0.02 for mMMP-9), and the reaction was carried out for more than 16 hours. The cleavage efficiencies of hMMP-9 and mMMP-9 were confirmed by performing SDS-PAGE on the resulting product under reducing conditions (Figures 20a to 20c and Table 49).

In addition, the hMMP-2 and hMMP-9 were mixed and then mixed with a multispecific fusion protein to confirm the cleavage efficiency of the proteolytic enzyme mixture. This experiment was performed in the same manner as the method used to analyze the cleavage efficiency of hMMP-9, and the mixing ratios of hMMP2, hMMP-9, and the multispecific fusion protein used are listed in Table 50. In addition, the results of the analysis of the cleavage efficiency of the proteolytic enzyme mixture are shown in Figures 21a to 21c and Table 50.

[Table 49]

Cut efficiency: No, no cut band; Low, <10%; Medium, 10~<50%; High, >50%; Partial, chain preference							
Part Number					Protein code	Sample : Protease	Cleavage by hMMP-2
A55	B1	C13	DH2	DL2	BA-0109-004	1 : 0.02	High
A55	B2	C13	DH2	DL2	BA-0109-005	1 : 0.02	No
A55	B3	C13	DH2	DL2	BA-0109-006	1 : 0.02	High
A55	B4	C13	DH2	DL2	BA-0109-007	1 : 0.02	No
A55	B5	C13	DH2	DL2	BA-0109-009	1 : 0.02	No
A55	B6	C13	DH2	DL2	BA-0109-010	1 : 0.02	No
Part Number					Protein code	Sample : Protease	Cleavage by hMMP-9
A55	B1	C13	DH2	DL2	BA-0109-004	1 : 0.02	Low
A55	B1	C13	DH2	DL2	BA-0109-004	1 : 0.06	High
A55	B2	C13	DH2	DL2	BA-0109-005	1 : 0.02	No
A55	B3	C13	DH2	DL2	BA-0109-006	1 : 0.02	High
A55	B4	C13	DH2	DL2	BA-0109-007	1 : 0.02	Low
A55	B5	C13	DH2	DL2	BA-0109-009	1 : 0.02	Low

A55	B6	C13	DH2	DL2	BA-0109-010	1 : 0.02	No
A55	B6	C13	DH2	DL2	BA-0109-010	1 : 0.06	Low
Part Number					Protein code	Sample : Protease	Cleavage by mMMP-9
A55	B1	C13	DH2	DL2	BA-0109-004	1 : 0.02	Low
A55	B2	C13	DH2	DL2	BA-0109-005	1 : 0.02	No
A55	B3	C13	DH2	DL2	BA-0109-006	1 : 0.02	High
A55	B4	C13	DH2	DL2	BA-0109-007	1 : 0.02	No
A55	B5	C13	DH2	DL2	BA-0109-009	1 : 0.02	Low
A55	B6	C13	DH2	DL2	BA-0109-010	1 : 0.02	No

[Table 50]

Cut efficiency: No, no cut band; Low, <10%; Medium, 10~<50%; High, >50%; Partial, chain preference							
Part Number					Protein code	Sample : hMMP-2 : hMMP-9	Cleavage by hMMP-2 & hMMP-9
A58	B2	C1	DH1	DL2	BA-0102-001	1 : 0.02 : 0.02	Low
A58	B3	C1	DH3	DL2	BA-0102-002	1 : 0.02 : 0.02	High
A55	B3	C1	DH3	DL2	BA-0102-009	1 : 0.02 : 0.02	High
A55	B1	C1	DH3	DL2	BA-0102-015	1 : 0.02 : 0.02	No
A33	B3	C1	DH3	DL2	BA-0102-016	1 : 0.02 : 0.02	High
A55	B3	C3	DH1	DL1	BA-0107-001	1 : 0.02 : 0.06	High
A55	B3	C5	DH1	DL1	BA-0107-002	1 : 0.02 : 0.02	High
A55	B1	C3	DH1	DL1	BA-0107-004	1 : 0.02 : 0.06	High
A55	B2	C3	DH1	DL1	BA-0107-005	1 : 0.02 : 0.06	Low
A55	B4	C3	DH1	DL1	BA-0107-006	1 : 0.02 : 0.06	High
A55	B1	C5	DH1	DL1	BA-0107-007	1 : 0.02 : 0.02	Medium
A55	B2	C5	DH1	DL1	BA-0107-008	1 : 0.02 : 0.02	No
A55	B4	C5	DH1	DL1	BA-0107-009	1 : 0.02 : 0.02	No
A55	B5	C5	DH1	DL1	BA-0107-010	1 : 0.02 : 0.02	No
A55	B6	C5	DH1	DL1	BA-0107-011	1 : 0.02 : 0.02	No
A55	B7	C5	DH1	DL1	BA-0107-012	1 : 0.02 : 0.02	No
A55	B8	C5	DH1	DL1	BA-0107-013	1 : 0.02 : 0.02	High
A55	B6	C3	DH1	DL1	BA-0107-014	1 : 0.02 : 0.06	Low

A55	B1	C11	DH2	DL2	BA-0109-011	1 : 0.02 : 0.02	Medium
A55	B1	C11	DH2	DL2	BA-0109-011	1 : 0.02 : 0.06	High
A55	B2	C11	DH2	DL2	BA-0109-012	1 : 0.02 : 0.02	Low
A55	B2	C11	DH2	DL2	BA-0109-012	1 : 0.02 : 0.06	Low
A55	B3	C11	DH2	DL2	BA-0109-013	1 : 0.02 : 0.02	High
A55	B3	C11	DH2	DL2	BA-0109-013	1 : 0.02 : 0.06	High
A55	B4	C11	DH2	DL2	BA-0109-014	1 : 0.02 : 0.02	Low
A55	B4	C11	DH2	DL2	BA-0109-014	1 : 0.02 : 0.06	Medium
A55	B5	C11	DH2	DL2	BA-0109-015	1 : 0.02 : 0.02	No
A55	B5	C11	DH2	DL2	BA-0109-015	1 : 0.02 : 0.06	Medium
A55	B6	C11	DH2	DL2	BA-0109-016	1 : 0.02 : 0.02	Low
A55	B6	C11	DH2	DL2	BA-0109-016	1 : 0.02 : 0.06	Low or No
A55	B7	C11	DH2	DL2	BA-0109-017	1 : 0.02 : 0.02	No
A55	B7	C11	DH2	DL2	BA-0109-017	1 : 0.02 : 0.06	Low
A55	B8	C11	DH2	DL2	BA-0109-018	1 : 0.02 : 0.02	Medium
A55	B8	C11	DH2	DL2	BA-0109-018	1 : 0.02 : 0.06	High
A55	B9	C11	DH2	DL2	BA-0109-028	1 : 0.02 : 0.02	No
A55	B9	C11	DH2	DL2	BA-0109-028	1 : 0.02 : 0.06	Low, Partial
A55	B6	C11	DH2	DL4	BA-0109-030	1 : 0.02 : 0.02	No
A59	B2	C11	DH2	DL2	BA-0109-031	1 : 0.02 : 0.02	No
A62	B2	C11	DH2	DL2	BA-0109-032	1 : 0.02 : 0.02	No
A65	B2	C11	DH2	DL2	BA-0109-034	1 : 0.02 : 0.02	No
A68	B2	C11	DH2	DL2	BA-0109-036	1 : 0.02 : 0.02	No
A55	B6	C20	DH2	DL4	BA-0113-015	1 : 0.02 : 0.02	No

As a result, as shown in Figures 19 to 21c and Table 47, it was confirmed that various types of multispecific fusion proteins comprising a ReleaDome comprising the first cleavable linker of the present invention (including PRS and PRS variants), are cleaved by hMMP-2 and/or hMMP-9, or mMMP-9. In addition, it was confirmed that the cleavage efficiency varied depending on the amino acid sequence included in each first cleavable linker (PRS), the type of the first domain (UNIT1) or the second domain (UNIT2) of the ReleaDome, and the morphology of the multispecific fusion protein. In addition, it was confirmed that the cleavage efficiency of the first cleavable linker was increased when the concentration of the proteolytic enzyme was increased or when treated with a mixture of hMMP-2 and hMMP-9. As an example of confirming the cleavage efficiency by proteolytic enzymes across species, the cleavage efficiency by MMP-9 between humans and mice was observed to be at a similar level.

Based on the above results, it is believed that substrate affinity may be increased or decreased or substrate selectivity may be expanded depending on the concentration and activity level of the MMP enzymes used. This suggests that the cleavage efficiency may be increased or decreased depending on the composition and activity level of proteolytic enzymes, including the above proteolytic enzyme, in the tumor microenvironment.

Example 5. Analysis of binding efficiency of multispecific fusion protein

The binding avidity of the multispecific fusion proteins to each antigen protein was confirmed using ELISA (enzyme-linked immunosorbent assay) or flow cytometry (FC).

Example 5.1. Confirmation of antigen binding ability of multispecific fusion protein with and without treatment of proteolytic enzyme

The antigen binding ability of the multispecific fusion proteins with and without treatment of a proteolytic enzyme was confirmed using the ELISA method.

Specifically, the recombinant antigen proteins used in the ELISA method were produced in the same manner as in Example 2.1 and Example 2.2 above. In this case, the amino acid sequences of the antigen proteins used are listed in Table 51. In this case, the amino acid sequences are described sequentially from the N-terminus to the C-terminus. In addition, the HER2-His antigen was purchased (Sinobio, #10004-H8H) and used. Each of the recombinant antigen proteins was diluted (to a concentration of 0.5 ug/mL) in PBS solution (#P0750-N10L, Biowest), and 100 uL aliquots were applied to a 96-well plate (#15142, Thermo) to coat each well (room temperature, 1 hour, Multi-shaker; #3D-300, FinePCR), and the plate was prepared by washing twice with a washing solution (0.05% Tween-20/PBS). Each multispecific fusion protein or isotype control group (#31154, Thermo) was diluted in a dilution solution (4% skim milk/0.05% Tween-20/PBS), applied to the prepared 96-well plate, and reacted with mixing at room temperature for 1 hour. After the reaction, the plate was washed twice. Thereafter, detection antibody (#31413, ThermoFisher) was diluted to a ratio of 1:3000 and each well was treated with 0.1 mL of detection antibody. Thereafter, the reaction was carried out at room temperature for 1 hour with mixing, followed by two washes. each well was treated with 0.1 mL of TMB substrate solution (#T0440, Sigma), and the reaction was carried out in the dark. Once color development was observed, 0.05 mL of 1 N sulfuric acid solution (#S1408, Samchun) was added to each well to stop the reaction. The absorbance (450 nm) of the resulting products was measured using a spectrometer (#GM3000, Promega), and the results were analyzed using the Graphpad Prism 9 program to analyze the binding avidity to the antigen protein.

In this case, the multispecific fusion protein used as a sample was prepared and used under conditions before and after treatment with a proteolytic enzyme, and the proteolytic enzyme was treated in the same manner as in Example 4 above. In addition, as the isotype control group, a single antibody that binds to the antigen of the first domain or the antigen of the second domain, respectively, was used.

[Table 51]

Protein	Recombinant antigen protein	Amino acid sequence for antigen	Space amino-acid	Tag
Human ANXA1(P04083)	hAA1-fl	MAMVSEFLKQAWFIENEEQEYVQTVKSSKGGPGSAVSPYPTFNPSSDVAALHKAIMVKGVDEATIIDILTKRNNAQRQQIKAAYLQETGKPLDETLKKALTGHLEEVVLALLKTPAQFDADELRAAMKGLGTDEDTLIEILASRTNKEIRDINRVYREELKRDLAKDITSDTSGDFRNALLSLAKGDRSEDFGVNEDLADSDARALYEAGERRKGTDVNVFNTILTTRSYPQLRRVFQKYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1616)	AS	HHHHHH (SEQ ID NO:1624)
Human ANXA1(P04083)	hAA1-d26	SSKGGPGSAVSPYPTFNPSSDVAALHKAIMVKGVDEATIIDILTKRNNAQRQQIKAAYLQETGKPLDETLKKALTGHLEEVVLALLKTPAQFDADELRAAMKGLGTDEDTLIEILASRTNKEIRDINRVYREELKRDLAKDITSDTSGDFRNALLSLAKGDRSEDFGVNEDLADSDARALYEAGERRKGTDVNVFNTILTTRSYPQLRRVFQKYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1617)	AS or (-)	HHHHHH (SEQ ID NO:1624)
Human ANXA1(P04083)	hAA1-d42	NPSSDVAALHKAIMVKGVDEATIIDILTKRNNAQRQQIKAAYLQETGKPLDETLKKALTGHLEEVVLALLKTPAQFDADELRAAMKGLGTDEDTLIEILASRTNKEIRDINRVYREELKRDLAKDITSDTSGDFRNALLSLAKGDRSEDFGVNEDLADSDARALYEAGERRKGTDVNVFNTILTTRSYPQLRRVFQKYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1618)	AS	HHHHHH (SEQ ID NO:1624)
Human ANXA1(P04083)	hAA1-d113	TPAQFDADELRAAMKGLGTDEDTLIEILASRTNKEIRDINRVYREELKRDLAKDITSDTSGDFRNALLSLAKGDRSEDFGVNEDLADSDARALYEAGERRKGTDVNVFNTILTTRSYPQLRRVFQKYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1619)	AS	HHHHHH (SEQ ID NO:1624)
Human ANXA1(P04083)	hAA1-d190	DFGVNEDLADSDARALYEAGERRKGTDVNVFNTILTTRSYPQLRRVFQKYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1620)	AS	HHHHHH (SEQ ID NO:1624)
Human ANXA1(P04083)	hAA1-d270	ATSKPAFFAEKLHQAMKGVGTRHKALIRIMVSRSEIDMNDIKAFYQKMYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1621)	AS	HHHHHH (SEQ ID NO:1624)
Mouse ANXA1(P10	mAA1-d26	MSYKGGPGSAVSPYPSFNVSSDVAALHKAIMVKGVDEATIIDILTKRTNAQRQQIKAAYLQENGKPLDEVL	-	HHHHHH (SEQ ID

107)		RKALTGHLEEVVLAMLKTPAQFDADELRGAMKGL GTDEDTLIEILTTRSNEQIREINRVYREELKRDLAKDI TSDTSGDFRKALLALAKGDRCQDLSVNQDLADTDA RALYEAGERRKGTDVNVFTTILTSRSFPHLRRVFQN YGKYSQHDMNKALDLELKGDIEKCLTTIVKCATST PAFFAEKLYEAMKGAGTRHKALIRIMVSRSEIDMNE IKVFYQKKYGISLCQAILDETKGDYEKILVALCGGN(SEQ ID NO:1622)		NO:1624)
Monkey ANXA1(F7D2H1)	moAA1-d26	MSSKGGPGSAVSPYPTFNPSSDVAALHKAIMVKGV DEATIIDILTKRNNAQRQQIKAAYLQETGKPLDETL KKALMGHLEEVVLALLKTPAQFDADELRAAMKGL GTDEDTLIEILASRTNKEIRDINRVYREELKRDLAKD ITSDTSGDFRNALLSLAKGDRSEDFGVNEDLADSDA RALYEAGERRKGTDVNVFNTILTTRSYPHLRRVFQ KYTKYSKHDMNKVLDLELKGDIEKCLTAIVKCATS KPAFFAEKLHQAMKGAGTRHKALIRIMVSRSEIDM NDIKAFYQKMYGISLCQAILDETKGDYEKILVALCG GN(SEQ ID NO:1623)	-	HHHHHH (SEQ ID NO:1624)

As a result, as shown in Table 52, the multi fusion protein BA-0102-009 or BA-0102-R004, which comprises Y829 as the first domain (UNIT1), was bound to ANXA1. However, the multispecific fusion proteins ((+)BA-0102-009 or (+)BA-0102-R004) treated with MT-SP1 was not bound to ANXA1.

In addition, as shown in Table 53 and Figure 22d, BA-0102-009 exhibited a weak binding avidity to HER2. However, the multispecific fusion protein ((+)BA-0102-009) treated with MT-SP1 was bound to HER2 in a concentration-dependent manner.

[Table 52]

ELISA	ANXA1 binding
Sample [0.67 nM]	OD450 nm
IgG	0.08
MA-02-001	0.078
MA-01-Y829	2.751
BA-0102-009	2.73
(+)BA-0102-009	0.089
BA-0102-R004	2.767
(+)BA-0102-R004	0.114
	(+), cut by MT-SP1

[Table 53]

ELISA	HER2 binding	ANXA1 binding
Sample [0.67 nM]	OD450nm	OD450nm

IgG	0.075	0.063
MA-02-001	3.706	0.063
MA-01-Y829	0.077	1.954
BA-0102-009	1.469	1.902
(+)BA-0102-009	4.053	0.094
ELISA	HER2 binding	
Sample [3.75 nM]	OD450nm	
IgG	0.085	
MA-02-001	2.737	
BA-0102-001	0.578	
(+)BA-0102-001	2.940	
(+), cut by MT-SP1		

In addition, as shown in Table 53 and Figures 22a to 22c, a multispecific fusion protein comprising S001 in the first domain (UNIT1) also has a weak HER2 binding avidity. On the other hand, the multispecific fusion protein treated with MT-SP1 showed increased binding avidity to HER2 in a concentration-dependent manner. Figure 22e shows, as an example, the results of confirming the binding avidity to ANXA1 and HER2 proteins of each multispecific fusion protein comprising a first domain (UNIT1) that binds to each of the various antigens.

Based on the above results, it was confirmed that the first domain (UNIT1) of the ReleaDome included in the multispecific fusion protein can mask the antigen binding ability of the second domain (UNIT2), and that the masking ability may vary depending on the type of the first domain (UNIT1), the type of first cleavable linker (PRS) (in this case, variants 1 to 2), and the morphology of the multispecific fusion protein (e.g., DVD-Ig or ReleaBody).

Example 5.2. Confirmation of ANXA1 antigen binding site of ReleaDome that binds to ANXA1

The ANXA1 antigen binding site (Epitope) of the first domain (UNIT1) of the ReleaDome that binds to the ANXA1 protein was mapped using the ELISA method. The experiment was performed in the same manner as in Example 5.1 above using 0.5 ug/mL of recombinant ANXA1 protein and 0.1 ug/mL of the UNIT1 clone.

As a result, as shown in Table 54 and Figure 23, it was confirmed that each UNIT1 clone, with the exception of MA-01-001 (Table 46), binds to an antigen comprising a site consisting of the 43th to 113th amino acids from the N-terminus of the ANXA1 protein. Meanwhile, in the case of MA-01-001, its binding affinity is estimated to be weak according to the ELISA measurement method.

[Table 54]

Antigen protein (aa) [0.5 ug/mL]	hAA1-fl (1~346)	hAA1-d26 (27~346)	hAA1-d42 (43~346)	hAA1-d113 (114~346)	hAA1-d190 (191~346)
Sample [0.1 ug/mL]	OD450nm	OD450nm	OD450nm	OD450nm	OD450nm
IgG	0.09	0.09	0.09	0.09	0.09
MA-01-Y031	2.63	3.05	3.38	0.07	0.07
MA-01-Y041	1.78	2.93	3.04	0.08	0.08
MA-01-Y065	2.58	2.71	3.08	0.08	0.08
MA-01-Y091	2.11	3.03	2.94	0.09	0.08
MA-01-Y097	2.18	2.92	3.27	0.09	0.08
MA-01-Y108	2.33	2.96	3.25	0.09	0.08
MA-01-Y829	2.27	3.59	2.96	0.08	0.09
MA-01-Y722	0.37	2.07	2.12	0.09	0.09
MA-01-Y723	0.75	2.53	3.03	0.09	0.09
MA-01-Y741	2.57	2.88	2.98	0.09	0.09

Example 5.3. Confirmation of binding avidity of multispecific fusion protein at cellular level

The binding avidity of multispecific fusion proteins to antigen proteins at the cellular level was confirmed by flow cytometry (FC). In this case, the cell lines and growth media used were listed in Tables 55 and 56, respectively.

Specifically, in order to confirm the binding avidity to ANXA1, each cell line was suspended in 0.5 mL of DPBS (#SH30028.02, Hyclone) at a concentration of 5×10^5 cells and dispensed into a 96-deep well plate (#90063, Bioneer). each well was treated with 0.5 mL of cold 4% paraformaldehyde (#PC2031-050-00, Biosesang) solution and reacted at room temperature for 10 minutes to fix the cells. The fixed cells were centrifuged (Avanti J-15R, Beckman, 4 ℃, 1,000 rpm, 3 min) to remove the supernatant, and the cells were washed twice with a washing solution (2% FBS/DPBS) to collect the cell pellet. The pellet was suspended in the washing solution (1×10^6 cells/mL) and dispensed at a rate of 0.1 mL per well into a 96-deep well plate to prepare each cell. In order to confirm the binding avidity to other antigens (B7H3, CD47, DLK-1, EGFR, to HER2), each cell line was prepared by washing twice with a washing solution, suspending at 1×10^6 cells/mL, and dispensing 0.1 mL aliquots into a 96-deep well plate.

The cells prepared as as described above were treated with 0.1 mL aliquots of an isotype control group (#31154, ThermoFisher), a single antibody comprising the first domain (UNIT1) of the ReleaDome (Table 46), or a multispecific fusion protein diluted in a washing solution, and then the reaction was carried out at 4 °C for 1 hour. In this case, the multispecific fusion protein was prepared and used under conditions before and after proteolytic enzyme treatment as in

Example 5.1 above.

After the reaction was completed, centrifugation and washing were performed twice, and the supernatant was removed. The secondary antibody (#FI-3000, Vectorlab) was diluted in a washing solution in a ratio of 1:100, and each cell was treated with 0.1 mL. Thereafter, the reaction was carried out in the dark at 4 °C for 30 minutes. The reaction mixture was centrifuged and washed twice with a washing solution, and then the supernatant was removed. The cell pellet obtained from the above process was suspended in 0.3 mL of DPBS and analyzed using a flow cytometer (#CytoFlexS, Beckman) under light-blocking conditions at 4 °C. The concentration-dependent binding avidity of the multispecific fusion protein to the antigen protein was analyzed using the Graphpad Prism 9 program.

[Table 55]

Cell line	Cell type	Cell source
HUVEC	Human umbilical vein endothelial cell	#C-003-5C, Thermo
EA.hy926	Human somatic cell hybrid cell	#CRL-2922, ATCC
A549	Human lung carcinoma cell	#10185, KCLB
NIH-3T3	Mouse fibroblast cell	#21658, KCLB
BT-474	Human breast carcinoma cell	#60062, KCLB
NCI-N87	Human gastric carcinoma cell	#60113, KCLB
SK-BR-3	Human breast carcinoma cell	#30030, KCLB
SK-OV-3	Human ovary adenocarcinoma cell	#30077, KCLB
JIMT-1	Human breast carcinoma cell	#ACC589, DSMZ
CT-26	Mouse colon cancer cell	#80009, KCLB
4T-1	Mouse breast cancer cell	#CRL-2539, ATCC
HCT-116	Human colorectal cancer cell	#10247, KCLB
MDA-MB-231	Human breast cancer cell	#30026, KCLB
MDA-MB-453	Human breast cancer cell	#30131, KCLB
MCF-7	Human breast cancer cell	#30022, KCLB

[Table 56]

Cell line	Growth media
HUVEC	EGM(#CC-3162, Lonza), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
EA.hy926	DMEM(#SH30243.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
A549	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)

NIH-3T3	DMEM(#SH30243.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
BT-474	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
NCI-N87	RPMI(#A1049101, Gibco), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
SK-BR-3	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
SK-OV-3	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
JIMT-1	DMEM(#SH30243.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
CT-26	DMEM(#SH30243.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
4T-1	RPMI(#A1049101, Gibco), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
HCT-116	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
MDA-MB-231	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
MDA-MB-453	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)
MCF-7	RPMI(#SH30027.01, Hyclone), 10% FBS(#SH30919.03, Hyclone), 1x Antibiotic Antimycotic solution (#SV30079.01, Hyclone)

As a result, as shown in Table 57, it was confirmed that the single antibody comprising the first domain (UNIT1), which has binding avidity to ANXA1, did not bind to each cell line expressing HER2. On the other hand, as shown in Table 58, it was confirmed that the multispecific fusion protein BA-0102-001 (anti-ANXA1-anti-HER2) did not show binding avidity to the hHER2 antigen compared to the single antibody MA-01-001 (Trastuzumab); however, the binding affinity to HER2 was increased after treatment with MT-SP1 (under conditions where the cleavage efficiency reached a maximum of about 50% (antibody:enzyme = 1:0.02)).

In addition, as shown in Table 59 and Figures 24a to 24c, it was confirmed that various types of multispecific fusion proteins [anti-ANXA1-anti-HER2] comprising ANXA1 binding sites with different sequences as the first domain (UNIT1) did not bind to each cell line

expressing HER2. Based on the above results, it was confirmed that the binding avidity of the second domain was masked by the first domain.

[Table 57]

						MFI on NCI-N87		MFI on JIMT-1	
Part Number					Protein code	2 ug/mL	Fold	10 ug/mL	Fold
A58	-	-	DH1	DL1	MA-01-001	7246	0.9	N/D	N/D
A33	-	-	DH1	DL1	MA-01-Y559	6831	0.9	40997	0.8
A55	-	C19	DH1	DL1	MA-01-Y829	7773	1.0	56447	1.1
N/A	N/A	N/A	N/A	N/A	IgG	7859	1.0	50152	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	5598	0.7	39044	0.8
N/D, Not determined; N/A or '-', Not associated; Italic type, Control in fold change									

[Table 58]

						MFI on NCI-N87		MFI on BT-474	
Part Number					Protein code	15 nM	Fold	15 nM	Fold
-	-	C1	DH1	DL2	MA-02-001	24173	6.0	3979375	33.5
A58	B2	C1	DH1	DL2	BA-0102-001	4487	1.1	182545	1.5
A58	B2	C1	DH1	DL2	(+)BA-0102-001	19620	4.8	2349443	19.8
N/A	N/A	N/A	N/A	N/A	IgG	4046	1.0	118773	1.0
						MFI on SK-BR-3		MFI on SK-OV-3	
Part Number					Protein code	15 nM	Fold	15 nM	Fold
-	-	C1	DH1	DL2	MA-02-001	5406233	58.1	4701701	50.1
A58	B2	C1	DH1	DL2	BA-0102-001	156204	1.7	509526	5.4
A58	B2	C1	DH1	DL2	(+)BA-0102-001	2195481	23.6	3369560	35.9
N/A	N/A	N/A	N/A	N/A	IgG	93113	1.0	93881	1.0
						MFI on JIMT-1		N/D, Not determined; N/A or '-', Not associated; Italic type, Control in fold change	
Part Number					Protein code	15 nM	Fold		
-	-	C1	DH1	DL2	MA-02-001	957969	15.1		
A58	B2	C1	DH1	DL2	BA-0102-001	185611	2.9		
A58	B2	C1	DH1	DL2	(+)BA-0102-001	389822	6.2		
N/A	N/A	N/A	N/A	N/A	*IgG*	63335	*1.0*		

[Table 59]

						MFI on NCI-N87		MFI on BT-474	
Part Number					Protein code	13 nM	Fold	13 nM	Fold
-	-	C1	DH1	DL2	MA-02-001	2019986	340.1	1500034	114.5
A58	B3	C1	DH3	DL2	BA-0102-002	53245	9.0	40226	3.1
A9	B3	C1	DH3	DL2	BA-0102-005	100897	17.0	66564	5.1
A55	B3	C1	DH3	DL2	BA-0102-009	394466	66.4	206938	15.8
A55	B1	C1	DH3	DL2	BA-0102-015	160993	27.1	82418	6.3
N/A	N/A	N/A	N/A	N/A	IgG	5940	1.0	13098	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	5166	0.9	10095	0.8
N/D, Not determined; N/A or '-', Not associated; Italic type, Control in fold change									

In addition, as shown in Table 60, no binding avidity was confirmed for UNIT1 (in this case, Y829) in MDA-MB-231 cells expressing CD47. It was confirmed that the binding avidity of the multispecific fusion protein (anti-ANXA1-anti-CD47) to the CD47 protein was decreased in various patterns compared to the cell binding avidity of the single antibody MA-07-001 (Candidate 14). A similar masking effect was also observed in the results shown in Table 61. In addition, it was observed that the binding avidity of the multispecific fusion protein (anti-ANXA1-anti-CD47) to cells was decreased in various patterns compared to the control antibody MA-07-002 (Magrolimab).

From the results in Tables 60 and 61 above, it was confirmed that even if the same type of first domain (UNIT1) and second domain (UNIT2) are included, the degree of masking against antigen binding of the second domain (UNIT2) may vary depending on the type of first cleavable linker (PRS).

As shown in the results in Table 62, it was confirmed that the binding avidity of BA-0107-001, a multispecific fusion protein (anti-ANXA1-anti-CD47), was reduced by about twofold compared to MA-07-001, which has cross binding avidity, in CT-26 cells expressing mouse CD47. In addition, in MA-07-002 or BA-0107-002, which lack cross binding avidity, no binding avidity was observed for the cells. In MDA-MB-231 cells expressing human CD47, it was confirmed that the binding masking ability of the two types of multispecific fusion proteins to the CD47 antigen was weak (about 1.2 times) compared to a single antibody. The concentration-dependent binding avidities of various multispecific fusion proteins (anti-ANXA1-anti-CD47) to the CD47+ cells are shown in Figures 25a to 25f.

Based on the above results, it was confirmed that the first domain (UNIT1) of the ReleaDome can mask the binding avidity of various types of second domains (UNIT2) to the antigens, and that this effect may vary depending on the type of first cleavable linker (PRS) or the type of second domain (UNIT2).

Table 63 shows the results of confirming the binding avidity of a multispecific fusion

protein (anti-ANXA1-anti-EGFR) to EGFR in MDA-MB-231 cells expressing EGFR. In MDA-MB-231 cells expressing EGFR, it was confirmed that the binding avidity of the multispecific fusion protein was masked compared to the antigen binding avidity of a single antibody used as a control group. In this case, it was confirmed that the masking ability of the first domain (UNIT1) to the second domain (UNIT2) may vary depending on the type of the first cleavable linker (PRS) or the type of the second domain (UNIT2). In addition, as shown in Table 64, binding of MA-01-Y829, the single antibody MA-09-003.01, and the multispecific fusion protein (anti-ANXA1-anti-EGFR) was not observed in MDA-MB-453 cells, a cell line in which EGFR is hardly expressed. The concentration-dependent binding avidities of various multispecific fusion proteins (anti-ANXA1-anti-EGFR) are shown in Figures 26a to 26e.

Based on the above results, it was confirmed that the antigen binding avidity of the second domain (UNIT2) can be masked by the first domain (UNIT1) of the ReleaDome, and that said masking ability may vary depending on the type of the first domain (UNIT1), the first cleavable linker (PRS), and the second domain (UNIT2), as well as the morphology of the multispecific fusion protein. In addition, it was confirmed that the antigen binding avidity of the second domain (UNIT2) can be restored after the first domain (UNIT1) is cleaved.

[Table 60]

						MFI on MDA-MB-231	
Part Number					Protein code	16.7 nM	Fold
A55	-	C19	DH1	DL1	MA-01-Y829	13618	0.7
-	-	C3	DH1	DL1	MA-07-001	500203	26.8
A55	B6	C3	DH1	DL1	BA-0107-014	50120	2.7
N/A	N/A	N/A	N/A	N/A	IgG	18698	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	13215	0.7
-	-	C3	DH1	DL1	MA-07-001	962313	29.4
A55	B1	C3	DH1	DL1	BA-0107-004	583791	17.8
A55	B2	C3	DH1	DL1	BA-0107-005	544800	16.6
A55	B3	C3	DH1	DL1	BA-0107-001	741635	22.6
A55	B4	C3	DH1	DL1	BA-0107-006	759361	23.2
N/A	N/A	N/A	N/A	N/A	IgG	32762	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	29443	0.9
N/A or '-', Not associated; Italic type, Control in fold change							

[Table 61]

						MFI on MDA-MB-231	
Part Number					Protein code	16.7 nM	Fold
A55	-	C19	DH1	DL1	MA-01-Y829	14878	0.9
-	-	C5	DH1	DL1	MA-07-002	741257	46.5
A55	B1	C5	DH1	DL1	BA-0107-007	411093	25.8
A55	B2	C5	DH1	DL1	BA-0107-008	393602	24.7
A55	B3	C5	DH1	DL1	BA-0107-002	653256	40.9
A55	B4	C5	DH1	DL1	BA-0107-009	606849	38.0
A55	B5	C5	DH1	DL1	BA-0107-010	456780	28.6
A55	B6	C5	DH1	DL1	BA-0107-011	177216	11.1
A55	B7	C5	DH1	DL1	BA-0107-012	624500	39.1
A55	B8	C5	DH1	DL1	BA-0107-013	403670	25.3
N/A	N/A	N/A	N/A	N/A	IgG	15958	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	14706	0.9
N/A or '-', Not associated; Italic type, Control in fold change							

[Table 62]

						MFI on CT-26		MFI on MDA-MB-231	
Part Number					Protein code	16.7 nM	Fold	16.7 nM	Fold
-	-	C3	DH1	DL1	MA-07-001	180850	11.5	843766	67.5
A55	B3	C3	DH1	DL1	BA-0107-001	86701	5.5	689863	55.2
-	-	C5	DH1	DL1	MA-07-002	14340	0.9	851837	68.1
A55	B3	C5	DH1	DL1	BA-0107-002	16301	1.0	698841	55.9
N/A	N/A	N/A	N/A	N/A	IgG	15671	1.0	12501	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	9888	0.6	10241	0.8
N/A or '-', Not associated; Italic type, Control in fold change									

[Table 63]

						MFI on MDA-MB-231	
Part Number					Protein code	2.5 nM	Fold
A55	-	C19	DH1	DL1	MA-01-Y829	-	-
-	-	C13	DH2	DL2	MA-09-003.01	428146	35.4
A55	B1	C13	DH2	DL2	BA-0109-004	293585	24.3
A55	B2	C13	DH2	DL2	BA-0109-005	159013	13.2
A55	B3	C13	DH2	DL2	BA-0109-006	399524	33.1
A55	B4	C13	DH2	DL2	BA-0109-007	236235	19.5
A55	B5	C13	DH2	DL2	BA-0109-009	226984	18.8
A55	B6	C13	DH2	DL2	BA-0109-010	40607	3.4
N/A	N/A	N/A	N/A	N/A	IgG	12084	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	18703	1.5
N/A or '-', Not associated; Italic type, Control in fold change							

[Table 64]

						MFI on MDA-MB-453	
Part Number					Protein code	2.0 nM	Fold
A55	-	C19	DH1	DL1	MA-01-Y829	4974	0.9
-	-	C13	DH2	DL2	MA-09-003.01	6353	1.1
A55	B1	C13	DH2	DL2	BA-0109-004	6546	1.1
A55	B2	C13	DH2	DL2	BA-0109-005	5792	1.0
A55	B3	C13	DH2	DL2	BA-0109-006	6345	1.1
A55	B4	C13	DH2	DL2	BA-0109-007	6575	1.1
A55	B5	C13	DH2	DL2	BA-0109-009	6027	1.0
A55	B6	C13	DH2	DL2	BA-0109-010	5303	0.9
N/A	N/A	N/A	N/A	N/A	IgG	5802	1.0
N/A	N/A	N/A	N/A	N/A	2nd antibody	4959	0.9
N/A or '-', Not associated; Italic type, Control in fold change							

Example 6. Analysis of in vitro transport capacity of multispecific fusion protein

The in vitro transport capacity (in vitro transcytosis; endothelial cell transcytosis) of a multispecific fusion protein was analyzed using a co-culture system of human vascular endothelial cells and cancer cells. In this case, the co-culture was performed using a transwell, by inoculating human vascular endothelial cells into the transwell, which serves as the lumen or apical side, and inoculating cancer cell lines into the bottom-well, which serves as the basolateral side. In this case, human vascular endothelial cells were HUVEC cells or EA.hy926 cells, and cancer cells were human breast cancer cells (MCF-7 cells).

First, the in vitro transport capacity was measured using the following method.

Briefly, a transwell (#353095, Falcon or #662640, Greiner) was coated with an extracellular matrix (Gelatin (Sigma-0.1% w/v), Collagen (Fisher-20 ug/cm^2), or Fibronectin

(Sigma-20 ug/cm²)) (37°C, 1 hour), and then human vascular endothelial cell lines (HUVEC cells or EA.hy926 cells) were inoculated at a concentration of 1×10^4 cells/transwell or 1×10^5 cells/transwell suspended in each growth medium. Once the cells adhered, the growth medium was replaced with differentiation medium (EGM (#CC-3162, Lonza), 2% FBS (#SH30919.03, Hyclone), 1× Antibiotic Antimycotic solution (#SV30079.01, Hyclone)), and cancer cell lines were inoculated into a bottom-well plate (#3526, Corning) by suspending them in the growth medium at a concentration of 5×10^5 cells/bottom-well. The cells were cultured for an additional 4 or 5 days (Steri-Cycle i160 CO_2 incubator (#51030303-TIF, Forma), 37 ℃). In order to measure the in vitro transport efficiency, the growth medium was removed, and a multispecific fusion protein, a single antibody, or an IgG isotype control group diluted in reaction medium (EGM (#CC-3162, Lonza), 1× Antibiotic Antimycotic solution (#SV30079.01, Hyclone)) was added to the transwell, while fresh growth medium was added to the bottom-well. The cells were then cultured for an additional 24 hours, and the medium from the bottom-well was collected at hourly intervals. The IgG concentration in the collected medium was measured using an IgG total Human ELISA kit (#BMS2091, Invitrogen) according to the manufacturer's instructions. Standard quantification curve analysis was performed using the 4PL Sigmoidal curve function of the Graphpad Prism 9 program.

The in vitro transport efficiency and recycling efficiency were measured using the following method.

Specifically, the transwell prepared as described above was transferred to a new bottom-well plate, the medium was removed, and then a multispecific fusion protein or IgG isotype control group diluted in the reaction medium was added. The reaction medium was then added to the bottom-well, and the reaction was carried out for 1 hour. After the reaction, the medium on both sides was removed and washed with the reaction medium. Then, new reaction medium was added and the culture was incubated for an additional 24 hours, and the culture solution was collected at different times. The concentration of IgG in the collected medium was measured using a Human IgG ELISA kit (#ab195215, Abcam) according to the manufacturer's instructions. Standard quantification curve analysis was performed using the 4PL Sigmoidal curve function of the Graphpad Prism 9 program.

As a result, as shown in Figures 27a to 27c, it was confirmed that the transport rate of each single antibody with binding avidity to ANXA1 was increased by about 1.3 times to about 3.1 times compared to the IgG isotype treatment group. Based on the above results, it was confirmed that a single antibody or a multispecific fusion protein exhibiting binding avidity to ANXA1, which is overexpressed in microvascular cells of growing cancer tissue, can pass through vascular endothelial cells and be delivered to cancer cells.

Example 7. Evaluation of cytotoxicity of multispecific fusion protein

The toxicity of the multispecific fusion protein-drug conjugate to tumor cells was

confirmed.

Specifically, the cancer cell lines listed in Table 65 above were each inoculated into a 96-well plate (#83.3924, Sarstedt) and then cultured for 24 hours. In this case, the number of cells inoculated per cell line is listed in Table 65 below. The cells were treated with the multispecific fusion protein-drug conjugate or the isotype control group (#31154, Thermo) and cultured for an additional 96 hours. Then, each well was treated with 20 uL of MTS solution (#G3581, Promega), and then the mixture was reacted in a CO_2 incubator for 4 hours. The absorbance of the reaction solution was measured at a wavelength of 490 nm using a spectrometer (#GM3000, Promega), and the results were analyzed using GraphPad Prism 9 program and are shown in Table 66.

In this experiment, the multispecific fusion protein was prepared under conditions before and after treatment with a proteolytic enzyme. In this case, the treatment with a proteolytic enzyme was carried out in the same manner as in Example 4 above.

[Table 65]

Cell line	BT-474	NCI-N87	SK-BR-3	JIMT-1	MCF-7	MDA-MB-231
Cell number/well	10,000	10,000	8,000	4,000	4,000	3,000

As an example of a multispecific fusion protein-drug conjugate, TD-0102-001.017 was produced as an MMAF drug polymer that exhibits binding avidity to HER2. The above TD-0102-001.017 comprises S001 in the first domain (UNIT1) of the ReleaDome, thereby exhibiting binding masking ability to HER2. It was confirmed that the above TD-0102-001.017 exhibited weak cytotoxicity compared to the single antibody MA-02-001 in NCI-N87, BT-474, SK-BR-3, and JIMT-1 cells expressing HER2; however, after the first domain (UNIT1) was cleaved by a proteolytic enzyme, it showed cytotoxicity similar to that of AD-02-001 (Figures 28a to 28d). In addition, as shown in Figure 28e, a relatively weak cytotoxic effect was observed in SK-OV-3 cells, which are known to exhibit weak cytotoxic efficacy despite confirmed to have HER2 expression.

[Table 66]

NCI-N87	MA-02-001	AD-02-001	TD-0102-001.017	(+)*TD-0102-001.017
IC50 [nM]	0.175	0.040	2.536	0.035
% cytotoxicity at 4.17 nM	26	77	35	96
BT-474	MA-02-001	AD-02-001	TD-0102-001.017	(+)TD-0102-001.017
IC50 [nM]	0.383	0.024	1.750	0.032

% cytotoxicity at 4.5 nM	58	79	53	79
% cytotoxicity at 0.5 nM	40	79	2	75
SK-BR-3	MA-02-001	AD-02-001	TD-0102-001.017	(+)TD-0102-001.017
IC50 [nM]	0.140	0.005	0.316	0.007
% cytotoxicity at 4.5 nM	24	80	74	77
% cytotoxicity at 0.2 nM	13	78	7	78
JIMT-1	MA-02-001	AD-02-001	TD-0102-001.017	(+)TD-0102-001.017
IC50 [nM]	> 4.5	0.046	> 4.5	0.199
% cytotoxicity at 4.5 nM	1	52	1	44
(+)*, cut by MT-SP1 & uPA; (+), cut by MT-SP1 ; IC50, inhibitory concentration 50, inhibition concentration ; % cytotoxicity, the percentage inhibition of cell proliferation				

In addition, Figure 29 shows the results of confirming the cytotoxicity of a multispecific fusion protein (anti-ANXA1-anti-EGFR)-drug conjugate in the MDA-MB-231 cell line. MDA-MB-231 is a triple negative breast cancer cell line known to secrete proteolytic enzymes into the culture solution under in vitro culture conditions. When the MDA-MB-231 cells were treated with each multispecific fusion protein-drug conjugate conjugated with the MMAE drug, the cytotoxicity was increased in a drug concentration-dependent manner. In addition, it was observed that the cytotoxic efficacy of TD-0109-010.327, a drug conjugate of the multispecific fusion protein (BA-0109-010; Figure 26b) comprising the first cleavable linker (PRS5) which was confirmed to have the highest masking ability in the results of Example 5.3 above, appeared most delayed. Based on the above results, it was confirmed that the binding masking ability of the first domain (UNIT1) can reduce the induction of cytotoxicity, and that protein cleavage efficiency can be higher under cell culture conditions than under in vitro conditions. Based on the above, it can be predicted that more dynamic and active proteolytic enzyme activity may be exhibited in the in vivo tumor microenvironment.

Example 8. Analysis of thermal stability of multispecific fusion protein

The thermal stability of a multispecific fusion protein was analyzed using differential scanning fluorimetry.

Specifically, a multispecific fusion protein (preferably 5 uM, total 45 uL) diluted in DPBS solution and a fluorescent dye (Sypro orange; #S6651, Thermo) (200×, total 5 uL) were mixed and dispensed into a qPCR tube (#TLS0801, Biorad). The mixture was reacted in a real-time gene amplifier (CFX Duet Real-Time PCR Detection System, Biorad) under the condition

of [reacting while increasing the temperature by 0.5°C at 30-second intervals within the range of 25°C to 99°C, and completing the reaction after standing at 25°C for 10 minutes]. The intensity of fluorescence in the sample solution during the reaction was measured in real time and analyzed using the GraphPad Prism 9 program.

Tables 67 to 71 show the results of measuring the melting temperature (Tm) of each multispecific fusion protein, and Figures 30a to 30j show examples of melting curves and melting peaks. The melting temperature of each multispecific fusion protein was measured within a range similar to the melting temperature (67.5°C) of the single antibody MA-02-001. In addition, for some fusion proteins, two or more melting temperatures were measured, or a low melting temperature of 60°C or lower was measured.

[Table 67]

Part Number					Protein code	Tm (℃)			
A58	B2	C1	DH1	DL2	BA-0102-001	78.0	67.5	N/A	N/A
A58	B3	C1	DH3	DL2	BA-0102-002	65.0	N/A	N/A	N/A
A4	B3	C1	DH3	DL2	BA-0102-003	41.5	75.5	47.0	63.0
A5	B3	C1	DH3	DL2	BA-0102-004	53.5	61.5	75.0	N/A
A9	B3	C1	DH3	DL2	BA-0102-005	62.5	75.0	N/A	N/A
A9	B2	C1	DH3	DL2	BA-0102-005.1	N/D	N/A	N/A	N/A
A13	B3	C1	DH3	DL2	BA-0102-006	63.5	75.0	N/A	N/A
A28	B3	C1	DH3	DL2	BA-0102-007	51.5	64.0	N/A	N/A
A48	B3	C1	DH3	DL2	BA-0102-008	64.5	56.5	75.0	N/A
A55	B3	C1	DH3	DL2	BA-0102-009	75.0	63.0	N/A	N/A
A11	B3	C1	DH3	DL2	BA-0102-010	55.5	65.5	75.5	N/A
A25	B3	C1	DH3	DL2	BA-0102-011	65.0	54.0	76.0	N/A
A30	B3	C1	DH3	DL2	BA-0102-012	65.5	75.5	56.0	N/A
A42	B3	C1	DH3	DL2	BA-0102-013	66.0	75.5	N/A	N/A
A43	B3	C1	DH3	DL2	BA-0102-014	65.5	75.0	53.5	N/A
A55	B1	C1	DH3	DL2	BA-0102-015	62.5	75.0	N/A	N/A
A33	B3	C1	DH3	DL2	BA-0102-016	63.0	75.5	N/A	N/A
A1	B3	C1	DH3	DL2	BA-0102-017	64.5	78.0	N/A	N/A
A2	B3	C1	DH3	DL2	BA-0102-018	53.0	63.0	42.5	75.0
A3	B3	C1	DH3	DL2	BA-0102-019	65.0	75.5	N/A	N/A
A6	B3	C1	DH3	DL2	BA-0102-020	64.5	77.0	N/A	N/A
A7	B3	C1	DH3	DL2	BA-0102-021	64.5	75.5	N/A	N/A
A8	B3	C1	DH3	DL2	BA-0102-022	63.0	75.5	N/A	N/A
A10	B3	C1	DH3	DL2	BA-0102-023	63.0	75.5	N/A	N/A
A27	B3	C1	DH3	DL2	BA-0102-024	65.0	58.0	74.5	N/A
A14	B3	C1	DH3	DL2	BA-0102-025	N/D	N/A	N/A	N/A
A15	B3	C1	DH3	DL2	BA-0102-026	64.0	75.0	N/A	N/A
A16	B3	C1	DH3	DL2	BA-0102-027	63.5	76.5	49.5	N/A
A17	B3	C1	DH3	DL2	BA-0102-028	66.5	54.5	75.5	N/A
A18	B3	C1	DH3	DL2	BA-0102-029	65.5	75.0	N/A	N/A
A20	B3	C1	DH3	DL2	BA-0102-030	66.5	73.5	N/A	N/A
A21	B3	C1	DH3	DL2	BA-0102-031	67.0	74.5	N/A	N/A
A22	B3	C1	DH3	DL2	BA-0102-032	64.5	75.5	N/A	N/A

A23	B3	C1	DH3	DL2	BA-0102-033	66.5	74.5	N/A	N/A
A24	B3	C1	DH3	DL2	BA-0102-034	65.0	75.0	N/A	N/A
A26	B3	C1	DH3	DL2	BA-0102-035	64.0	75.0	N/A	N/A
A29	B3	C1	DH3	DL2	BA-0102-036	64.0	76.0	N/A	N/A
A31	B3	C1	DH3	DL2	BA-0102-037	65.0	58.5	76.5	N/A
A32	B3	C1	DH3	DL2	BA-0102-038	65.5	76.5	50.5	N/A
A34	B3	C1	DH3	DL2	BA-0102-039	65.0	77.5	N/A	N/A
A35	B3	C1	DH3	DL2	BA-0102-040	62.5	75.5	52.5	N/A
A36	B3	C1	DH3	DL2	BA-0102-041	65.0	75.0	51.0	N/A
A37	B3	C1	DH3	DL2	BA-0102-042	59.0	66.0	74.5	N/A
A38	B3	C1	DH3	DL2	BA-0102-043	66.0	77.0	N/A	N/A
A39	B3	C1	DH3	DL2	BA-0102-044	66.0	75.0	52.0	N/A
A40	B3	C1	DH3	DL2	BA-0102-045	63.5	75.0	N/A	N/A
A41	B3	C1	DH3	DL2	BA-0102-046	66.5	51.5	74.5	N/A
A44	B3	C1	DH3	DL2	BA-0102-047	58.0	66.0	75.5	N/A
A45	B3	C1	DH3	DL2	BA-0102-048	61.0	66.5	75.5	N/A
A46	B3	C1	DH3	DL2	BA-0102-049	64.5	75.0	52.0	N/A
A47	B3	C1	DH3	DL2	BA-0102-050	74.0	61.5	N/A	N/A
A49	B3	C1	DH3	DL2	BA-0102-051	64.0	75.0	N/A	N/A
A50	B3	C1	DH3	DL2	BA-0102-052	65.0	75.0	N/A	N/A
A51	B3	C1	DH3	DL2	BA-0102-053	65.5	74.0	N/A	N/A
A52	B3	C1	DH3	DL2	BA-0102-054	58.5	65.5	76.0	N/A
A53	B3	C1	DH3	DL2	BA-0102-055	65.5	75.0	N/A	N/A
A54	B3	C1	DH3	DL2	BA-0102-056	62.5	75.5	N/A	N/A
A56	B3	C1	DH3	DL2	BA-0102-057	59.5	66.0	N/A	N/A
A57	B3	C1	DH3	DL2	BA-0102-058	61.5	65.0	75.0	N/A

[Table 68]

Part Number					Protein code	Tm (℃)		
A55	B3	C3	DH1	DL1	BA-0107-001	62.5	N/A	N/A
A55	B3	C5	DH1	DL1	BA-0107-002	67.5	56.5	N/A
A55	B3	C7	DH1	DL1	BA-0107-003	N/D	N/A	N/A
A55	B1	C3	DH1	DL1	BA-0107-004	61.0	N/A	N/A
A55	B2	C3	DH1	DL1	BA-0107-005	59.5	N/A	N/A
A55	B4	C3	DH1	DL1	BA-0107-006	N/D	N/A	N/A
A55	B1	C5	DH1	DL1	BA-0107-007	57.0	67.5	N/A
A55	B2	C5	DH1	DL1	BA-0107-008	67.5	58.0	N/A
A55	B4	C5	DH1	DL1	BA-0107-009	58.0	67.0	81.5
A55	B5	C5	DH1	DL1	BA-0107-010	63.0	81.5	N/A
A55	B6	C5	DH1	DL1	BA-0107-011	64.0	74.5	N/A
A55	B7	C5	DH1	DL1	BA-0107-012	65.0	81.5	N/A
A55	B8	C5	DH1	DL1	BA-0107-013	81.5	63.0	N/A
A55	B6	C3	DH1	DL1	BA-0107-014	60.0	N/A	N/A

N/D, Not determined; N/A or '-', Not associated

[Table 69]

Part Number					Protein code	Tm (℃)		
A55	B3	C9	DH3	DL2	BA-0109-001	58.5	66.0	N/A
A55	B3	C11	DH3	DL2	BA-0109-002	57.0	65.5	N/A
A55	B3	C13	DH3	DL2	BA-0109-003	N/D	N/A	N/A
A55	B1	C13	DH2	DL2	BA-0109-004	60.5	67.5	79.5
A55	B2	C13	DH2	DL2	BA-0109-005	60.0	67.5	N/A
A55	B3	C13	DH2	DL2	BA-0109-006	61.0	67.5	79.0
A55	B4	C13	DH2	DL2	BA-0109-007	61.0	67.5	78.5
A33	B4	C13	DH2	DL2	BA-0109-008	67.5	76.5	N/A
A55	B5	C13	DH2	DL2	BA-0109-009	60.5	67.5	79.5
A55	B6	C13	DH2	DL2	BA-0109-010	61.0	67.5	77.5
A55	B1	C11	DH2	DL2	BA-0109-011	61.5	N/A	N/A
A55	B2	C11	DH2	DL2	BA-0109-012	64.0	N/A	N/A
A55	B3	C11	DH2	DL2	BA-0109-013	61.5	N/A	N/A
A55	B4	C11	DH2	DL2	BA-0109-014	63.0	N/A	N/A
A55	B5	C11	DH2	DL2	BA-0109-015	63.5	N/A	N/A
A55	B6	C11	DH2	DL2	BA-0109-016	62.0	N/A	N/A
A55	B7	C11	DH2	DL2	BA-0109-017	65.0	N/A	N/A
A55	B8	C11	DH2	DL2	BA-0109-018	60.5	N/A	N/A
A55	B3	C12	DH2	DL2	BA-0109-019	61.5	67.0	78.5
A55	B3/B7	C11	DH2	DL2	BA-0109-020	78.0	67.5	61.5
A55	B7/B3	C11	DH2	DL2	BA-0109-021	60.0	68.0	78.0
A33	B6	C11	DH2	DL2	BA-0109-024	71.0	N/A	N/A
A33	B7	C11	DH2	DL2	BA-0109-025	67.0	78.0	73.5
A58	B6	C11	DH2	DL2	BA-0109-026	75.0	66.5	N/A
A58	B7	C11	DH2	DL2	BA-0109-027	66.5	76.5	N/A
A55	B9	C11	DH2	DL2	BA-0109-028	68.0	59.0	N/A
A55	B2	C11	DH2	DL4	BA-0109-029	58.5	68.0	N/A
A55	B6	C11	DH2	DL4	BA-0109-030	58.5	68.5	N/A
A59	B2	C11	DH2	DL2	BA-0109-031	54.0	68.0	N/A
A62	B2	C11	DH2	DL2	BA-0109-032	67.5	56.0	N/A
A63	B2	C11	DH2	DL2	BA-0109-033	58.5	67.5	N/A
A65	B2	C11	DH2	DL2	BA-0109-034	56.0	68.0	N/A
A66	B2	C11	DH2	DL2	BA-0109-035	57.0	68.0	N/A
A68	B2	C11	DH2	DL2	BA-0109-036	61.5	N/A	N/A

A62	B2	C11	DH2	DL2	BA-0109-037	65.0	57.0	N/A
A65	B2	C11	DH2	DL2	BA-0109-038	56.0	67.5	78.5
A68	B2	C11	DH2	DL2	BA-0109-039	61.0	67.5	78.5
A62	B6	C11	DH2	DL2	BA-0109-040	67.5	56.5	74.5
A65	B6	C11	DH2	DL2	BA-0109-041	56.0	68.0	74.5
A68	B6	C11	DH2	DL2	BA-0109-042	N/D	N/A	N/A

N/D, Not determined; N/A or '-', Not associated

[Table 70]

Part Number					Protein code	Tm (℃)		
A55	B1	C20	DH2	DL4	BA-0113-010	58.5	77.5	66.0
A55	B2	C20	DH2	DL4	BA-0113-011	61.0	77.5	N/A
A55	B3	C20	DH2	DL4	BA-0113-012	59	77.5	66.5
A55	B4	C20	DH2	DL4	BA-0113-013	58.5	76.5	67
A55	B5	C20	DH2	DL4	BA-0113-014	60	77.5	N/A
A55	B6	C20	DH2	DL4	BA-0113-015	62	75	N/A
A55	B7	C20	DH2	DL4	BA-0113-016	78	62	N/A
A55	B8	C20	DH2	DL4	BA-0113-017	60.5	77	N/A
A55	B9	C20	DH2	DL4	BA-0113-018	63	77	N/A
A69	B2	C20	DH2	DL4	BA-0113-019	60.5	77.5	67
A69	B6	C20	DH2	DL4	BA-0113-020	75	63	N/A
A55/A55	B3/B7	C11/C11	DH4/DH5	DL2/DL3	BA-0109-022	62	N/A	N/A
A55/-	B3/-	C11/C11	DH4/DH5	DL2/DL3	BA-0109-023	63	N/A	N/A

N/D, Not determined; N/A or '-', Not associated

[Table 71]

Part Number					Protein code	Tm (℃)	
A58	B2	C2	DH7	-	BA-0102-R001	68.0	N/A
A13	B3	C2	DH7	-	BA-0102-R002	N/D	N/A
A13	B3	C2	DH9	-	BA-0102-R003	N/D	N/A
A55	B3	C2	DH9	-	BA-0102-R004	63.0	N/A
A9	B3	C2	DH6	-	BA-0102-R005	64.5	N/A
A13	B3	C2	DH6	-	BA-0102-R006	N/D	N/A
A28	B3	C2	DH6	-	BA-0102-R007	52.5	64.5
A33	B3	C2	DH6	-	BA-0102-R008	67.0	N/A
A55	B3	C2	DH6	-	BA-0102-R009	63.5	60.0
A9	B3	C2	DH9	-	BA-0102-R010	64.0	N/A
A28	B3	C2	DH9	-	BA-0102-R011	52.5	64.0

A33	B3	C2	DH9	-	BA-0102-R012	67.5	N/A
A58	B2	C15	DH7	-	BA-0104-R001	N/D	N/A
A9	B3	C15	DH8	-	BA-0104-R002	61.0	N/A
A28	B3	C15	DH8	-	BA-0104-R003	51.5	61.0
A55	B3	C15	DH8	-	BA-0104-R005	60.0	N/A
A9	B3	C16	DH8	-	BA-0104-R006	52.0	N/A
A28	B3	C16	DH8	-	BA-0104-R007	N/D	N/A
A33	B3	C16	DH8	-	BA-0104-R008	63.0	N/A
A55	B3	C16	DH8	-	BA-0104-R009	58.0	N/A
A55	B3	C4	DH8	-	BA-0107-R001	56.5	65.0
A9	B3	C4	DH8	-	BA-0107-R002	55.5	64.5
A28	B3	C4	DH8	-	BA-0107-R003	49.5	N/A
A33	B3	C4	DH8	-	BA-0107-R004	59.0	N/A
A9	B3	C6	DH8	-	BA-0107-R005	64.0	N/A
A28	B3	C6	DH8	-	BA-0107-R006	53.5	64.0
A33	B3	C6	DH8	-	BA-0107-R007	65.0	N/A
A55	B3	C6	DH8	-	BA-0107-R008	59.5	N/A
A9	B3	C8	DH8	-	BA-0107-R009	N/D	N/A
A28	B3	C8	DH8	-	BA-0107-R010	N/D	N/A
A33	B3	C8	DH8	-	BA-0107-R011	42.0	63.0
A55	B3	C8	DH8	-	BA-0107-R012	49.5	N/A
A9	B3	C10	DH9	-	BA-0109-R001	N/D	N/A
A28	B3	C10	DH9	-	BA-0109-R002	N/D	N/A
A33	B3	C10	DH9	-	BA-0109-R003	62.0	N/A
A55	B3	C10	DH9	-	BA-0109-R004	60.0	N/A
A9	B3	C12	DH9	-	BA-0109-R005	N/D	N/A
A33	B3	C14	DH9	-	BA-0109-R011	65.0	N/A
A33	B3	C12	DH8	-	BA-0109-R015	61.0	N/A
A55	B3	C12	DH8	-	BA-0109-R016	58.0	N/A
A9	B3	C14	DH8	-	BA-0109-R017	64.5	49.0
A28	B3	C14	DH8	-	BA-0109-R018	52.5	N/A
A9	B3	C18	DH9	-	BA-0111-R001	63.5	N/A
A28	B3	C18	DH9	-	BA-0111-R002	53.0	62.5
A33	B3	C18	DH9	-	BA-0111-R003	65.5	N/A
A55	B3	C18	DH9	-	BA-0111-R004	59.5	62.0

N/D, Not determined; N/A or '-', Not associated

Example 9. Analysis of plasma stability of multispecific fusion protein

The plasma stability was analyzed by mixing the multispecific fusion proteins conjugated with the fluorescent dyes of Table 44 above with plasma, reacting the mixture at 37 °C, obtaining samples on a daily basis, and then confirming the multispecific fusion proteins within the samples.

Specifically, 20 uL of plasma (mouse plasma, #029-APSC-PMG, Biochemed) or human plasma (#752PR-SC-PMG, Biochemed) (about 150 uL) comprising the test fluorescent dye-conjugated multispecific fusion protein (about 10 ug) was dispensed and reacted at 37 °C, and samples were obtained on days 0, 1, 3, and 6, respectively. The samples were diluted in 180 uL of the assay solution (1×PBS pH 7.4, 0.01% Tween-20), mixed with Dynabeads™ Protein A (0.3 mg), and then reacted at room temperature for 10 minutes. The multiple specific fusion protein in the reaction solution was purified using a magnet according to the manufacturer's instructions, and the purified product was obtained with 20 uL of extraction solution (50 mM glycine, 100 mM sodium citrate, pH 3.5). The purified product was neutralized by adding 8 uL of neutralization solution (1 M Tris-HCl, pH 8; #15568-025, Invitrogen), and then SDS-PAGE was performed under reducing conditions. The resulting products were verified by measuring fluorescence (FITC) (#iBright™ FL1500, Thermo) or by Coomassie Brilliant Blue staining.

As a result, as shown in Figures 31a to 31c, it was confirmed that the plasma stability of TD-0109-013.336, which comprises PRS2 (first cleavable linker), was gradually decreased on days 3 and 6, whereas the other fusion proteins maintained stability until day 6.

Example 10. Pharmacokinetic analysis of multispecific fusion protein

In order to analyze the pharmacokinetic patterns of multispecific fusion proteins, blood was collected at each time point after a single intravenous administration to rodents, and the fusion proteins in the plasma were analyzed using the ELISA method. The rodent experiments for this pharmacokinetic analysis were commissioned to a specialized research service provider (Keyfron Bio). In this case, BA-0109-012, BA-0109-016, and BA-0109-018 were used as multiple specific fusion protein samples, respectively.

Specifically, a multispecific fusion protein, which is one embodiment of the present invention, was administered intravenously to rodents (mice or rats) at doses (3 mg/kg, 10 mg/kg), and then blood was collected (orbital vein or jugular vein) at intervals (before administration, 3 minutes, 1 hour, 3 hours, 6 hours, 1 day, 2 days, 3 days, 4 days, 7 days, and 10 days after administration), treated with an anticoagulant (K3EDTA to heparin), centrifuged (12,000 rpm, 3 minutes, 4 °C), and plasma was separated. The plasma (plasma biosample) separated as described above was provided by the service provider in a quenched state and was stored in an ultra-low temperature freezer (-80 °C) until analysis. The multispecific fusion proteins in the plasma were measured using the ELISA method as in Example 5.1 above. In

addition, the measured values were analyzed using the BA Calc 2007 analysis program.

As a result, as shown in Figures 32a to 32c, it was confirmed that the half-lifes (t1/2) of BA-0109-012, BA-0109-016, and BA-0109-018 in mouse blood were an average of 152.24 hours, 154.07 hours, and 157.64 hours, respectively.

Example 11. Confirmation of distribution of multispecific fusion proteins in cancer tissue

In order to confirm the in vivo tissue distribution of multispecific fusion proteins, optical tomographic imaging analysis was performed by commissioning a research service provider (APEX).

Specifically, frozen human cancer cell lines (JIMT-1 cells or NCI-N87 cells) held by APEX were used. The cells were subcultured at intervals of 3 to 4 days. When the cell viability was 90% or higher, the cells were harvested and prepared by suspending them in cold saline at a concentration of 5×10^6 cells/50 uL/mouse per mouse for transplantation.

BALB/c nude mice were used. After 1 week of stabilization, at 6 weeks of age, a mixture (100 uL) of prepared cells (5×10^6 cells/50 uL) and 50 uL of Matrigel was subcutaneously transplanted into the flanks of mice using a disposable syringe. After cell transplantation, once the tumor began to grow, the long and short axes of the tumor were measured, and the tumor volume was calculated using the following <Mathematical Equation I>. On the day of administration, mice with tumor volumes of 200 ± 20 mm^3 to 300 ± 20 mm^3 were selected using the paired-matching method and separated into groups.

<Mathematical Equation I>

Tumor volume (mm^3) = (a × 2b) / 2, where a is the short axis and b is the long axis.

Some of the multispecific fusion proteins described in Tables 44 to 49, which are embodiments of the multispecific fusion proteins of the present invention, were used as test substances and diluted in a buffer solution (PBS; #SH30256.01, Hyclone) and administered as a single dose via intravenous (i.v.) injection at concentrations of 2.7 mg/kg or 4 mg/kg, respectively. In this case, a buffer solution (PBS; #SH30256.01, Hyclone) was used as a control group. Images were obtained before administration of the test substance (-1 hour) and at each time point after administration of the test substance (1, 2, 3, 4, 6, 24, 48, 72 hours). Images of the mice were obtained by performing whole body IVIS imaging after placing the mice in the device so that the dorsal portion of the mice was photographed after inhalation anesthesia. IRdye-800CW (excitation: 774 nm, emission: 789 nm) was used as the labeling dye, and measurements were taken in C mode for 2 or 3 mice per group. At the end of the test, tumors and major organs (liver, lungs, kidneys, spleen, and heart) were extracted, and the distribution of drugs within the tumors and each organ was confirmed via IVIS imaging. The obtained images were analyzed using 'Living Image® 4.7.3 (64-bit, Perkin Elmer)'. The extracted tumors were weighed and photographed. In addition, the body weight of each subject was measured at the time of group

separation and at the end of the test. The results measured as described above are shown in Figures 33a to 34b.

Figure 33a shows a cell-derived xenograft (CDX) model produced by subcutaneously transplanting HER2-expressing NCI-N87 cells (human gastric cancer cell line). Administration of each test substance (2.7 mg/kg) was initiated when the tumor size reached 310 ± 55 mm^3, and IVIS images were analyzed before administration of each test substance and at 4 hours after administration. As a result, organ distribution was observed differently depending on the type of first domain (UNIT1) of the ReleaDome included in the multispecific fusion protein. Specifically, in the group administered with TD-0102-005-CW comprising Y065 as the first domain (UNIT1), strong fluorescence was observed in the kidney, while in the group administered with TD-0102-002-CW comprising S001 as the first domain (UNIT1), relatively low fluorescence intensity was observed. In addition, fluorescence was observed in the tumor tissue of the group administered with TD-0102-009-CW comprising Y829 as the first domain (UNIT1).

Figure 33b shows a CDX model transplanted with HER2-expressing JIMT-1 cells (human breast cancer cell line). When the tumor size reached 197 ± 15 mm^3, administration of each test substance (3 mg/kg, 4 mg/kg) was initiated, and IVIS images were analyzed 24 hours after administration of each test substance. As a result, strong fluorescence was observed in the whole body and tumor in the group administered with the single antibody AD-02-CW (3 mg/kg). On the other hand, in the group administered with TD-0102-009-CW (in this case, PRS2) or TD-0102-015-CW (in this case, PRS0), which comprise Y829 as the first domain (UNIT1), systemic fluorescence intensity was observed to be weak, but strong fluorescence was observed in the tumor tissue.

Figure 34a shows a CDX model transplanted with EGFR-expressing JIMT-1 cells. When the tumor size reached 280 ± 26 mm^3, administration of each test substance was initiated, and IVIS images were analyzed at time intervals after administration of each test substance (3 mg/kg, 4 mg/kg). As a result, strong systemic fluorescence was observed during the first 6 hours after administration in the group administered with the single antibody AD-09-003-CW (3 mg/kg). On the other hand, in the group administered with TD-0109-003-CW comprising Y829 as the first domain (UNIT1), systemic fluorescence intensity was relatively weak or was not detected. As a result of observing IVIS images on a daily basis after administration of the test substance, strong fluorescence was observed in tumor tissues in both the group administered with AD-09-003-CW and the group administered with TD-0109-003-CW. In addition, as a result of observing IVIS images of tumor tissues and each organ extracted 72 hours after administration of the test substance, weak fluorescence was observed in the non-lesion organs (lung, kidney, and spleen) of the group administered with TD-0109-003-CW compared to the group administered with AD-09-003-CW, while strong fluorescence was observed in the tumor tissues.

In this case, no pathological findings, such as body weight loss in the subject, were observed.

Based on the above results, it was confirmed that the first domain (UNIT1) of the ReleaDome can mask the antigen binding avidity of the second domain (UNIT2) while simultaneously targeting microvessels surrounding cancer tissue to facilitate drug transport. Therefore, the ReleaDome can reduce systemic drug toxicity and drug accumulation in non-lesion tissues, and promote drug accumulation specifically in cancer tissue.

Example 12. In vivo toxicity analysis of multispecific fusion protein

The in vivo toxicity (safety) of multispecific fusion proteins was evaluated by the research service provider (APEX). The toxicity evaluation was performed by administering the test substance to BALB/c-nude mice or monkeys and then analyzing hematological changes over time.

For the hematological analysis of mice, the test substance was administered intravenously according to the predetermined concentration and dosage regimen, and the body weight of all subjects was measured twice a week from the first blood collection until the end of the test. In addition, blood from each subject was collected by orbital blood collection 3 days before the administration of the test substance and on the 4th day after administration, and by cardiac blood collection on the end of the test (day 11). The collected blood was mixed with an anticoagulant, and then total WBC, total RBC, platelet, hemoglobin, and reticulocyte in the blood were analyzed using a blood cell analyzer (#ADIVA 2120i, SIMENS). In this experiment, the multispecific fusion protein BA-0107-005 was administered as a single dose at a concentration of 28 mg/kg as the test substance, and the anti-CD47 single antibody MA-07-001 was administered as a single dose at a concentration of 20 mg/kg (administered with the same number of molecules as BA-0107-005) with CD47 as the positive control.

As a result, as shown in Figure 35, an increase in reticulocytes was observed in the group administered with MA-07-001 on the 4th day after administration, and a decrease in platelets was observed on the 11th day after administration. In addition, on the 11th day after administration, it was confirmed that the viscosity of the blood collected from some subjects was increased and the white blood cell (WBC) count was decreased. On the other hand, in the group administered with BA-0107-005, it was confirmed that the increase in reticulocytes on the 4th day after administration was about 50% less compared to the group administered with MA-07-001. In addition, no decrease in platelets or increase in blood viscosity was observed even on the 11th day after administration. In this case, the results of the blood cell analysis (total WBC, total platelet, and reticulocyte) in the collected blood are shown in Figure 35.

The above results suggest that while anti-CD47 single antibodies can cause hematotoxicity by lysing red blood cells (RBCs) or platelets, ReleaDome can reduce hematotoxicity and systemic toxicity by masking the binding avidity of the second domain (UNIT2) to the CD47 protein in a non-lesion environment.

Example 13. Evaluation of anticancer activity of multispecific fusion protein in mouse model

The anticancer activity of multispecific fusion proteins at the animal level was confirmed using xenograft tumor mouse models commissioned to the research service providers (Dt&CRO, APEX, and Keyfron Bio).

Specifically, human-derived cancer cell lines held by each research service provider were mixed with an equal amount of Matrigel and transplanted subcutaneously into the flanks of Athymic nude or BALB/c nude mice. The tumor volume was calculated in the same manner as in Example 11 above, and on the day of administration, mice with tumor volumes meeting the criteria were selected and separated into groups using the paired-matching method. The test substance was administered as a single dose via intravenous (i.v.) injection at a predetermined dosage concentration. After administration of the test substance, tumor volume and clinical symptoms were measured twice a week, and the tumor growth inhibition (TGI) was calculated using <Mathematical Equation II>.

<Mathematical Equation II>

Tumor Growth Inhibition (TGI: IR (%) = (1 - T/C) × 100

wherein, T is the average tumor weight of the group administered with the test substance and the positive control group, and C is the tumor weight of the negative control group.

Upon completion of the observation period, each subject was euthanized, and their respective tumor tissues were extracted, weighed, and photographed. All data obtained during the test period were recorded in an Excel format.

Figures 36a and 36b show the results obtained by measuring the tumor size and tumor weight (day 62 after administration) by date after administering each test substance as a single intravenous dose at a concentration of 0.02 umol/kg (3 mg/kg based on the single antibody, 4 mg/kg based on the multispecific fusion protein-DVD-Ig form) in a HER2-expressing NCI-N87 cell (human gastric cancer cell line) CDX model. As a result of measuring the tumor volume and tumor weight of 5 mice per group, the anticancer activity of the multispecific fusion protein-drug conjugate was confirmed. The anticancer activity was superior compared to Kadcyla (T-DM1), and no pathological findings were observed.

Figures 37a and 37b show the results obtained by measuring the tumor size and subject body weight after administering each test substance (multispecific fusion protein-drug conjugate) as a single intravenous dose at a concentration of 0.033 umol/kg (5 mg/kg based on the single antibody) in an EGFR-expressing MDA-MB-231 cell (human triple negative breast cancer cell line) CDX model. As a result, the single antibody-drug conjugate (AD-09-003) and the multispecific fusion protein-drug conjugate exhibited similar levels of anticancer activity. In addition, no pathological findings, such as body weight loss, were observed in the group administered with the test substance.

Figures 38a and 38b show the results of measuring the tumor size and subject body weight by date after administering a single antibody-drug conjugate (5 mg/kg based on 0.0338 umol/kg) or a multispecific fusion protein-drug conjugate (3.5 mg/kg based on 0.0175 umol/kg) in a HER2-expressing JIMT-1 CDX cell (human breast cancer cell line) model. As a result, the multispecific fusion protein-drug conjugate exhibited anticancer activity similar to that of the single antibody-drug conjugate, even though it was administered at half the concentration compared to the single antibody-drug conjugate. In addition, no pathological findings, such as body weight loss, were observed in the group administered with the multispecific fusion protein.

Based on the above results, it was confirmed that a multispecific fusion protein comprising a ReleaDome can exhibit anticancer activity without signs of pathological abnormalities in xenograft tumor mouse models of various cancer types.

The multispecific fusion protein comprising a ReleaDome according to the present invention demonstrated the potential to reduce systemic toxicity, including hematotoxicity, through the antigen binding masking ability of the second domain of the ReleaDome. In addition, the disease site-specific drug transport capacity of the ReleaDome demonstrated the potential to exhibit excellent anticancer activity even with low-dose drug administration by specifically transporting and concentrating drug molecules to the disease site.

Claims

[Claim 1]

A fusion protein comprising: a first domain comprising a site that specifically binds to a first target; and a second domain comprising a site that specifically binds to an immune modulator or a second target;

wherein the first target is a protein that is overexpressed in vascular cells or basal cells at a disease site, and the second target is a protein that is overexpressed or secreted on the surface of cancer cells or immune cells.

[Claim 2]

The fusion protein according to claim 1, wherein the first domain masks the second domain at a non-disease site, and/or is cleaved at a disease site to induce the activity of the second domain.

[Claim 3]

The fusion protein according to claim 1, wherein the first domain comprises a site that binds to any one protein selected from the group consisting of Annexin A1, albumin, App2, B7H3, Cav-1, CD36, EphA2, EphA3, EphB1, FAPα (Fibroblast activation protein alpha), ICAM1, Integrins, KDR (VEGF2), TEM8, TSP-1, ED-B, Endothelin-1, Endoglin (CD105), VEGFR1 (FLT1), PDGFR, PSMA, and VCAM-1.

[Claim 4]

The fusion protein according to claim 1, wherein the first domain is any one selected from the group consisting of an antibody or a fragment thereof, a ligand or a fragment thereof, and a receptor or a fragment thereof, a peptide, and an aptamer.

[Claim 5]

The fusion protein according to claim 4, wherein the first domain is an antibody or a fragment thereof.

[Claim 6]

The fusion protein according to claim 5, wherein the first domain comprises:

a heavy chain variable region comprising:

HCDR1 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 277, 284, 291, 298, 304, 310, 320, 326, 332, 336, 338, 344, 355, 370, 382, 392, 396, 398, 405, 411, 417, 420, 427, 432, 436, 441, 444, 449, 456, 460, 465, 470, 475, 478 and

489,

HCDR2 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 279, 286, 293, 300, 305, 322, 328, 334, 340, 346, 351, 357, 365, 372, 378, 386, 394, 400, 406, 413, 422, 429, 434, 442, 446, 451, 458, 462, 467, 472, 480, 486, 491, 494, 495, 496, 497 and 498, and

HCDR3 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 281, 288, 295, 302, 307, 312, 317, 324, 330, 342, 348, 353, 359, 361, 362, 374, 380, 388, 402, 408, 415, 424, 453 and 492; and

a light chain variable region comprising:

LCDR1 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 500, 512, 525, 531, 538, 551, 557, 564, 570, 575, 580, 592, 595, 599, 603, 608, 616, 621, 625, 631, 636, 645, 651, 654, 659, 667, 670, 675, 678, 684, 690, 698, 704, 708, 711 and 714,

LCDR2 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 502, 508, 514, 523, 527, 533, 540, 547, 553, 559, 566, 582, 587, 609, 617, 632, 639, 647, 663, 680, 685 and 716, and

LCDR3 comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 504, 510, 516, 529, 535, 542, 544, 549, 555, 561, 568, 572, 578, 584, 586, 588, 590, 597, 602, 606, 611, 613, 619, 624, 627, 630, 634, 641, 643, 649, 653, 662, 665, 669, 673, 674, 682, 687, 689, 693, 696, 697, 718 and 719.

[Claim 7]

The fusion protein according to claim 4, wherein the first domain comprises:

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 277, HCDR2 comprising the amino acid sequence of SEQ ID NO: 279, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 281; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 504 (A1);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 284, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 288; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 508, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 510 (A2);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and

HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 516 (A3);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 298, HCDR2 comprising the amino acid sequence of SEQ ID NO: 300, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 302; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 504 (A4);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 304, HCDR2 comprising the amino acid sequence of SEQ ID NO: 305, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 307; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 523, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 510 (A5);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 310, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 312; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 525, LCDR2 comprising the amino acid sequence of SEQ ID NO: 527, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 529 (A6);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 317; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 531, LCDR2 comprising the amino acid sequence of SEQ ID NO: 533, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 535 (A7);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 322, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 324; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 538, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 542 (A8);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 326, HCDR2 comprising the amino acid sequence of SEQ ID NO: 328, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 330; and a light chain variable

region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 500, LCDR2 comprising the amino acid sequence of SEQ ID NO: 502, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 544 (A9);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 332, HCDR2 comprising the amino acid sequence of SEQ ID NO: 334, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 547, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 549 (A10);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 336, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 551, LCDR2 comprising the amino acid sequence of SEQ ID NO: 553, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 555 (A11);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 338, HCDR2 comprising the amino acid sequence of SEQ ID NO: 340, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 342; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 557, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 561 (A12);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 344, HCDR2 comprising the amino acid sequence of SEQ ID NO: 346, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 348; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 564, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 568 (A13);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 353; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 570, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 555 (A14);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 355, HCDR2 comprising the amino acid sequence of SEQ ID NO: 357, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2

comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 572 (A15);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 361; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 575, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 578 (A16);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 362; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 584 (A17);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 365, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 586 (A18);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 587, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 588 (A19);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 370, HCDR2 comprising the amino acid sequence of SEQ ID NO: 372, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 374; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 564, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 590 (A20);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 592, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino

acid sequence of SEQ ID NO: 572 (A21);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 355, HCDR2 comprising the amino acid sequence of SEQ ID NO: 378, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 380; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 595, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 597 (A22);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 382, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 572 (A23);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 286, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 599, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A24);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 386, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 388; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 603, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 606 (A25);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 608, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 611 (A26);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 613 (A27);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 392, HCDR2 comprising the amino acid sequence of SEQ ID NO: 394, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 616, LCDR2 comprising the amino acid sequence of SEQ ID NO: 617, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 619 (A28);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 621, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A29);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 608, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 624 (A30);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 396, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 625, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 627 (A31);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 398, HCDR2 comprising the amino acid sequence of SEQ ID NO: 400, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 402; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 625, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 630 (A32);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 405, HCDR2 comprising the amino acid sequence of SEQ ID NO: 406, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 408; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 631, LCDR2 comprising the amino acid sequence of SEQ ID NO: 632, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 634 (A33);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence

of SEQ ID NO: 411, HCDR2 comprising the amino acid sequence of SEQ ID NO: 413, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 415; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 636, LCDR2 comprising the amino acid sequence of SEQ ID NO: 639, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 641 (A34);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 603, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 643 (A35);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 420, HCDR2 comprising the amino acid sequence of SEQ ID NO: 422, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 424; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 645, LCDR2 comprising the amino acid sequence of SEQ ID NO: 647, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 649 (A36);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 651, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 653 (A37);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 427, HCDR2 comprising the amino acid sequence of SEQ ID NO: 429, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 654, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A38);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 432, HCDR2 comprising the amino acid sequence of SEQ ID NO: 434, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 624 (A39);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 436, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and

HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 659, LCDR2 comprising the amino acid sequence of SEQ ID NO: 582, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 662 (A40);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 531, LCDR2 comprising the amino acid sequence of SEQ ID NO: 663, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 665 (A41);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 667, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 669 (A42);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 320, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 670, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 673 (A43);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 674 (A44);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 441, HCDR2 comprising the amino acid sequence of SEQ ID NO: 442, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 675, LCDR2 comprising the amino acid sequence of SEQ ID NO: 553, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 643 (A45);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 444, HCDR2 comprising the amino acid sequence of SEQ ID NO: 446, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable

region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 678, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 682 (A46);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 449, HCDR2 comprising the amino acid sequence of SEQ ID NO: 451, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 453; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 684, LCDR2 comprising the amino acid sequence of SEQ ID NO: 685, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 687 (A47);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 456, HCDR2 comprising the amino acid sequence of SEQ ID NO: 458, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 689 (A48);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 460, HCDR2 comprising the amino acid sequence of SEQ ID NO: 462, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 690, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 693 (A49);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 465, HCDR2 comprising the amino acid sequence of SEQ ID NO: 467, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 696 (A50);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 470, HCDR2 comprising the amino acid sequence of SEQ ID NO: 472, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 697 (A51);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 475, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 698, LCDR2

comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 627 (A52);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 478, HCDR2 comprising the amino acid sequence of SEQ ID NO: 480, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 514, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 696 (A53);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 704, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A54);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A55/A69/A77/A77-1/A79/A82);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 359; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 711, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A56);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 486, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 678, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 682 (A57);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 489, HCDR2 comprising the amino acid sequence of SEQ ID NO: 491, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 492; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 714, LCDR2 comprising the amino acid sequence of SEQ ID NO: 716, and LCDR3 comprising the amino

acid sequence of SEQ ID NO: 718 (A58);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 719 (A59);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 512, LCDR2 comprising the amino acid sequence of SEQ ID NO: 609, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 719 (A60);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 494, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A61/A62);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 495, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A63);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 496, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A64/A65);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 497, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A66); or

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 498, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (A67/A68).

[Claim 8]

The fusion protein according to claim 7, wherein the first domain comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2 (A1),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 (A2),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6 (A3),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8 (A4),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 9 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10 (A5),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 11 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12 (A6),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 13 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (A7),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 15 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 16 (A8),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 17 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18 (A9),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 20 (A10),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 21 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22 (A11),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 24 (A12),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 26 (A13),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28 (A14),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (A15), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32 (A16), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 33 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 34 (A17), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 36 (A18), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 37 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 38 (A19), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 39 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 40 (A20), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 41 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 42 (A21), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 43 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 44 (A22), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 45 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 46 (A23), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 47 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 48 (A24), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 49 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (A25), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 51 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 52 (A26), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 54 (A27), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56 (A28), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 57 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58 (A29), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60 (A30), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 61 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 62 (A31), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 63 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 64 (A32), a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65

and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 66 (A33),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 68 (A34),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 70 (A35),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 72 (A36),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 74 (A37),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 75
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 76 (A38),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 77
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78 (A39),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80 (A40),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82 (A41),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 84 (A42),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 85
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86 (A43),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 87
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 88 (A44),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 89
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 90 (A45),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 92 (A46),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94 (A47),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 95
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96 (A48),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 97
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98 (A49),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 99
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100 (A50),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 101
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102 (A51),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 103 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 104 (A52),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 105 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 106 (A53),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 107 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 108 (A54),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 109 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A55/A82),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 111 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 112 (A56),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 113 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 114 (A57),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 115 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 116 (A58),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 109 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 117 (A59),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 117 (A60),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A61),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A62),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 121 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A63),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 122 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A64),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 123 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A65),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 124 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A66),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A67),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 126 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (A68),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110

(A69/A77/A77-1), or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 143 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 144 (A79).

[Claim 9]

The fusion protein according to claim 5, wherein the antibody fragment comprises a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 291, HCDR2 comprising the amino acid sequence of SEQ ID NO: 293, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295 (A78).

[Claim 10]

The fusion protein according to claim 9, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 142 (A78).

[Claim 11]

The fusion protein according to claim 5, wherein the first domain comprises:

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 721, HCDR2 comprising the amino acid sequence of SEQ ID NO: 723, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 725; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 763, LCDR2 comprising the amino acid sequence of SEQ ID NO: 765, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 767 (A70/A81);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 727, HCDR2 comprising the amino acid sequence of SEQ ID NO: 729, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 731; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 770, LCDR2 comprising the amino acid sequence of SEQ ID NO: 772, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 774 (A71);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 733, HCDR2 comprising the amino acid sequence of SEQ ID NO: 735, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 736; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 775, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 778 (A72);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 738, HCDR2 comprising the amino acid sequence of SEQ ID NO: 740, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 742; and a light chain variable

region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 781, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 784 (A73);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 745, HCDR2 comprising the amino acid sequence of SEQ ID NO: 747, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 749; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 786, LCDR2 comprising the amino acid sequence of SEQ ID NO: 788, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 790 (A74);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 751, HCDR2 comprising the amino acid sequence of SEQ ID NO: 753, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 755; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 792, LCDR2 comprising the amino acid sequence of SEQ ID NO: 794, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 796 (A75); or

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 757, HCDR2 comprising the amino acid sequence of SEQ ID NO: 759, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 761; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 799 (A76).

[Claim 12]

The fusion protein according to claim 11, wherein the fusion protein comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 127 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 128 (A70/A81),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 129 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130 (A71),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 131 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 132 (A72),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 133 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 134 (A73),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 136 (A74),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 137 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 138 (A75),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 140 (A76).

[Claim 13]

The fusion protein according to claim 4, wherein the first domain is a peptide.

[Claim 14]

The fusion protein according to claim 13, wherein the first domain comprises the amino acid sequence of SEQ ID NO: 145 (A80/A80-1).

[Claim 15]

The fusion protein according to claim 1, wherein the immune modulator is a cytokine or a chemokine or a fragment thereof.

[Claim 16]

The fusion protein according to claim 1, wherein the second domain comprises a site that binds to any one selected from the group consisting of 4-1-BB, 5T4, ACE, ADAM9, ADRB3, AKAP4, ALK, ANXA1, ANXA2, ANXA5, ASCT2, AXL, B7H3, B7H4, BCL2, BCMA, CA125, CA6, CA9, CCL11, CCR5, CEN106, CD2, CD4, CD5, CD15, CD16, CD19, CD20, CD22, CD23, CD24, CD25, CD27, CD30, CD33, CD37, CD38, CD40, CD41, CD44, CD44v6, CD46, CD48, CD51, CD52, CD54, CD56, CD62, CD70, CD71, CD72, CD73, CD74, CD79, CD80, CD90, CD97, CD99, CD105, CD117, CD123, CD133, CD135, CD138, CD142, CD163, CD171, CD205, CD242, CD319, CD352, CDCP1, CEA, CLDN3, CLDN6, CLDN9, CLDN18.2, CXCR2, CXCR4, CXCR5, CFC1B, CEACAM5, CEACAM6, c-Met, c-Kit, CTLA4, DLL3, DLK-1, DR5, DPEP3, Dectin-2, ED-B, EGFR, Endothelin-1, Endoglin, ENPP3, EpCAM, EphA2, ETA, FAPα, FGFR1, FGFR2, FGFR3, FRα, GD2, GD3, GloboH, GPC3, GPR20, GPRC5D, HER2, HER3, ICAM1, ICAM2, ICOS-L, IGF-1R, KAAG-1, L1CAM, LCK, LGR5, LIV-1, LRRC15, LY6E, MAGE, Mesothelin, MUC1, MUC16, MMP-14, NCAM1, Nectin-4, Notch3, NaPi2b, PDGFR, PD-L1, PD-L2, PSCA, PSMA, PTK7, RAGE-1, RANKL, RNF43, RON, ROR1, ROR2, SAP-1, SLAMF7, SLC44A4, Survivin, SAIL, STn, SSEA-4, SEZ6, SLC44A4, SLTRK6, TEM1, TEM8, TM4SF1, TNFLYPD3, TF, TIE2, TIM-1, TRAC, TROP-2, VEGFR1 (FLT1), VEGFR2 (KDR), VCAM-1, VSIG4, VISTA, and XAGE-1.

[Claim 17]

The fusion protein according to claim 1, wherein the second domain is any one selected from the group consisting of an antibody or a fragment thereof, a ligand or a fragment thereof,

and a receptor or a fragment thereof.

[Claim 18]

The fusion protein according to claim 17, wherein the second domain is an antibody or a fragment thereof.

[Claim 19]

The fusion protein according to claim 18, wherein the second domain comprises:

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 802, HCDR2 comprising the amino acid sequence of SEQ ID NO: 804, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 806; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 913, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 915 (C1/C2);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 809, HCDR2 comprising the amino acid sequence of SEQ ID NO: 811, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 813; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 918, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 922 (C3/C4);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 815, HCDR2 comprising the amino acid sequence of SEQ ID NO: 817, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 819; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 926, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 929 (C5/C6);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 821, HCDR2 comprising the amino acid sequence of SEQ ID NO: 823, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 825; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 932, LCDR2 comprising the amino acid sequence of SEQ ID NO: 934, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 936 (C7/C8);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 829, HCDR2 comprising the amino acid sequence of SEQ ID NO: 832, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 834; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 939, LCDR2 comprising the amino acid sequence of SEQ ID NO: 941, and LCDR3 comprising the amino

acid sequence of SEQ ID NO: 943 (C9/C10);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 838, HCDR2 comprising the amino acid sequence of SEQ ID NO: 840, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 842; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 903, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 906 (C11/C12/C30);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 844, HCDR2 comprising the amino acid sequence of SEQ ID NO: 846, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 848; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 937 (C13/C14);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 850, HCDR2 comprising the amino acid sequence of SEQ ID NO: 852, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 854; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 948, LCDR2 comprising the amino acid sequence of SEQ ID NO: 949, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 951 (C15);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 855, HCDR2 comprising the amino acid sequence of SEQ ID NO: 857, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 858; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 952, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 954 (C16);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 757, HCDR2 comprising the amino acid sequence of SEQ ID NO: 759, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 761; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 799 (C17/C18);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 417, HCDR2 comprising the amino acid sequence of SEQ ID NO: 351, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 295; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 708, LCDR2 comprising the amino acid sequence of SEQ ID NO: 540, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 602 (C19);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 861, HCDR2 comprising the amino acid sequence of SEQ ID NO: 863, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 865; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 957, LCDR2 comprising the amino acid sequence of SEQ ID NO: 958, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 960 (C20);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 866, HCDR2 comprising the amino acid sequence of SEQ ID NO: 868, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 870; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 962, LCDR2 comprising the amino acid sequence of SEQ ID NO: 964, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 966 (C21/C29);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 872, HCDR2 comprising the amino acid sequence of SEQ ID NO: 874, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 876; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 968, LCDR2 comprising the amino acid sequence of SEQ ID NO: 559, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 971 (C22);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 878, HCDR2 comprising the amino acid sequence of SEQ ID NO: 880, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 882; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 973 (C23);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 721, HCDR2 comprising the amino acid sequence of SEQ ID NO: 723, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 725; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 763, LCDR2 comprising the amino acid sequence of SEQ ID NO: 765, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 767 (C24);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 751, HCDR2 comprising the amino acid sequence of SEQ ID NO: 753, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 755; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 792, LCDR2 comprising the amino acid sequence of SEQ ID NO: 794, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 796 (C25);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence

of SEQ ID NO: 884, HCDR2 comprising the amino acid sequence of SEQ ID NO: 886, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 888; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 975, LCDR2 comprising the amino acid sequence of SEQ ID NO: 977, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 979 (C26);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 890, HCDR2 comprising the amino acid sequence of SEQ ID NO: 892, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 894; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 580, LCDR2 comprising the amino acid sequence of SEQ ID NO: 566, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 981 (C27);

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 895, HCDR2 comprising the amino acid sequence of SEQ ID NO: 898, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 900; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 982, LCDR2 comprising the amino acid sequence of SEQ ID NO: 680, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 984 (C28/C31); or

a heavy chain variable region comprising HCDR1 comprising the amino acid sequence of SEQ ID NO: 908, HCDR2 comprising the amino acid sequence of SEQ ID NO: 910, and HCDR3 comprising the amino acid sequence of SEQ ID NO: 912; and a light chain variable region comprising LCDR1 comprising the amino acid sequence of SEQ ID NO: 986, LCDR2 comprising the amino acid sequence of SEQ ID NO: 920, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 989 (C33).

[Claim 20]

The fusion protein according to claim 19, wherein the second domain comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 185 (C1),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 186 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 187 (C2),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 188 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 189 (C3),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 190 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 191 (C4),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 192 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 193 (C5),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 194

and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 195 (C6),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 196
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 197 (C7),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 198
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 199 (C8),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 200
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 201 (C9),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 202
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 203 (C10),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 204
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 205 (C11/C30),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 206
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 207 (C12),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 208
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 209 (C13),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 210
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 211 (C14),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 212
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 213 (C15),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 214
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 215 (C16),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 139
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 140 (C17),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 216
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 217 (C18),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 109
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110 (C19),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 218
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 219 (C20),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 220
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 221 (C21),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 222
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 223 (C22),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 224
and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 225 (C23),
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 127

and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 128 (C24),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 137 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 138 (C25),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 226 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 227 (C26),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 228 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 229 (C27),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 230 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 231 (C28/C32),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 232 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 233 (C29),

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 237 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 236 (C31), or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 239 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 240 (C33).

[Claim 21]

The fusion protein according to claim 1, wherein the first domain and the second domain are linked via a linker.

[Claim 22]

The fusion protein according to claim 21, wherein the linker is a cleavable linker or a non-cleavable linker.

[Claim 23]

The fusion protein according to claim 21, wherein the cleavable linker comprises any one selected from the group consisting of SEQ ID NO: 159 to SEQ ID NO: 176, and combinations thereof.

[Claim 24]

The fusion protein according to claim 1, wherein the fusion protein comprises the following structural formulas (I) and (II):

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-C' (I);

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I) and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L1, L2', L2", and L3 are each independently peptide linkers, wherein L2' and L2" are cleavable or non-cleavable, and

a, b, c, and d are each independently 0 or 1.

[Claim 25]

The fusion protein according to claim 1, wherein the fusion protein comprises the following structural formulas (IV) and (V):

N'-T2-(L7)-I2'-((L8)f-CR1)g-C' (IV);

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV) and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L7 and L8 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and z are each independently 0 or 1, wherein g and h are identical.

[Claim 26]

The fusion protein according to claim 24 or 25, wherein the fusion protein further comprises an anticancer agent.

[Claim 27]

The fusion protein according to claim 26, wherein the anticancer agent is linked to the fusion protein via a linker.

[Claim 28]

The fusion protein according to claim 27, wherein the linker is a non-cleavable linker or a cleavable linker.

[Claim 29]

The fusion protein according to claim 1, wherein the fusion protein further comprises an Fc region or a variant thereof.

[Claim 30]

The fusion protein according to claim 29, wherein the fusion protein comprises the following structural formulas (I') and (II):

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-Fc region or variant thereof-C' (I'); and

N'-T1''-((L1)a-CR2)b-(L2'')-I1''-((L3)c-CR4)d-C' (II)

in the structural formulas (I') and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L1, L2', L2", L3, and L5 are peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, and d are each independently 0 or 1.

[Claim 31]

The fusion protein according to claim 29, wherein the fusion protein comprises the following structural formulas (IV') and (V):

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-Fc region or variant thereof-C' (IV');

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV') and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

L7, L8, and L9 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, and h are each independently 0 or 1, wherein g and h are identical.

[Claim 32]

The fusion protein according to claim 30 or 31, wherein the fusion protein further comprises an antigen binding site.

[Claim 33]

The fusion protein according to claim 32, wherein the antigen binding site is linked to the fusion protein via a linker.

[Claim 34]

The fusion protein according to claim 32, wherein the fusion protein comprises the following structural formulas (I") and (II):

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-Fc region or variant thereof-(L6)e-O-C' (I"); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I") and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

O is an antigen binding site,

L1, L2', L2", L3, L5, and L6 are each independently peptide linkers, wherein L2' and

L2" are cleavable or non-cleavable linkers, and

a, b, c, d, and e are each independently 0 or 1.

[Claim 35]

The fusion protein according to claim 32, wherein the fusion protein comprises the following structural formulas (IV") and (V):

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-Fc region or variant thereof-(L10)i-P-C' (IV");

N'-I2"-((L8)f-CR2)h-C' (V)

in the structural formulas (IV") and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

P is an antigen binding site,

L7, L8, L9, and L10 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and i are each independently 0 or 1.

[Claim 36]

A fusion protein dimer in which the two fusion proteins selected from the group consisting of claims 30, 31, 34, and 35 are linked to each other.

[Claim 37]

The fusion protein dimer according to claim 36, wherein the fusion protein dimer is a homodimer or a heterodimer.

[Claim 38]

A fusion protein dimer in which the fusion protein according to any one selected from

the group consisting of claims 30, 31, 34, and 35; and the fusion protein comprising the following structural formulas (VI) and (VII) are linked to each other:

N'-I3'-(L11)k-CR1-(L12)-Fc region or variant thereof-((L13)l-V)m-C' (VI); and

N'-I3"-(L11)k-CR2-C' (VII)

in the structural formulas (VI) and (VII),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

I3' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I3" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I3' and I3" form a binding site (I3) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

V is an antigen binding site,

L11, L12, and L13 are each independently peptide linkers, and

k, l, and m are each independently 0 or 1.

[Claim 39]

A fusion protein dimer in which the fusion protein according to any one selected from the group consisting of claims 30, 31, 34, and 35; and the fusion protein comprising the following structural formula (VIII) are linked to each other:

N'-I3'"-(L14)-Fc region or variant thereof-((L15)n-W)o-C' (VIII)

in the structural formula (VIII),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

I3'" is an antibody fragment that specifically binds to the second target,

W is an antigen binding site,

L14 and L15 are each independently peptide linkers, and

n and o are each independently 0 or 1.

[Claim 40]

The fusion protein according to claim 1, wherein the fusion protein is a fusion protein in which the Fc region of the fusion protein according to claim 30 or 31 or a variant thereof is substituted with an antigen binding site.

[Claim 41]

The fusion protein according to claim 40, wherein the antigen binding site is a heavy chain variable region or a light chain variable region of an antibody.

[Claim 42]

The fusion protein according to claim 41, wherein the fusion protein comprises the following structural formulas (I''') and (II):

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-(L18)s-Q'-C' (I''); and

N'-T1''-((L1)a-CR2)b-(L2'')-I1''-((L3)c-CR4)d-C' (II)

in the structural formulas (I''') and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1'' are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1'' are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

Q' is a heavy chain variable region (VH) of an antibody that specifically binds to a third target,

L1, L2', L2'', L3, L5, and L18 are each independently peptide linkers, wherein L2' and L2'' are cleavable or non-cleavable linkers, and

a, b, c, d, and s are each independently 0 or 1, wherein b and d are identical.

[Claim 43]

The fusion protein according to claim 41, wherein the fusion protein comprises the

following structural formulas (I"") and (II):

N'-T1'-((L1)a-CR1)b-(L2')-I1'-((L3)c-CR3)d-(L5)-(L18)s-Q"-C' (I""); and

N'-T1"-((L1)a-CR2)b-(L2")-I1"-((L3)c-CR4)d-C' (II)

in the structural formulas (I"") and (II),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the first target,

T1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the first target,

T1' and T1" are linked to each other to form a binding site (T1) that specifically binds to the first target,

I1' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I1" is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I1' and I1" are linked to each other to form a binding site (I1) that specifically binds to the second target,

CR1, CR2, CR3, and CR4 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical, and CR3 and CR4 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

Q" is a light chain variable region (VL) of an antibody that specifically binds to a target,

L1, L2', L2", L3, L5, and L18 are each independently peptide linkers, wherein L2' and L2" are cleavable or non-cleavable linkers, and

a, b, c, d, and s are each independently 0 or 1, wherein b and d are identical.

[Claim 44]

The fusion protein according to claim 42 or 43, wherein Q' in claim 42 and Q" in claim 43 are linked to each other to form an antigen binding site (Q) of an antibody that binds to the third target.

[Claim 45]

The fusion protein according to claim 44, wherein the third target is a protein that is overexpressed or specifically expressed or activated in target cells at a disease site.

[Claim 46]

The fusion protein according to claim 41, wherein the fusion protein comprises the following structural formulas (IV''') and (V):

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L9)-(L19)t-S'-C' (IV''');

N'-I2''-((L8)f-CR2)h-C' (V)

in the structural formulas (IV''') and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2'' are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

S' is a heavy chain variable region (VH) of an antibody that specifically binds to a fourth target,

L7, L8, L9, and L19 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and t are each independently 0 or 1, wherein g and h are identical.

[Claim 47]

The fusion protein according to claim 41, wherein the fusion protein comprises the following structural formulas (IV'''') and (V):

N'-T2-(L7)-I2'-((L8)f-CR1)g-(L10)-S''-C' (IV'''');

N'-I2''-((L8)f-CR2)h-C' (V)

in the structural formulas (IV'''') and (V),

N' is the N-terminus of the fusion protein,

C' is the C-terminus of the fusion protein,

T2 is a peptide or an antibody fragment that specifically binds to the first target,

I2' is a heavy chain variable region (VH) or a light chain variable region (VL) that specifically binds to the second target,

I2'' is a light chain variable region (VL) or a heavy chain variable region (VH) that specifically binds to the second target,

I2' and I2" are linked to each other to form a binding site (I2) that specifically binds to the second target,

CR1 and CR2 are each independently CH1 or CL,

wherein CR1 and CR2 are not identical,

CH1 is a heavy chain constant region, and

CL is a light chain constant region,

S" is a light chain variable region (VL) of an antibody that specifically binds to a fourth target,

L7, L8, L10, and L19 are each independently peptide linkers, wherein L7 is a cleavable or non-cleavable linker, and

f, g, h, and t are each independently 0 or 1, wherein g and h are identical.

[Claim 48]

The fusion protein according to claim 46 or 47, wherein S' in claim 46 and S" in claim 47 are linked to each other to form an antigen binding site (S) that binds to a fourth target.

[Claim 49]

The fusion protein according to claim 48, wherein the fourth target is a protein that is overexpressed or specifically expressed or activated in target cells at a disease site.

[Claim 50]

A fusion protein dimer in which the fusion protein according to claim 42 or 46; and the fusion protein according to claim 43 or 47 are linked to each other.

[Claim 51]

A polynucleotide encoding the fusion protein according to any one of claims 1 to 35 and claims 40 to 49.

[Claim 52]

A polynucleotide encoding the fusion protein dimer according to any one of claims 36 to 39 and claim 50.

[Claim 53]

A vector comprising the polynucleotide according to claim 51 or 52.

[Claim 54]

A transformed cell into which the vector according to claim 53 has been introduced.

[Claim 55]

A method for producing a fusion protein or a fusion protein dimer, the method comprising the steps of:

i) culturing the transformed cell according to claim 54; and

ii) obtaining the fusion protein or the fusion protein dimer from the cell culture solution.

[Claim 56]

A fusion protein-drug conjugate comprising the following structural formula (IX):

X-[(L16)-Y]p (IX)

in the structural formula (IX),

X is the fusion protein according to any one of claims 24, 25, 30, 31, 34, 35, and 42 to 49,

Y is a drug,

L16 is a linker, and

p is 0 or 1.

[Claim 57]

The fusion protein-drug conjugate according to claim 56, wherein the drug is an anticancer agent.

[Claim 58]

A fusion protein dimer-drug conjugate comprising the following structural formula (IX'):

X'-[(L17)-Z]q (IX')

in the structural formula (IX'),

X' is the fusion protein dimer according to any one of claims 36 to 39 and 50,

Z is a drug,

L17 is a linker, and

q is 0 or 1.

[Claim 59]

The fusion protein dimer-drug conjugate according to claim 58, wherein the drug is an anticancer agent.

[Claim 60]

A pharmaceutical composition for the prevention or treatment of a disease, comprising the fusion protein according to claim 1; the fusion protein dimer according to any one of claims

36 to 39 and 50; the fusion protein-drug conjugate according to claim 56; or the fusion protein dimer-drug conjugate according to claim 58 as an active ingredient.

[Claim 61]

The pharmaceutical composition according to claim 60, wherein the disease is cancer or a degenerative brain disease.

[Claim 62]

The pharmaceutical composition according to claim 61, wherein the cancer is any one selected from the group consisting of gastric cancer, liver cancer, lung cancer, large intestine cancer, breast cancer, prostate cancer, gallbladder cancer, bladder cancer, kidney cancer, esophageal cancer, skin cancer, rectal cancer, osteosarcoma, multiple myeloma, glioma, ovarian cancer, pancreatic cancer, cervical cancer, endometrial cancer, thyroid cancer, laryngeal cancer, testicular cancer, mesothelioma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, brain tumor, neuroblastoma, retinoblastoma, head and neck cancer, salivary gland cancer, and lymphoma.

[Claim 63]

The pharmaceutical composition according to claim 61, wherein the degenerative brain disease is any one selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, mild cognitive impairment, cerebral amyloid angiopathy, Down syndrome, amyloid stroke, systemic amyloid disease, Dutch amyloidosis, Niemann-Pick disease, senile dementia, amyotrophic lateral sclerosis, spinocerebellar atrophy, Tourette's syndrome, Friedrich's ataxia, Machado-Joseph's disease, Lewy body dementia, dystonia, progressive supranuclear palsy, and frontotemporal dementia.

[Claim 64]

A cleavable peptide comprising any one amino acid sequence selected from the group consisting of SEQ ID NOs: 159, 160, 173 to 176, and combinations thereof.

[Claim 65]

The cleavable peptide according to claim 64, wherein the cleavable peptide is characterized by being cleaved by a proteolytic enzyme that is specifically overexpressed or overactivated at a disease site compared to a non-disease site.

[Claim 66]

The cleavable peptide according to claim 65, wherein the cleavable peptide is cleaved by

any one proteolytic enzyme selected from the group consisting of MMP-2, MMP-9, uPA, MT-SP1, MMP-3, MMP-7, and combinations thereof.

[Claim 67]

A use of the fusion protein according to claim 1; the fusion protein dimer according to any one of claims 36 to 39 and 50; the fusion protein-drug conjugate according to claim 56; or the fusion protein dimer-drug conjugate according to claim 58 for the prevention or treatment of a disease.

[Claim 68]

A method for the prevention or treatment of a disease, comprising administering the fusion protein according to claim 1; the fusion protein dimer according to any one of claims 36 to 39 and 50; the fusion protein-drug conjugate according to claim 56; or the fusion protein dimer-drug conjugate according to claim 58 to a subject.