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LINKED TO IMMUNE ACTIVATOR FOR
CANCER TREATMENT**(71) Applicant: **TORAY INDUSTRIES, INC.**, Tokyo
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(57) **ABSTRACT**

The present invention provides a conjugate of an antibody or a fragment thereof linked to an immune activator, wherein the antibody or the fragment thereof has immunological reactivity with a CAPRIN-1 protein, and a pharmaceutical composition comprising the conjugate as an active ingredient for treatment and/or prevention of a cancer which is superior in antitumor activity to conventional antibodies or conjugates of an antibody and an immune activator.

Specification includes a Sequence Listing.

CONJUGATE OF CAPRIN-1 ANTIBODY LINKED TO IMMUNE ACTIVATOR FOR CANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of copending application Ser. No. 16/344,689, filed on Apr. 24, 2019, is the National Phase of PCT International Application No. PCT/JP2017/038986, filed on Oct. 27, 2017, which claims priority under 35 U.S.C. § 119 (a) to Application No. 2016-211376, filed in Japan on Oct. 28, 2016, all of which are hereby expressly incorporated by reference into the present application.

REFERENCE TO ELECTRONIC SEQUENCE LISTING

[0002] This application contains a Sequence Listing which has been submitted electronically in .XML format and is hereby incorporated by reference in its entirety. Said .XML copy, created on Apr. 14, 2025, is named “1254-0620PUS2.xml” and is 364,594 bytes in size. The sequence listing contained in this .XML file is part of the specification and is hereby incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0003] The present invention relates to a conjugate of an antibody against a CAPRIN-1 protein and an immune activator, and medical use thereof as a therapeutic and/or preventive agent for a cancer, etc.

BACKGROUND ART

[0004] Various antibody drugs targeting specific antigenic proteins on cancer cells are applied as therapeutic drugs for cancers with fewer adverse reactions to cancer treatment because of their cancer specificity. For example, cytoplasmic-activation and proliferation-associated protein 1 (CAPRIN-1) is expressed on the cell membrane surface of many solid cancers, and antibodies against this CAPRIN-1 protein have been known to be promising in medical use for the treatment and/or prevention of cancers (Patent Literature 1). [0005] In recent years, studies have been made to enhance the pharmacological effects of the antibody drugs. Particularly, antibody-drug conjugates (ADCs) in which an antibody is conjugated with a drug having the strong ability to directly kill cells have been actively developed (Non Patent Literatures 1 and 2). As examples of ADCs, Kadcyla® (trastuzumab emtansine) comprising an existing antibody drug trastuzumab linked to a drug emtansine (DM1) which exhibits a cell-killing activity, and Adcetris® (brentuximab vedotin) comprising an anti-CD30 monoclonal antibody linked to monomethyl auristatin E (MMAE) are used in the treatment of some cancers. These ADCs have been found to prolong survival rates as compared with conventional treatment methods and found to be useful over existing methods for treating cancers (Non Patent Literatures 3 and 4).

[0006] In other cases, studies have also been made in an attempt to enhance pharmacological effects by conjugating immune activators to antibody drugs against cancers. For example, a conjugate of an existing antibody drug trastuzumab or cetuximab with resiquimod, one of the immune activators, or conjugates of an antibody drug rituximab against CD20 as a target antigen with various

immune activators have been found to have an effect of enhancing the pharmacological effect of the antibody in animal models (Patent Literatures 2 and 3).

[0007] As described above, attempts have been made to enhance the pharmacological effects of antibody drugs against cancers by conjugating various factors to various antibodies. However, antitumor effects strong enough to completely regress various cancers have not yet been obtained. Furthermore, effects of preventing cancer recurrence or metastasis, etc. have not been found.

CITATION LIST

Patent Literature

[0008] Patent Literature 1: WO2010/016526

[0009] Patent Literature 2: WO2014/012479

[0010] Patent Literature 3: U.S. Pat. No. 8,951,528

Non Patent Literature

[0011] Non Patent Literature 1: Lancet Oncol 2016; 17: e254-62

[0012] Non Patent Literature 2: Pharm Res. 2015 November; 32 (11): 3526-40

[0013] Non Patent Literature 3: New England Journal of Medicine 367; 19 (8), 2012, p. 1783-1791.

[0014] Non Patent Literature 4: MAbs 2012; 4 (4): 458-65

SUMMARY OF INVENTION

Technical Problem

[0015] An object of the present invention is to provide a solution to enhance the antitumor effect of an antibody or a fragment thereof against a CAPRIN-1 protein expressed on the cell membrane surface of cancer cells.

Solution to Problem

[0016] The present inventor has conducted diligent studies and consequently completed the present invention by finding that: a conjugate of an antibody or a fragment thereof against a CAPRIN-1 protein and an immune activator exerts a much stronger antitumor effect than that of the antibody against the CAPRIN-1 protein or the fragment thereof used alone; and the effect of enhancing the antitumor effect by conjugating the antibody against the CAPRIN-1 protein or the fragment thereof to the immune activator is much superior to the effect of enhancing the antitumor effect by conjugating an existing antibody drug for a cancer to the immune activator.

[0017] Specifically, the present invention has the following features (1) to (14):

[0018] (1) A conjugate of an antibody or a fragment thereof linked to an immune activator, wherein the antibody or the fragment thereof has immunological reactivity with a CAPRIN-1 protein having an amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence.

[0019] (2) The conjugate according to (1), wherein the antibody or the fragment thereof has immunological reactivity with a partial polypeptide of the CAPRIN-1 protein, wherein the partial polypeptide has an amino acid sequence represented by any of SEQ ID NOs: 31

to 35 and 296 to 299, 308, and 309 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence.

[0020] (3) The conjugate according to (1) or (2), wherein the antibody is a monoclonal antibody or a polyclonal antibody.

[0021] (4) The conjugate according to any of (1) to (3), wherein the antibody or the fragment thereof is any of the following (A) to (M):

[0022] (A) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 36, 37, and 38 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 40, 41, and 42 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0023] (B) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 44, 45, and 46 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 48, 49, and 50 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0024] (C) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 52, 53, and 54 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 56, 57, and 58 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0025] (D) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 60, 61, and 62 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 64, 65, and 66 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0026] (E) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 170, 171, and 172 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 173, 174, and 175 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0027] (F) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 176, 177, and 178 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 179, 180, and 181 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0028] (G) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 182, 183, and 184 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 185, 186, and 187 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0029] (H) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 188, 189, and 190 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 191, 192, and 193 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0030] (I) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 146, 147, and 148 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 149, 150, and 151 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0031] (J) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 272, 273, and 274 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 275, 276, and 277 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0032] (K) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 290, 291, and 292 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 293, 294, and 295 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

[0033] (L) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein, and

[0034] (M) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 134, 135, and 136 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 137, 138, and 139 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein.

acid sequence of SEQ ID NO: 108 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 109,

[0061] (z) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 110 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 111,

[0062] (aa) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 112 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 113,

[0063] (ab) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 115,

[0064] (ac) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 117,

[0065] (ad) an antibody or a fragment thereof, comprising 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: 119,

[0066] (ae) an antibody or a fragment thereof, comprising 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: 121,

[0067] (af) an antibody or a fragment thereof, comprising 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: 123,

[0068] (ag) an antibody or a fragment thereof, comprising 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: 125,

[0069] (ah) an antibody or a fragment thereof, comprising 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: 127,

[0070] (ai) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129,

[0071] (aj) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 131,

[0072] (ak) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 133, and

[0073] (al) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

[0074] (6) The conjugate according to any of (1) to (5), wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, or a single-chain antibody.

[0075] (7) The conjugate according to any of (1) to (6), wherein the immune activator is a ligand or an agonist binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR).

[0076] (8) The conjugate according to (7), wherein the Toll-like receptor (TLR) is TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, or TLR10.

[0077] (9) The conjugate according to (7) or (8), wherein the ligand or the agonist binding to the Toll-like receptor (TLR), or a derivative thereof is any of the following (i) to (vii):

[0078] (i) a TLR2-binding ligand or agonist selected from the group consisting of peptidoglycan, lipoprotein, lipopolysaccharide, and zymosan,

[0079] (ii) a TLR3-binding ligand or agonist selected from the group consisting of poly(I: C) and poly(A: U),

[0080] (iii) a TLR4-binding ligand or agonist selected from the group consisting of lipopolysaccharide (LPS), HSP60, RS09, and MPLA,

[0081] (iv) a TLR5-binding ligand or agonist selected from the group consisting of flagellin and FLA,

[0082] (v) a TLR7- or TLR8-binding ligand or agonist selected from the group consisting of an imidazoquinoline compound and single-stranded RNA,

[0083] (vi) a TLR9-binding ligand or agonist selected from the group consisting of bacterial DNA, non-methylated CpG DNA, hemozoin, ODN1585, ODN1668, and ODN1826, and

[0084] (vii) a TLR10-binding ligand or agonist selected from the group consisting of profilin and a uropathogenic bacterium.

[0085] (10) The conjugate according to any of (1) to (9), wherein the antibody or the fragment thereof is linked to the immune activator via a linker.

[0086] (11) A pharmaceutical composition for the treatment and/or prevention of a cancer, comprising the conjugate according to any of (1) to (10) as an active ingredient.

[0087] (12) The pharmaceutical composition according to (11), wherein the cancer is a cancer expressing s CAPRIN-1 protein on the cell membrane surface.

[0088] (13) The pharmaceutical composition according to (11) or (12), wherein the cancer is a cancer selected from the group consisting of breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, and head and neck cancer.

[0089] (14) A method for treating and/or preventing a cancer, comprising administering the conjugate accord-

ing to any of (1) to (10) or the pharmaceutical composition according to any of (11) to (13) to a subject.

Advantageous Effects of Invention

[0090] The conjugate according to the present invention not only exerts a much stronger antitumor effect than that of an antibody against a CAPRIN-1 protein used alone but is superior in antitumor effect to a known conjugate of an antibody drug for a cancer and an immune activator. Also, the effect of enhancing the antitumor effect by the conjugate according to the present invention is superior to the effect of enhancing the antitumor effect by conjugating an existing antibody drug for a cancer to the immune activator. Thus, the conjugate according to the present invention is effective for the treatment or prevention of a cancer.

DESCRIPTION OF EMBODIMENTS

[0091] The conjugate of an antibody or a fragment thereof against a CAPRIN-1 protein (hereinafter, referred to as an “anti-CAPRIN-1 antibody”) and an immune activator used in the present invention can be evaluated for its antitumor activity, as mentioned later, by examining *in vivo* the inhibition of tumor growth in a cancer-bearing animal.

[0092] In the present invention, the “conjugate” refers to an antibody linked to an immune activator via a covalent bond. The linking between the antibody and the immune activator may be done by a linker.

[0093] The anti-CAPRIN-1 antibody that is a constituent of the conjugate according to the present invention may be a monoclonal antibody or a polyclonal antibody and is preferably a monoclonal antibody. The anti-CAPRIN-1 antibody may be any type of antibody as long as the conjugate of the present invention can exert antitumor activity. The antibody is a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, or a non-human animal antibody.

[0094] The immune activator that is a constituent of the conjugate according to the present invention can be any factor activating immunocytes and is preferably a ligand or an agonist, or a derivative thereof, binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR), more preferably a ligand or an agonist, or a derivative thereof, binding to Toll-like receptor (TLR).

[0095] The subject to be treated and/or prevented for cancer according to the present invention is a mammal such as a human, a pet animal, livestock, or a sport animal, and a preferred subject is a human.

[0096] Hereinafter, the anti-CAPRIN-1 antibody, the immune activator, the conjugate of the anti-CAPRIN-1 antibody and the immune activator, the pharmaceutical composition comprising the conjugate, and the method for treating and/or preventing a cancer using the conjugate, according to the present invention will be described.

<Anti-CAPRIN-1 Antibody>

[0097] Among CAPRIN-1 proteins having an amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30 and having immunological reactivity with the anti-CAPRIN-1 antibody used in the present invention, the amino acid sequences represented by SEQ ID NOs: 6, 8, 10, 12, and 14 are the amino acid sequences of canine CAPRIN-1 proteins; the amino acid

sequence represented by SEQ ID NOs: 2 and 4 are the amino acid sequences of human CAPRIN-1 proteins; the amino acid sequence represented by SEQ ID NO: 16 is the amino acid sequence of a bovine CAPRIN-1 protein; the amino acid sequence represented by SEQ ID NO: 18 is the amino acid sequence of an equine CAPRIN-1 protein; the amino acid sequences represented by SEQ ID NOs: 20 to 28 are the amino acid sequences of mouse CAPRIN-1 proteins; and the amino acid sequence represented by SEQ ID NO: 30 is the amino acid sequence of a chicken CAPRIN-1 protein.

[0098] The anti-CAPRIN-1 antibody used in the present invention may have immunological reactivity with a variant of the CAPRIN-1 protein having 80% or more, preferably 90% or more, more preferably 95% or more, further preferably 99% or more sequence identity to the amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30. In this context, the term “% sequence identity” means a percentage (%) of the number of identical amino acids (or bases) to the total number of amino acids (or bases) when two sequences are aligned so that the maximum degree of similarity can be achieved with or without introducing a gap.

[0099] In the present invention, the anti-CAPRIN-1 antibody that is used for preparing the conjugate means an antibody or a fragment thereof having immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof. In this context, the “immunological reactivity” means the property of the antibody binding to the CAPRIN-1 protein or a partial polypeptide thereof *in vivo*.

[0100] The anti-CAPRIN-1 antibody used in the present invention may be a monoclonal antibody or a polyclonal antibody.

[0101] The polyclonal antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof (anti-CAPRIN-1 polyclonal antibody) can be obtained, for example, by immunizing a mouse, a human antibody-producing mouse, a rat, a rabbit, a chicken, or the like with a naturally occurring CAPRIN-1 protein, or a fusion protein thereof with GST or the like, or a partial peptide thereof and obtaining serum therefrom, and applying the obtained serum to ammonium sulfate precipitation, protein A, protein G, a DEAE ion-exchange column, an affinity column linked to a CAPRIN-1 protein or a partial peptide, or the like.

[0102] As for the full-length CAPRIN-1 protein or the fragment thereof to be used in the immunization, the nucleotide sequences and amino acid sequences of CAPRIN-1 and homologs thereof are available, for example, by accessing GenBank (NCBI, USA) and using an algorithm such as BLAST or FASTA (Karlin and Altschul, Proc. Natl. Acad. Sci. USA, 90:5873-5877, 1993; and Altschul et al., Nucleic Acids Res. 25:3389-3402, 1997). Also, a method for preparing the CAPRIN-1 protein is available with reference to WO2014/012479, or can be carried out using, for example, cells expressing the CAPRIN-1 protein.

[0103] The monoclonal antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof (anti-CAPRIN-1 monoclonal antibody) can be obtained, for example, by: administering SK-BR-3 (breast cancer cells expressing CAPRIN-1) or the full-length CAPRIN-1 protein or the fragment thereof, or the like to a mouse for immunization; fusing spleen cells separated from the mouse with myeloma cells; and selecting a clone producing anti-CAPRIN-1 monoclonal antibodies from among

the obtained fusion cells (hybridomas). The antibody produced from the hybridoma thus selected can be prepared in the same way as the method for purifying the polyclonal antibody mentioned above.

[0104] The antibody used in the present invention includes human antibodies, humanized antibodies, chimeric antibodies, and non-human animal antibodies.

[0105] The human antibody can be obtained by: sensitizing EB virus-infected human lymphocytes, with the protein, protein-expressing cells, or lysates thereof; fusing the sensitized lymphocytes with human-derived myeloma cells such as U266 cells; and obtaining an antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof from the obtained fusion cells.

[0106] The humanized antibody, also called reshaped human antibody, is an engineered antibody. The humanized antibody is constructed by grafting complementarity-determining regions of an antibody derived from an immunized animal onto complementarity-determining regions of a human antibody. A genetic engineering technique commonly used for constructing humanized antibodies is also well-known. Specifically, DNA sequences designed to link complementarity-determining regions of, for example, a mouse or rabbit antibody, to framework regions of a human antibody are synthesized by PCR from several prepared oligonucleotides having overlapping terminal portions. The obtained DNAs are ligated with DNAs encoding human antibody constant regions. The resulting ligation products are incorporated into expression vectors, which are then transferred to hosts for antibody production to obtain the antibody of interest. See, European Patent Application Publication No. EP239400 and International Publication No. WO96/02576). The framework regions of a human antibody connected via the complementarity-determining regions are selected so that the complementarity-determining regions form a favorable antigen-binding site. If necessary, an amino acid in the framework regions of antibody variable regions may be substituted so that the complementarity-determining regions of a reshaped human antibody form an appropriate antigen-binding site (Sato K. et al., Cancer Research 1993, 53:851-856). In addition, these framework regions may be replaced with framework regions derived from various human antibodies (see WO99/51743).

[0107] Antibodies are typically heteromultimeric glycoproteins each comprising at least two heavy chains and two light chains. The antibodies are each composed of two identical light chains and two identical heavy chains. Each heavy chain has a heavy chain variable region at one end, followed by a series of constant regions. Each light chain has a light chain variable region at one end, followed by a series of constant regions. The variable regions contain certain variable regions called complementarity-determining regions (CDRs) and impart binding specificity to the antibody. Portions relatively conserved in the variable regions are called framework regions (FRs). The complete heavy chain and light chain variable regions each contain four FRs connected via three CDRs (CDR1 to CDR3).

[0108] The sequences of human-derived heavy chain and light chain constant regions and variable regions are available from, for example, NCBI (USA; GenBank, UniGene, etc.). For example, the following sequences can be referred to: Accession No. J00228 for a human IgG1 heavy chain constant region; Accession No. J00230 for a human IgG2

heavy chain constant region; Accession Nos. V00557, X64135, X64133, etc., for a human light chain κ constant region; and Accession Nos. X64132, X64134, etc., for a human light chain λ constant region.

[0109] A chimeric antibody is an antibody prepared from a combination of sequences derived from different animals and may be, for example, an antibody composed of heavy chain and light chain variable regions of a mouse antibody and constant regions of heavy chain and light chain variable regions of a human antibody. The chimeric antibody can be prepared using a method known in the art and is obtained, for example, by: ligating DNAs encoding the antibody V regions to DNAs encoding the human antibody C regions; incorporating the resulting ligation products into expression vectors; and transferring the vectors into hosts for antibody production.

[0110] The non-human animal antibody is obtained by immunizing an animal with a sensitizing antigen according to a method known in the art and, as a general method, by intraperitoneally, intracutaneously, or subcutaneously injecting a sensitizing antigen to an animal such as a mouse. For the injection of the sensitizing antigen, the antigen is mixed in an appropriate amount with various adjuvants including CFA (complete Freund's adjuvant), and the mixture is administered to the animal a plurality of times. The animal is immunized and then verified to contain anti-CAPRIN-1 antibodies in serum. The serum can be obtained and applied, as mentioned above, to ammonium sulfate precipitation, protein A, protein G, a DEAE ion-exchange column, an affinity column bound with a CAPRIN-1 protein or a partial peptide, or the like to obtain the non-human animal antibody. In the case of obtaining a monoclonal antibody from a non-human animal, immunocytes can be collected from an immunized animal and subjected to cell fusion with myeloma cells to obtain the monoclonal antibody. The cell fusion between the immunocytes and the myeloma cells can be carried out according to a method known in the art (see Kohler, G. and Milstein, C. Methods Enzymol. (1981) 73, 3-46).

[0111] The antibody used in the present invention may be also obtained as a recombinant antibody produced using a genetic engineering technique by cloning genes of the antibody from a hybridoma; incorporating the antibody genes into appropriate vectors; and transferring the vectors into hosts (see Carl, A. K. Borrebaek, James, W. Lerrick, THERAPEUTIC MONOCLOINAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990).

[0112] The anti-CAPRIN-1 antibody that is used for obtaining the conjugate of the present invention may be an antibody in which an amino acid in a variable region (e.g., FR) or a constant region is substituted with another amino acid. The amino acid substitution is the substitution of one or more, for example, less than 15, less than 10, 8 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less amino acids, preferably 1 to 9 amino acids. The substituted antibody should be an antibody that has the property of specifically binding to the antigen and binding affinity for the antigen equivalent to or greater than those of the corresponding unsubstituted antibody and causes no rejection when applied to humans.

[0113] The anti-CAPRIN-1 antibody used in the present invention is expected to have a stronger antitumor effect, the higher binding affinity for the CAPRIN-1 protein on cancer

cell surface the antibody has. Its association constant (affinity constant) K_a (kon/koff) is preferably at least 10^7 M^{-1} , at least 10^8 M^{-1} , at least $5 \times 10^8 \text{ M}^{-1}$, at least 10^9 M^{-1} , at least $5 \times 10^9 \text{ M}^{-1}$, at least 10^{10} M^{-1} , at least $5 \times 10^{10} \text{ M}^{-1}$, at least 10^{11} M^{-1} , at least $5 \times 10^{11} \text{ M}^{-1}$, at least 10^{12} M^{-1} , or at least 10^{13} M^{-1} .

[0114] The binding activity of the anti-CAPRIN-1 antibody used in the present invention against effector cells can be improved by substituting one, two or several amino acids in the heavy chain constant region of the antibody or by removing fucose added to N-acetylglucosamine in a N-glycoside-linked sugar chain attached to the heavy chain constant region. Such an antibody may have the amino acid substitution alone or may be in a composition comprising a fucosylated antibody.

[0115] The antibody in which one, two or several amino acids in the heavy chain constant region are substituted can be prepared with reference to, for example, WO2004/063351, WO2011/120135, U.S. Pat. No. 8,388,955, WO2011/005481, U.S. Pat. No. 6,737,056, and/or WO2005/063351.

[0116] The antibody lacking fucose added to N-acetylglucosamine in a N-glycoside-linked sugar chain in the heavy chain constant region has been removed, or cells producing the antibody, can be prepared with reference to U.S. Pat. No. 6,602,684, European Patent No. 1914244, and/or U.S. Pat. No. 7,579,170. A composition of the antibody lacking fucose added to N-acetylglucosamine in a N-glycoside-linked sugar chain attached to the heavy chain constant region, and the antibody having the fucose, or cells producing the composition can be prepared with reference to, for example, U.S. Pat. No. 8,642,292.

[0117] Methods for preparing and purifying the anti-CAPRIN-1 polyclonal antibody, the anti-CAPRIN-1 monoclonal antibody, and the antibody used in the present invention, and a method for preparing the CAPRIN-1 protein or the partial polypeptide thereof to be used in immunization can be carried out with reference to WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125630, WO2013/125640, WO2013/147169, WO2013/147176 and WO2015/020212.

[0118] Specific examples of the anti-CAPRIN-1 antibody according to the present invention include anti-CAPRIN-1 antibodies disclosed in WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125630, WO2013/125640, WO2013/147169, WO2013/147176 and WO2015/020212 mentioned above. Preferred examples of the anti-CAPRIN-1 antibody include the following.

[0119] An antibody or a fragment thereof having immunological reactivity with the amino acid sequence represented by SEQ ID NO: 2 or SEQ ID NO: 4 or a partial polypeptide of the CAPRIN-1 protein having an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or

more, still further preferably 99% or more) sequence identity to the amino acid sequence represented by SEQ ID NO: 2 or SEQ ID NO: 4.

[0120] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 31 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 36, 37, and 38 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 40, 41, and 42 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein; an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 140, 141, and 142 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 143, 144, and 145 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 164, 165, and 166 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 167, 168, and 169 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising 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: 43; an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 71; or an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79.

[0121] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 33 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 60, 61, and 62 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 64, 65, and 66 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof comprising 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: 67.

[0122] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAP-

RIN-1 protein having the amino acid sequence represented by SEQ ID NO: 32 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 52, 53, and 54 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 56, 57, and 58 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising 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: 59.

[0123] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 34 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 170, 171, and 172 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 173, 174, and 175 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 176, 177, and 178 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 179, 180, and 181 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 81; or an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83.

[0124] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 35 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 182, 183, and 184 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 185, 186, and 187 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 188, 189, and 190 (CDR1,

CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 191, 192, and 193 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85; or an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87.

[0125] An antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 44, 45, and 46 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 48, 49, and 50 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. Preferably, an antibody or a fragment thereof comprising 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: 51.

[0126] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 296 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 146, 147, and 148 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 149, 150, and 151 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 73.

[0127] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 297 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOS: 272, 273, and 274 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOS: 275, 276, and 277 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 115.

[0128] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 298 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 290, 291, and 292 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 293, 294, and 295 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising 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: 121.

[0129] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 299 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

[0130] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 308 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 134, 135, and 136 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 137, 138, and 139 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0131] An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 309 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a

fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 134, 135, and 136 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 137, 138, and 139 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0132] Also, the following anti-CAPRIN-1 antibodies are preferably used.

[0133] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0134] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 71.

[0135] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 73.

[0136] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 74 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 75.

[0137] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 76 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77.

[0138] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79.

[0139] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 81.

[0140] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83.

[0141] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85.

[0142] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87.

[0143] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 88 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 89.

[0144] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 90 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 91.

[0145] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 92 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 93.

[0146] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 94 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 95.

[0147] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 96 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97.

[0148] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 98 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 99.

[0149] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 100 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 101.

[0150] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 102 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103.

[0151] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 104 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 105.

[0152] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 106 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 107.

[0153] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 108 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 109.

[0154] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 110 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 111.

[0155] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid

sequence of SEQ ID NO: 112 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 113.

[0156] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 115.

[0157] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 117.

[0158] An antibody or a fragment thereof comprising 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: 119.

[0159] An antibody or a fragment thereof comprising 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: 121.

[0160] An antibody or a fragment thereof comprising 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: 123.

[0161] An antibody or a fragment thereof comprising 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: 125.

[0162] An antibody or a fragment thereof comprising 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: 127.

[0163] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129.

[0164] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 131.

[0165] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 133.

[0166] An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

[0167] In Examples mentioned later, conjugates with an immune activator were prepared using the polyclonal antibody or the monoclonal antibody against the full-length CAPRIN-1 protein or a polypeptide of a partial region thereof expressed on the cell membrane surface of cancer cells, and verified to have a strong antitumor effect.

<Immune Activator>

[0168] Herein, the immune activator according to the present invention is a factor activating various immunocytes and means a compound, a nucleic acid, or a naturally occurring compound capable of maintaining or enhancing the immune functions of the cells. In this context, the "immunocytes" are T lymphocytes, B lymphocytes, NK cells, monocytes, dendritic cells, granulocytes, macrophages, myeloid-derived suppressor cells, Langerhans cells and precursor cell groups thereof, and these immunocyte groups present in tumor.

[0169] Specific examples of the immune activator used in the present invention include, but are not particularly limited to, ligands or agonists binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR).

[0170] Specific examples of the ligand or the agonist binding to Toll-like receptor (TLR) include ligands or agonists binding to TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, or TLR10.

[0171] Specific examples of the ligand or the agonist binding to TLR2 include substances selected from the group consisting of peptidoglycan, lipoprotein, lipopolysaccharide, and zymosan.

[0172] Specific examples of the ligand or the agonist binding to TLR3 include substances selected from the group consisting of poly(I: C), poly(A: U) polyICLC (Hiltonol), and Ampligen.

[0173] Specific examples of the ligand or the agonist binding to TLR4 include substances selected from the group consisting of lipopolysaccharide (LPS), HSP60, RS09, MPLA (monophosphoryl lipid A from *Salmonella minnesota* R595), GLA-SE, G100, and MPLA.

[0174] Specific examples of the ligand or the agonist binding to TLR5 include substances selected from the group consisting of flagellin and FLA.

[0175] Specific examples of the ligand or the agonist binding to TLR7 or TLR8 include low-molecular compounds such as imidazoquinoline compounds, and single-stranded RNA. Specific examples thereof include Imiquimod, Resiquimod, Loxorbine, 852A, 854A, S-34240, Motolimod (VTX-2337), DSR-6434, GS-9620, ANA773, AZD8848/DSP-3025, GSK2245035, Gardiquimod, CL264, UC-1V150, CL075, CL097, CL307, CL347, 3M-003, 3M-0043, 3M-052, CL264, IV209, ORN R-2176-dT, Poly (dT), ORN R-0006, ORN R-0002, ORN R-2336, PolyU, ORN R-1886, polyG3, DSR6434, RWJ21757, SM324405, p-IMDQ, m-IMDQ and GSK2245035.

[0176] Specific examples of the ligand or the agonist binding to TLR9 include substances selected from the group consisting of bacterial DNA, non-methylated CpG DNA, hemozoin, ODN1585, ODN1668, ODN1668, lefotolimod (MGN1703), SD-101, CYT003, CPG7909, DUK-CPG-001, and ODN1826.

[0177] Specific examples of the ligand or the agonist binding to TLR10 include substances selected from the group consisting of profilin and uropathogenic bacteria.

[0178] Among the ligands or the agonists binding to Toll-like receptor (TLR), the ligand or the agonist binding to TLR7 or TLR8 is preferably used in the present invention. A TLR7- or TLR8-binding ligand or agonist selected from the group consisting of imidazoquinoline compounds and single-stranded RNA is more preferably used as the ligand or the agonist binding to TLR7 or TLR8, and a TLR7- or

TLR8-binding ligand or agonist selected from imidazoquinoline compounds is further preferably used.

[0179] Preferred specific examples of the imidazoquinoline compound include compounds described in U.S. Pat. No. 8,951,528 and compounds disclosed in WO2015/103989, for example, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine (Imiquimod), 1-(4-amino-2-ethylaminomethylimidazo-[4,5-c]quinolin-1-yl)-2-methylpropan-2-ol (Gardiquimod), N-[4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl]-methanesulfonamide (PF-4878691), 4-amino-2-(ethoxymethyl)-a, a-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Resiquimod), 4-amino-aa-dimethyl-2-methoxyethyl-1H-imidazo[4,5-c]quinoline-1-ethanol, 1-(2-(3-(benzyloxy) propoxy)ethyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, 4-amino-2-ethoxymethyl-aa-dimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol, N-(2-{2-[4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-n'-phenylurea, 1-2-amino-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, 1-{4-[(3,5-dichlorophenyl) sulfonyl]butyl}-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine, N-(2-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-n'-cyclohexylurea, N-[3-{4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl}]propyl]-n'-(3-cyanophenyl)thiourea, N-[3-(4-amino-2-butyl-1H-imidazo[4,5-c]quinolin-1-yl)-2,2-dimethylpropyl] benzamide, 2-butyl-1-[3-(methylsulfonyl) propyl]-1H-imidazo[4,5-c]quinolin-4-amine, though the imidazoquinoline compound is not limited thereto as long as the imidazoquinoline compound binds to TLR7 or TLR8.

[0180] Specific examples of the ligand or the agonist binding to NOD-like receptor (NLR) include M-TriDAP and PGN. Other examples thereof include ligands or agonists against NOD1, for example, Tri-DAP, iE-DAP, and C12-iE. Further examples thereof include ligands or agonists against NOD2, for example, MDP, N-glycosyl-MDP, murabutide, M-TriLYS-D-ASN, M-TriLYS, and L18-MDP.

[0181] Specific examples of the ligand or the agonist binding to RIG-like receptor include 5'ppp-dsRNA, poly (dA:dT), poly(dG:dC), and poly(I:C).

[0182] Specific examples of the ligand or the agonist binding to C-type lectin receptor (CLR) include trehalose 6,6-dibehenate, zymosan, WGP, HKSC, HKCA, and curdlan AL.

<Conjugate of Anti-CAPRIN-1 Antibody and Immune Activator>

[0183] In the present invention, the mode of binding between the anti-CAPRIN-1 antibody and the immune activator in the conjugate of the anti-CAPRIN-1 antibody and the immune activator is not particularly limited as long as it allows antitumor activity against a cancer to be maintained. The mode of binding preferably has a linker structure formed between the anti-CAPRIN-1 antibody and the immune activator.

[0184] In this context, the linker means a compound capable of linking the anti-CAPRIN-1 antibody to the immune activator. Any of various linkers known in the art may be used, or an appropriate chemical modification to the structure of the activator may be used for directly binding the antibody to the activator.

[0185] The details of the type of the linker and the binding method can be basically in accordance with a method known

in the art (see, for example, Greg T. Hermanson Bioconjugate Techniques, Third Edition, WO2004010957, and WO2014/012479).

[0186] In an embodiment of the present invention, examples of reactive groups attached to the anti-CAPRIN-1 antibody, the immune activator, and the linker include the following.

[0187] Examples of the reactive group attached to the amino acid sequence of the antibody or a glycoprotein modifying an amino acid include primary amine (ϵ -amino group), carboxyl, thiol (sulfhydryl), carbonyl(ketone or aldehyde), and hydroxyl unless a special chemical modification is made. The primary amine exists at the N-terminus of a polypeptide or the side chain of a lysine residue and is positively charged under physiological conditions. The primary amine usually exists outside of the protein and can therefore be used in binding without denaturing the structure of the protein. The carboxyl exists at the C-terminus of a polypeptide or the side chain of aspartic acid or glutamic acid. The sulfhydryl exists at the side chain of cysteine and forms a disulfide bond that maintains the higher-order structure of the protein. The ketone or aldehyde group is generated in a glycoprotein by the oxidation of glycosyl with sodium metaperiodate.

[0188] The conjugate of the present invention is prepared by binding the linker to the reactive group of the antibody, binding thereto the immune activator bound with the linker, or directly binding the immune activator to the antibody.

[0189] Examples of the reactive groups attached to the linker and the immune activator include the following.

[0190] Reactive group capable of reacting with the amine: N-hydroxysuccinimide (NHS) ester, imide ester, pentafluorophenyl ester, hydroxymethyl phosphine, isothiocyanate, isocyanate, acyl azide, N-hydroxyl ester, sulfonyl chloride, aldehyde, glyoxal, epoxide, oxirane, carbonate, aryl, imide ester, carbodiimide, and carboxylic anhydride.

[0191] Reactive group capable of reacting with the carboxyl and the amine: carbodiimide, diazoalkane, diazoacetyl compounds, and carbonyldimidazole.

[0192] Reactive group capable of reacting with the thiol: maleimide, haloacetamide, pyridyl disulfide, thiosulfone, vinyl sulfone, haloacetyl, aziridine, acryloyl, and aryl.

[0193] Reactive group capable of reacting with the aldehyde: hydrazide and alkoxymine. Reactive group capable of reacting with the hydroxyl: epoxy, oxirane, carbonyldimidazole, N,N'-disuccinimidyl carbonate, N-hydroxysuccinimidyl chloroformate, and isocyanate.

[0194] Reactive group capable of reacting with the hydroxyl: isocyanate.

[0195] Photoreactive reactive group: diaziridine, aryl azide, aryl, benzophenol, and diazo compounds.

[0196] Specific examples of the linker having the reactive group include the following.

[0197] As a linker having the same reactive group ends, a linker having N-hydroxysuccinimide ester as a reactive group (e.g., Disuccinimidyl Glutarate (DSG), disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl)suberate (BS3), tris-(succinimidyl)aminotriacetate (TSAT), PEGylated bis(sulfosuccinimidyl)suberate (BS(PEG)₅, BS(PEG)₉), dithiobis(succinimidyl propionate) (DSP), (DTSSP), (EGS), (Sulfo-EGS), (DMA), (DMP), (DMS), (DTBP), (DFDNB), (DST), (BSOCOES), (EGS), (Sulfo-EGS)) and a linker

having maleimide as a reactive group (e.g., (BMOE), (BMB), (BMH), (TMEA), (BM(PEG)₂), (BM(PEG)₃), (DTME), and (DMDB)).

[0198] As a linker having different reactive group ends, a linker having NHS ester and maleimide as reactive groups (e.g., AMAS, BMPS, GMBS, Sulfo-MBS, MBS, Sulfo-MBS, SMCC, Sulfo-SMCC, EMCS, Sulfo-EMCS, SMPB, Sulfo-SMPB, SMPH, LC-SMCC, Sulfo-KMUS, SM(PEG)₂, SM(PEG)₄, SM(PEG)₆, SM(PEG)₈, SM(PEG)₁₂, and SM(PEG)₂₄), a linker having NHS ester and pyridylidithiol as reactive groups (e.g., SPDP, LC-SPDP, Sulfo-LC-SPDP, SMPT, PEG4-SPDP, and PEG12-SPDP), a linker having NHS ester and haloacetyl as reactive groups (e.g., SIA, SBAP, SIAB, and Sulfo-SIAB), a linker having NHS ester and aryl azide as reactive groups (e.g., ANB-NOS, Sulfo-SANPAH, and ATFB), a linker having NHS ester and diaziridine as reactive groups (e.g., SDA, Sulfo-SDA, LC-SDA, SDAD, and Sulfo-SDAD), a linker having carbodiimide as reactive groups (e.g., DCC, EDC, EDAC, NHS, and Sulfo-NHS), a linker having maleimide and hydrazide as reactive groups (e.g., BMPH, EMCH, MPBH, and KMUH), a linker having pyridylidithiol and hydrazide as a reactive group (e.g., PDPH), a linker having isocyanate and maleimide as reactive groups (e.g., PMPI), and a linker having NHS ester and psoralen as reactive groups (e.g., SPB).

[0199] As other linkers, a linker containing a polypeptide, for example, Fmoc-Ala-Ala-Asn-PAB, Fmoc-Ala-Ala-Asn (Trt)-PAB, Fmoc-PEG3-Ala-Ala-Asn (Trt)-PAB, Fmoc-PEG4-Ala-Ala-Asn (Trt)-PAB, Fmoc-Ala-Ala-Asn-PAB-PNP, Fmoc-Ala-Ala-Asn (Trt)-PAB-PNP, Azide-PEG4-Ala-Ala-Asn (Trt)-PAB-PNP, Mal-PEG4-Ala-Ala-Asn (Trt)-PAB-PNP, Fmoc-Val-Cit-PAB-OH, Val-Cit-PAB-OH, Fmoc-Val-Cit-PAB-PNP, MC-Val-Cit-PAB, MC-Val-Cit-PAB-PNP.

[0200] Also, Bis-PEG-acid, PEG Acid (e.g., Acid-PEG-TEMPO, Amino-PEG-acid, Amino-PEG-CH₂CO₂H, Aminoxy-PEG-acid, Azido-PEG-acid, Carboxy-PEG-sulfonic acid, Fmoc-N-amido-PEG-acid, Fmoc-N-amido-PEG-CH₂CO₂H, Fmoc-aminoxy-PEG-acid, Hydroxy-PEG-acid, Hydroxy-PEG-CH₂CO₂H, m-PEG-acid, m-PEG-(CH₂)₃-acid, Methoxytrityl-N-PEG-acid, N-methyl-N-(t-Boc)-PEG-acid, Propargyl-PEG-acid, Propargyl-PEG-CH₂CO₂H, Propargyl-PEG-(CH₂)₃-acid, t-Boc-N-amido-PEG-acid, t-Boc-N-amido-PEG-CH₂CO₂H, t-Boc-Aminoxy-PEG-acid, Acid-PEG-PFP ester, Miscellaneous PEG acid), PEG PFP ester (e.g., Acid-PEG-PFP ester, Bis-PEG-PFP ester), Bis-PEG-NHS, PEG Aldehyde (e.g., m-PEG-aldehyde, m-PEG-benzaldehyde, Ald-PEG-acid, Ald-PEG-amine, Ald-PEG-azide, Ald-PEG-NH-Boc, Ald-PEG-NHS ester, Ald-PEG-TFP ester, Ald-PEG-t-butyl ester), PEG Tosylate (e.g., Azido-PEG-Tos, Hydroxy-PEG-Tos, m-PEG-Tos, t-Boc-Aminoxy-PEG-Tos, Trifluoroethyl-PEG-Tos, Tos-PEG-acid, Tos-PEG-CH₂CO₂H, Tos-PEG-alkyne, Tos-PEG-t-butyl ester, Tos-PEG-CH₂CO₂tBu, Tos-PEG-Tos, S-acetyl-PEG6-Tos, N-Tos-N-(t-butoxycarbonyl)-aminoxy-PEG₄-Tos, Ms-PEG-Ms, Ms-PEG-t-butyl ester, PEG-Ms, Propargyl-PEG-Ms), Boc-PEG (e.g., Amino-PEG-t-Boc-Hydrazide, Azido-PEG-t-Boc-Hydrazide, Boc-NH-PEG-NH-Boc, Bromoacetamido-PEG-Boc-amine, m-PEG-ONHBoc, Mal-Alkyl-t-Boc-amine, N-Boc-PEG-alcohol, N-Boc-PEG-bromide, N-methyl-N-(t-Boc)-PEG-acid, t-Boc-N-amido-PEG-acid, t-Boc-N-amido-PEG-CH₂CO₂H, t-Boc-N-Amido-PEG-amine, t-Boc-N-amido-PEG-azide, t-Boc-N-amido-PEG-NHS ester, t-Boc-N-

amido-PEG-sulfonic acid), PEG NHS ester (e.g., Acid-PEG-NHS ester, Azido-PEG-NHS ester, Bis-PEG-NHS, Fmoc-PEG-NHS ester, m-PEG-NHS ester, m-PEG-NHS Carbonate, Mal-PEG-NHS ester, Propargyl-PEG-NHS ester, t-Boc-N-amido-PEG-NHS ester, t-Butoxycarbonyl-PEG-NHS ester), Fmoc-PEG (e.g., Fmoc-N-amido-PEG-acid, Fmoc-NH-PEG-CH₂CO₂H, Fmoc-PEG-NHS ester), Biotin PEG (e.g., Biotin PEG-acid, Biotin PEG-alcohol, Biotin PEG-alkyne, Biotin PEG-amine, Biotin PEG-azide, Biotin PEG-DBCO, Biotin PEG-hydrazide, Biotin-PEG-Mal, Biotin-PEG-NHS, Biotin-EDA-PEG-NHS, Biotin-PEG-oxyamine, Biotin-PEG-PFP, Biotin-EDA-PEG-PFP, Biotin-PEG-Tetrazine, Biotin-PEG-TFP, Azide-SS-biotin, Biotin-PEG3-SS-azide, DBCO-S-S-PEG3-Biotin, Dde Biotin-PEG4-Alkyne, Dde Biotin-PEG4-Azide, Dde Biotin-PEG4-DBCO, Diazo Biotin-PEG3-Alkyne, Diazo Biotin-PEG₃-Azide, Diazo Biotin-PEG3-DBCO, Diol Biotin-PEG₃-Alkyne, Diol Biotin-PEG₃-Azide, PC Biotin-PEG₃-Alkyne, PC-Biotin-PEG₄-PEG₄-Alkyne, PC-Biotin-PEG₄-PEG4-Alkyne, PC Biotin-PEG₃-Azide, PC-Biotin-PEG4-PEG3-Azide, PC-Biotin-PEG4-NHS carbonate, PC DBCO-PEG₃-Biotin, WSPC Biotin-PEG₃-DBCO, Fmoc-Lys (biotin-PEG)-OH, Fmoc-N-amido-(PEG-biotin)-acid, TAMRA-Azide-PEG-Biotin), PEG Phosphonate, Aminoxy PEG (e.g., Aminoxy-PEG-acid, Aminoxy-PEG-alcohol, Aminoxy-PEG-azide, Aminoxy-PEG-bromide, Aminoxy-PEG-methane, Aminoxy-PEG-Propargyl, Aminoxy-PEG-t-butyl ester, Aminoxy-PEG-Thiol, Bis-(Aminoxy)-PEG, t-Boc-Aminoxy-PEG-acid, t-Boc-Aminoxy-PEG-alcohol, t-Boc-Aminoxy-PEG-amine, t-Boc-Aminoxy-PEG-Azide, t-Boc-Aminoxy-PEG-Bromide, t-Boc-aminoxy-PEG-Methane, t-Boc-aminoxy-PEG-Propargyl, t-Boc-aminoxy-PEG-S-Ac, t-Boc-Aminoxy-PEG-Thiol, t-Boc-Aminoxy-PEG-Tos, Fmoc-aminoxy-PEG-acid, Trifluoroethyl-PEG-Aminoxy), Alkyne PEG (e.g., endo-BCN-PEG, exo-BCN-PEG, Propargyl-PEG-acid, Propargyl-PEG-CH₂CO₂H, Propargyl-PEG-(CH₂)₃-acid, Propargyl-PEG-(CH₂)₃-methyl ester, Propargyl-PEG-Acrylate, Propargyl-PEG-Alcohol, Propargyl-PEG-amine, Propargyl-PEG-methylamine, Aminoxy-PEG-Propargyl, Propargyl-PEG-azide, Propargyl-PEG-bromide, Propargyl-PEG-Maleimide, Propargyl-PEG-Ms, Propargyl-PEG-NHS ester, Propargyl-PEG-sulfonic acid, Propargyl-PEG-t-butyl ester, Propargyl-PEG-CH₂CO₂iBu, Propargyl-PEG-thiol, Propargyl-PEG-5-nitrophenyl carbonate, t-Boc-aminoxy-PEG-Propargyl, Bis-Propargyl-PEG, m-PEG-Propargyl), Azido PEG (e.g., Azido-PEG-acid, Azido-PEG-CH₂CO₂H, Azido-PEG-(CH₂)₃-methyl ester, Azido-PEG-Acrylate, Azido-PEG-alcohol, Azido-PEG-(CH₂)₃OH, Azido-PEG-amine, Azido-PEG-azide, Azido-PEG-Maleimide, Azido-PEG-methylamine, Azido-PEG-methyl ester, Azido-PEG-NHS ester, Azido-PEG-CH₂CO₂-NHS, Azido-PEG-oxazolidin-2-one, Azido-PEG-PFP ester, Azido-PEG-phosphonic acid, Azido-PEG-phosphonic acid ethyl ester, Azido-PEG-sulfonic acid, Azido-PEG-t-Boc-Hydrazide, Azido-PEG-t-butyl ester, Azido-PEG-CH₂CO₂t-butyl ester, Azido-PEG-TFP ester, Azido-PEG-Tos, Aminoxy-PEG-azide, Bromo-PEG-azide, Bromoacetamido-PEG-azide, Carboxyrhodamine 110-PEG-Azide, Isothiocyanato-PEG-Azide, Isothiocyanato-PEG-Azide, m-PEG-azide, Propargyl-PEG-azide, TAMRA-PEG-Azide, t-Boc-N-Amido-PEG-Azide, t-Boc-Aminoxy-PEG-Azide, Thiol-PEG-Azide, Trifluoroethyl-PEG-Azide, Azido-PEG-amino acid, Azido-PEG4-4-nitrophenyl carbonate, S-Acetyl-PEG3-Azido, Azide, Trityl-

PEG10-Azide), Alkyne PEG, DBCO-PEG, BCN-PEG, Propargyl-PEG, Bis-PEG-acid, Bis-PEG-NHS, Bis-PEG-PFP, Bis-Propargyl-PEG, Amine-PEG-Amine, Azido-PEG-azide, Bromo-PEG, or Mal PEG may be used.

[0201] The linker between the anti-CAPRIN-1 antibody and the immune activator may be composed of a single linker or composed of a plurality of linkers.

[0202] A method for preparing the conjugate of the anti-CAPRIN-1 antibody and the immune activator according to the present invention includes a method which involves binding the immune activator using a ε-amino group at the lysine side chain of the antibody, and a method which involves binding the immune activator using thiol formed by the reduction treatment of a cysteine residue constituting the disulfide bond of the antibody.

[0203] In the case of using a ε-amino group at the lysine residue of the antibody, for example, a method is used which involves reacting active ester (e.g., N-hydroxysuccinimide ester) therewith to form an amide bond. In this case, since the antibody contains many lysine residues, the binding reaction proceeds nonspecifically.

[0204] In the case of using thiol constituting a disulfide bond present at the cysteine side chain of the antibody, a method is used which involves forming thiol from the disulfide bond on the antibody using a reducing agent such as mercaptoethanol, and reacting the thiol with maleimide or α-haloamide. For example, a method using sulfone phenyloxadiazole, a 4-cyanoethoxyloxy derivative, or the like is used for stabilizing a thiol-mediated bond. These bonds are stable for a longer time than the bond based on the conjugate addition reaction of cysteine with maleimide. Also, a linker having an amino group near an imide group can be used because an imide ring with a thiol group added to maleimide is opened by hydrolysis so that stability is improved owing to the resulting amide bond. In the antibody, the thiols of cysteines form a disulfide bond. Thus, an alternative method involves binding the immune activator, etc. to between two thiols via the thiols. As an example, a cross-linked bond may be formed using a linker having two disulfide bond sites that can be formed from an amide group having two sulfones at the β position, or dibromomaleimide.

[0205] The conjugate of the present invention can be obtained by a method using, for example, the THIOMAB™ technique, which is a method capable of introducing a determined number of thiol groups at a particular site of an antibody (see Nature Biotechnology 26, 925-932 (2008)).

[0206] The conjugate of the present invention can be formed, for example, by reducing the antibody using a reducing agent dithiothreitol (DTT) in a phosphate buffer to obtain an antibody having a reactive thiol group, which is then conjugated with the immune activator. The conjugate can be obtained by adding a thiol group to primary amine at the lysine residue of the antibody by the introduction of a Traut's reagent (2-iminothiolane or N-succinimidyl S-acetylthioacetate (SATA)), instead of the method using a reducing agent.

[0207] The amount of the thiol added to the antibody can be determined, for example, by mixing a sample solution containing 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) and an SH group with a phosphate buffer solution (pH 8.0) and distilled water, adding a solution of DTNB dissolved in a phosphate buffer, a Good's buffer, or a Tris buffer to the mixture, and incubating the resulting mixture for a given

time, followed by the measurement of absorbance at 412 nm (see G. L. Ellman, Arch. Biochem. Biophys., 82, 70 (1959)).

[0208] The thiol group added by the cleavage of the disulfide bond of the antibody through reduction treatment is preferably treated (capped) in order to prevent the formation of a disulfide bond again. The capping can employ, for example, N-ethylmaleimide (NEM) or 2-iodoacetamide (IAA).

[0209] The conjugate through can be constructed binding the immune activator to the antibody using the thiol group added to the antibody according to a method known in the art. Specifically, the binding can be carried out using, for example, a linker reagent having a maleimide group or a bromoacetamide group as a linker reagent specifically binding to the thiol group of the reduced antibody. For example, N-succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC) is used as the linker having a maleimide group. In this case, the N-succinimide group of SMCC can form an amide bond with an amino group present in the immune activator to obtain the conjugate.

[0210] In another embodiment, an amide bond is first formed at an amino group present in the activator using SMCC. Then, the maleimide group of the SMCC bound with the immune activator can be reacted with the thiol group added to the antibody to obtain the conjugate.

[0211] In an alternative embodiment, the conjugate of the antibody and the immune activator may be formed using two linkers. For example, a primary amino group present at the lysine residue of the antibody is bound to the N-succinimide group of SATA (N-succinimidyl-S-acetylthioacetate) via an amide bond to add a thiol group to the antibody. SMCC is reacted with the immune activator containing an amino group or with the immune activator having an amino group added thereto according to an ordinary method to form an amide bond with the N-succinimide group of the SMCC. The maleimide group of the SMCC bound with the immune activator can be reacted with the thiol group of the SATA bound with the antibody to obtain the conjugate.

[0212] In a further alternative embodiment, examples of the preparation of the conjugate of the antibody and the immune activator include a method using maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl(MC-Val-Cit-PAB) as a linker. MC-Val-Cit-PAB is a linker cleavable by intracellular protease (e.g., cathepsin B). A thiol group is added to the antibody dissolved in a phosphate buffer using DTT or the like. Meanwhile, the immune activator having an amino group is reacted with the benzyloxycarbonyl (PAB) in MC-Val-Cit-PAB to prepare an immune activator bound with MC-Val-Cit-PAB, which can then be reacted with the thiol-added antibody mentioned above to obtain the conjugate.

[0213] In a further alternative embodiment, SATA is bound to a primary amino group at the lysine residue of the antibody to add a thiol group thereto. Meanwhile, succinimidyl 3-(2-pyridylidithio) propionate (SPDP) is reacted with the immune activator having an amino group to form an amide bond with the N-succinimide group of the SPDP. In order to obtain a composition comprising the antibody bound with the linker, for example, a peak fraction of a higher molecular weight as compared with the antibody before the binding of the linker can be separated by the application of gel filtration chromatography or the like.

[0214] The number of molecules of the bound immune activator per antibody molecule in the conjugate of the

anti-CAPRIN-1 antibody and the immune activator of the present invention can be characterized using a method such as mass spectrometry, ELISA, electrophoresis, or HPLC based on a method known in the art.

<Antitumor Effect of Conjugate>

[0215] The conjugate of the anti-CAPRIN-1 antibody and the immune activator of the present invention has cytotoxic activity in vitro or in vivo. Accordingly, the antitumor effect of the conjugate of the present invention may be determined by examining its cytotoxic activity against a cancer. The cytotoxic activity can be evaluated by: administering the conjugate to an organism having a cancer; and examining the size of the tumor over time via measuring the size of the tumor after the administration. The antitumor effect of the present invention can also be evaluated by examining a survival rate. Alternatively, the antitumor effect of the present invention may be evaluated by examining the ability to produce a cytokine or a chemokine. The antitumor effect of the conjugate of the present invention can be further determined by examining the prevention of a cancer, the prevention of metastasis, or the prevention of recurrence.

[0216] The conjugate of the present invention is expected to have a stronger antitumor effect, the higher binding affinity for the CAPRIN-1 protein on cancer cell surface the conjugate has. Its association constant (affinity constant) K_a (k_{on}/k_{off}) is preferably at least 10^7 M^{-1} , at least 10^8 M^{-1} , at least $5 \times 10^8 \text{ M}^{-1}$, at least 10^9 M^{-1} , at least $5 \times 10^9 \text{ M}^{-1}$, at least 10^{10} M^{-1} , at least $5 \times 10^{10} \text{ M}^{-1}$, at least 10^{11} M^{-1} , at least $5 \times 10^{11} \text{ M}^{-1}$, at least 10^{12} M^{-1} , or at least 10^{13} M^{-1} .

[0217] The ability of the conjugate of the present invention to bind to CAPRIN-1 can be identified through the use of binding assay using, for example, ELISA, Western blot, immunofluorescence, or flow cytometry.

[0218] The conjugate of the present invention enhances the antitumor effect as compared with the anti-CAPRIN-1 antibody alone, as mentioned above. The rate of the enhancement is preferably 30% or more, more preferably 40% or more, further preferably 50% or more, still further preferably 55% or more, even further preferably 60% or more, furthermore preferably 65% or more, most preferably 70% or more. The rate of enhancement in antitumor effect by the conjugate of the present invention with respect to the anti-CAPRIN-1 antibody alone can be calculated by administering their respective effective amounts to cancer-bearing mice under the same conditions, and comparing tumor volumes 10 days or later after the start of the administration.

<Pharmaceutical Composition and Method for Treating and/or Preventing Cancer>

[0219] The target of the pharmaceutical composition for the treatment and/or prevention of a cancer of the present invention is not particularly limited as long as the target is cancer (cells) expressing the CAPRIN-1 protein.

[0220] The terms "tumor" and "cancer" used in the present specification mean malignant neoplasm and are used interchangeably with each other.

[0221] The cancer targeted in the present invention may be any cancer expressing the CAPRIN-1 protein on the cell membrane surface. The cancer is preferably breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer,

Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer as mentioned above.

[0222] More specifically, examples of these cancers include, but are not limited to, breast adenocarcinoma, complex-type breast adenocarcinoma, malignant mixed tumor of the mammary gland, intraductal papillary adenocarcinoma, lung adenocarcinoma, squamous cell cancer, small-cell cancer, large-cell cancer, glioma which is tumor of neuroepithelial tissue, glioblastoma, neuroblastoma, ependymoma, neuronal tumor, embryonal neuroectodermal tumor, neurilemmoma, neurofibroma, meningioma, chronic lymphocytic leukemia, lymphoma, gastrointestinal lymphoma, alimentary lymphoma, small to medium cell-type lymphoma, cecal cancer, ascending colon cancer, descending colon cancer, transverse colon cancer, sigmoid colon cancer, rectal cancer, epithelial ovarian cancer, germ cell tumor, stromal cell tumor, pancreatic ductal carcinoma, invasive pancreatic ductal carcinoma, pancreatic adenocarcinoma, acinar cell carcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm, mucinous cystic neoplasm, pancreatoblastoma, islet-cell adenoma, Frants tumor, serous cystadenocarcinoma, solid-pseudopapillary tumor, gastrinoma, glucagonoma, insulinoma, multiple endocrine neoplasia type-1 (Wermer's syndrome), nonfunctional islet cell tumor, somatostatinoma, VIPoma, uterine cervix cancer, uterine body cancer, fibrosarcoma, sarcoma of bones or joints, Ewing's sarcoma, Wilms tumor, hepatoblastoma, soft tissue sarcoma, acute leukemia, chronic leukemia, spinal cord tumor, malignant soft tissue tumor, teratoma group tumor, and head and neck cancer including hypopharynx cancer, oropharynx cancer, tongue cancer, epipharynx cancer, oral cancer, lip cancer, sinus cancer, and throat cancer.

[0223] The subjects (patients) to be targeted are preferably mammals, for example, mammals including primates, pet animals, livestock, and sport animals and are particularly preferably humans, dogs, and cats.

[0224] In the case of using the conjugate used in the present invention in a pharmaceutical composition, the pharmaceutical composition can be formulated by a method known to those skilled in the art. For example, the pharmaceutical composition can be used in the form of a parenteral injection of an aseptic solution or suspension with water or any other pharmaceutically acceptable liquid. For example, the conjugate may be formulated in a unit dosage form required for generally accepted pharmaceutical practice, by mixing with pharmacologically acceptable carriers or media, specifically, sterilized water, physiological saline, a plant oil, an emulsifier, a suspending agent, a surfactant, a stabilizer, a fragrance, an excipient, a binder, etc in appropriate combination. The effective amount of the active ingredient in such a preparation is determined so that an appropriate dose within the prescribed range can be achieved.

[0225] An aseptic composition for injection can be formulated according to conventional pharmaceutical practice using a vehicle such as injectable distilled water. Examples of aqueous solutions for injection include physiological saline, isotonic solutions containing glucose and other auxiliary agents, for example, D-sorbitol, D-mannose, D-mannitol, and sodium chloride. These solutions may be used in combination with an appropriate solubilizer, for example, an alcohol (specifically, ethanol) or a polyalcohol (e.g., propylene glycol and polyethylene glycol), or a nonionic surfac-

tant, for example, Polysorbate 80TM or HCO-60. Examples of oil solutions include sesame oil and soybean oil. These solutions may be used in combination with benzyl benzoate or benzyl alcohol as a solubilizer. The solutions may be further mixed with a buffer (e.g., a phosphate buffer solution and a sodium acetate buffer solution), a soothing agent (e.g., procaine hydrochloride), a stabilizer (e.g., benzyl alcohol and phenol), and an antioxidant. The injection solutions thus prepared are usually filled into appropriate ampules. Examples of oil solutions include sesame oil and soybean oil. These solutions may be used in combination with benzyl benzoate or benzyl alcohol as a solubilizer.

[0226] The administration is carried out orally or parenterally, preferably parenterally. Specific examples of its dosage forms include injections, intranasal administration preparations, transpulmonary administration preparations, and percutaneous administration preparations. Examples of the injections include intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, and intratumoral administration, through which the pharmaceutical composition can be administered systemically or locally.

[0227] Also, the administration method can be appropriately selected in view of the age, weight, sex, symptoms, etc., of a patient. The dose of a pharmaceutical composition containing the antibody or a polynucleotide encoding the antibody can be selected within a range of, for example, 0.0001 to 1000 mg/kg of body weight per dose. Alternatively, the dose can be selected within a range of, for example, 0.001 to 100000 mg/body of a patient, though the dose is not necessarily limited to these numeric values. Although the dose and the administration method vary depending on the weight, age, sex, symptoms, etc., of a patient, those skilled in the art can appropriately select the dose and the method.

[0228] The pharmaceutical composition for the treatment and/or prevention of a cancer comprising the conjugate of the present invention as an active ingredient can be administered to a subject to treat and/or prevent the aforementioned cancer expressing CAPRIN-1 on the cell membrane surface, preferably breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer.

EXAMPLES

[0229] Hereinafter, the present invention will be specifically described with reference to Examples. However, the scope of the present invention is not intended to be limited by these specific examples.

Example 1 Anti-CAPRIN-1 Polyclonal Antibody

[0230] In order to obtain anti-CAPRIN-1 polyclonal antibodies having immunological reactivity with the CAPRIN-1 protein to be used in conjugates, 1 mg of a recombinant human CAPRIN-1 protein of SEQ ID NO: 2 or SEQ ID NO: 4 produced according to Example 3 of WO2010/016526 was mixed with an equal volume of incomplete Freund's adjuvant (IFA) solution, and this mixture was subcutaneously

administered to rabbits four times every 2 weeks. Then, blood was collected to obtain antiserum containing polyclonal antibodies. The obtained antiserum was purified using a (GE Healthcare Bio-Sciences Corp.) to prepare a polyclonal antibody against the CAPRIN-1 protein (anti-CAPRIN-1 polyclonal antibody #1). Also, the serum of a rabbit obtained without administering an antigen was purified using a protein G carrier in the same way as above and used as a rabbit control antibody.

[0231] The following polyclonal antibodies #2 to #6 against partial polypeptides of CAPRIN-1 were obtained in the same way as in the method for preparing the polyclonal antibody against the CAPRIN-1 protein.

[0232] Anti-CAPRIN-1 polyclonal antibody #2 against a partial CAPRIN-1 polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096528 (SEQ ID NO: 31 of the present specification), anti-CAPRIN-1 polyclonal antibody #3 against a partial polypeptide represented by SEQ ID NO: 5 disclosed in WO2013/018894 (SEQ ID NO: 32 of the present specification), anti-CAPRIN-1 polyclonal antibody #4 against a partial polypeptide represented by SEQ ID NO: 5 disclosed in WO2013/125654 (SEQ ID NO: 33 of the present specification), anti-CAPRIN-1 polyclonal antibody #5 against a partial polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096533 (SEQ ID NO: 34 of the present specification), and anti-CAPRIN-1 polyclonal antibody #6 against a partial polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096534 (SEQ ID NO: 35 of the present specification).

Example 2 Anti-CAPRIN-1 Monoclonal Antibody

[0233] The following anti-CAPRIN-1 monoclonal antibodies were used in the conjugate of the present invention.

[0234] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 39 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 43 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0235] The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 47 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 51 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0236] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096519, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region

consisting of the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 55 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 59 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0237] The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 63 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 67 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0238] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096517, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0239] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79.

[0240] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096533, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the amino acid sequence of

represented by the amino acid sequence of SEQ ID NO: 131; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0252] A nucleotide sequence was designed to express a heavy chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, which are from one of the above-mentioned anti-CAPRIN-1 monoclonal antibodies, and framework region sequences of a human antibody. The nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. Similarly, a nucleotide sequence was designed to express a light chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a light chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method, and a culture supernatant containing humanized monoclonal antibody #1 (humanized antibody #1) against CAPRIN-1 comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, was obtained from the cells.

[0253] Similarly, a nucleotide sequence was designed to express a heavy chain variable region represented by SEQ ID NO: 47 comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. Similarly, a nucleotide sequence was designed to express a light chain variable region represented by SEQ ID NO: 51 comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method, and a culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #2 (humanized antibody #2) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively, was obtained from the cells.

[0254] A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #3 (humanized antibody #3) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of

SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, was prepared in a similar way.

[0255] A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #4 (humanized antibody #4) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively, was prepared in a similar way.

[0256] Culture supernatants containing the following humanized anti-CAPRIN-1 monoclonal antibodies #9 to #41 (humanized antibodies #9 to #41) were prepared in a similar way.

[0257] Humanized monoclonal antibody #9 (humanized antibody #9) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0258] Humanized monoclonal antibody #10 (humanized antibody #10) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71.

[0259] Humanized monoclonal antibody #11 (humanized antibody #11) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73.

[0260] Humanized monoclonal antibody #12 (humanized antibody #12) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75.

[0261] Humanized monoclonal antibody #13 (humanized antibody #13) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77.

[0262] Humanized monoclonal antibody #14 (humanized antibody #14) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79.

[0263] Humanized monoclonal antibody #15 (humanized antibody #15) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81.

[0264] Humanized monoclonal antibody #16 (humanized antibody #16) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the amino acid sequence of

[0286] Humanized monoclonal antibody #38 (humanized antibody #38) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127.

[0287] Humanized monoclonal antibody #39 (humanized antibody #39) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129.

[0288] Humanized monoclonal antibody #40 (humanized antibody #40) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131.

[0289] Humanized monoclonal antibody #41 (humanized antibody #41) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0290] On the basis of humanized antibody #1 among these anti-CAPRIN-1 monoclonal antibodies, a nucleotide sequence was designed to express a heavy chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and framework region sequences of a human antibody. This nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1 in which serine (Ser) at amino acid position 239 in EU numbering is substituted with aspartic acid (Asp), and isoleucine (Ile) at amino acid position 332 in EU numbering is substituted with glutamic acid (Glu). Also, a nucleotide sequence was designed to express the amino acid sequence of a light chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and framework region sequences of a human antibody, and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a light chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method; and a culture supernatant containing humanized monoclonal antibody #5 (humanized antibody #5) against CAPRIN-1 composed of the full-length heavy chain amino acid sequence consisting of the heavy chain variable region designed above and the heavy chain constant region of human IgG1 in which serine (Ser) at amino acid position 239 in EU numbering is substituted with aspartic acid (Asp), and isoleucine (Ile) at amino acid position 332 in EU numbering is substituted with glutamic acid (Glu), and the full-length light chain amino acid sequence consisting of the light chain variable region designed above and the human light chain constant region, was obtained from the cells.

[0291] A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #6 (humanized antibody #6) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light

chain variable region of the humanized antibody #2 produced above was prepared in a similar way.

[0292] A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #7 (humanized antibody #7) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of the humanized antibody #3 produced above was prepared in a similar way.

[0293] A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #8 (humanized antibody #8) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of the humanized antibody #4 produced above was prepared in a similar way.

[0294] Culture supernatants containing each of humanized anti-CAPRIN-1 antibodies #42 to #74 (humanized antibodies #42 to #74) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of each of the humanized antibodies #9 to #41 produced above were prepared in a similar way.

[0295] The obtained culture supernatants containing each of the humanized anti-CAPRIN-1 monoclonal antibodies #1 to #74 were subjected to purification using Hitrap Protein A Sepharose FF (GE Healthcare) according to a conventional method. The buffer was replaced with PBS(-). The resultant was filtered through a 0.22 µm filter (Merck Millipore Corp.) to prepare the humanized antibodies.

Example 3 Preparation of Conjugate of Anti-CAPRIN-1 Antibody and Immune Activator

[0296] Conjugates of anti-CAPRIN-1 polyclonal antibodies #1 to #6 described in Example 1 with resiquimod, an immune activator, were prepared using maleimidocaproyl-valine-citrulline-p-aminobenzylloxycarbonyl(MC-val-Cit-PAB) as a linker. The preparation of these conjugates was carried out with reference to the method described in WO2014/012479.

[0297] 20 mg/mL of anti-CAPRIN-1 polyclonal antibody #0 described in Example 1 dissolved in PBS(-) was subjected to buffer replacement with a solution of 500 mM sodium borate and 500 mM sodium chloride (pH 8.0). After incubation of the antibody solution at 37° C. for 30 minutes with 100 mM dithiothreitol (DTT), the buffer was replaced with a PBS(-) solution containing 1 mM diethylenetriaminepentaacetic acid (DTPA) using Sephadex G25, and the resultant was cooled on ice to prepare “reduced” anti-CAPRIN-1 polyclonal antibody #0.

[0298] The amount of thiol per antibody molecule (thiol/antibody ratio) was determined by reacting the antibody with DTNB and measuring the absorbance at 412 nm and the absorbance at 280 nm.

[0299] Resiquimod (Enzo Life Sciences, Inc.) and MC-Val-Cit-PABC-PNP (Medchem Express) were mixed in DMSO to allow the amino group of resiquimod to react with MC-Val-Cit-PABC-PNP, thereby preparing a MC-val-Cit-PAB-bound resiquimod solution, which was then added to the reduced anti-CAPRIN-1 polyclonal antibody #1 prepared above for reaction thereof. After the reaction, an excess amount of maleimide was added to terminate the reaction, thereby preparing a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #1 described in Example 1 with resiquimod. The obtained conjugate was concentrated by ultrafiltration and desalting using Sephadex

G25 into a PBS(–) solution. The resultant was sterilized by filtration through a 0.22 µm filter to prepare a solution containing the conjugate of anti-CAPRIN-1 polyclonal antibody #1 and resiquimod (Conjugate 1).

[0300] A solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #2 and resiquimod (Conjugate 2), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #3 and resiquimod (Conjugate 3), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #4 and resiquimod (Conjugate 4), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #5 and resiquimod (Conjugate 5), and a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #6 and resiquimod (Conjugate 6) were prepared in the same way as described above.

[0301] As for the rabbit control antibody described in Example 1 unreactive with the CAPRIN-1 protein, a solution containing a conjugate of the rabbit control antibody and resiquimod (Control conjugate 1) was also prepared in the same way as described above.

[0302] A solution containing a conjugate of humanized antibody #1, which is an anti-CAPRIN-1 monoclonal antibody described in Example 2, with the immune activator resiquimod (Conjugate 7) was prepared using the humanized antibody #1 in the same way as above.

[0303] A solution containing a conjugate of humanized antibody #2, which is an anti-CAPRIN-1 antibody described in Example 2, with the immune activator resiquimod (Conjugate 8) was prepared using the humanized antibody #2 in the same way.

[0304] A solution containing a conjugate of humanized antibody #3 described in Example 2 with the immune activator resiquimod (Conjugate 9); a solution containing a conjugate of humanized antibody #4 with the immune activator resiquimod (Conjugate 10); a solution containing a conjugate of humanized antibody #5 with the immune activator resiquimod (Conjugate 11); a solution containing a conjugate of humanized antibody #6 with the immune activator resiquimod (Conjugate 12); a solution containing a conjugate of humanized antibody #7 with the immune activator resiquimod (Conjugate 13); a solution containing a conjugate of humanized antibody #8 with the immune activator resiquimod (Conjugate 14); and solutions containing conjugates of humanized antibodies #9 to #74 with the immune activator resiquimod (Conjugates 45 to 110), were each prepared as described above.

[0305] The prepared solutions containing Conjugates 1 to 14, Conjugates 45 to 110, and Control conjugate 1 were each filtered through a 0.22 µm filter (Merck Millipore Corp.) to prepare the conjugates.

Example 4 Preparation of Conjugate of Anti-CAPRIN-1 Antibody and Immune Activator

[0306] Conjugates of the anti-CAPRIN-1 polyclonal antibodies described in Example 1 with an immune activator were prepared by the following method. 1-(2-(2-aminoethoxy)-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, a resiquimod derivative made by two-carbon homologation of the tertiary hydroxy group of resiquimod and the addition of an amino group thereto, was prepared as an immune activator by synthesis according to an ordinary method.

[0307] Specifically, dry acetonitrile, triethylamine, and trityl chloride were added to resiquimod, and reacted in an argon atmosphere. After the reaction, the residue was puri-

fied by silica gel column chromatography. The purified product was dissolved in dehydrated DMF and reacted with added 3-Boc-1,2,3-oxathiazolidine 2,2-dioxide. The aqueous phase was subjected to extraction with ethyl acetate according to an ordinary method. The obtained organic phase was then purified by column chromatography to prepare the above-mentioned resiquimod derivative.

[0308] Next, the following procedure was carried out with reference to the method described in J. Med. Chem., (2008) 51, 6916-6926 in order to bind the obtained resiquimod derivative to succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC), as a linker.

[0309] The resiquimod derivative was dissolved in dehydrated dichloromethane in an argon atmosphere. To the solution, diisopropylethylamine and SMCC were added. The mixture was allowed to react at room temperature for 2 hours. The reaction mixture was subjected to purification to obtain a condensate of resiquimod with SMCC.

[0310] A conjugate of the condensate of resiquimod with the linker SMCC and anti-CAPRIN-1 antibody was prepared according to an ordinary method with reference to the methods described in U.S. Pat. No. 8,951,528 and JMD Reports-Case and Research Reports, 2012/5.

[0311] Specifically, to anti-CAPRIN-1 polyclonal antibody #1 dissolved in a phosphate buffer, N-succinimidyl S-acetylthioacetate (SATA) (Thermo Fischer Scientific, Inc.) dissolved in a 10-fold molar mass of DMSO relative to the antibody was added, and reacted at room temperature for 30 minutes at pH 8. Then, the buffer was replaced with a phosphate buffer containing 10 mM EDTA using a desalting column (Thermo Fischer Scientific, Inc.) to obtain a solution containing anti-CAPRIN-1 polyclonal antibody #1 bound with SATA. To the solution, a phosphate buffer containing 0.5 M hydroxylamine and 25 mM EDTA was added in a volume of 10% relative to the solution, and the mixture was deacetylated through reaction at room temperature for 2 hours. The buffer in the solution containing anti-CAPRIN-1 polyclonal antibody #1 bound with deacetylated SATA was replaced with a phosphate buffer using a desalting column as described above to prepare a solution containing a thiol group-added anti-CAPRIN-1 antibody.

[0312] The condensate prepared above, dissolved in a 10- to 50-fold molar mass of DMSO relative to such antibody, was added to the solution and the mixture was reacted at room temperature for 1 hour. After the reaction, the buffer was replaced with a PBS(–) solution using a desalting column, and the resultant was concentrated using an ultrafiltration column and sterilized by filtration through a 0.2 µm filter to obtain a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #1 described in Example 1 with the resiquimod derivative (Conjugate 15).

[0313] In the same way as above, a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #2 with the resiquimod derivative (Conjugate 16), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #3 with the immune activator (Conjugate 17), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #4 with the immune activator (Conjugate 18), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #5 with the immune activator (Conjugate 19), and a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #6 with the immune activator (Conjugate 20) were prepared.

[0314] As for the rabbit control antibody described in Example 1 unreactive with the CAPRIN-1 protein, a solution containing a conjugate (Control conjugate 2) was also prepared in the same way as above using the rabbit control antibody.

[0315] A solution containing a conjugate of humanized antibody #1, which is one of the anti-CAPRIN-1 monoclonal antibodies described in Example 2, with the resiquimod derivative (Conjugate 21) was prepared in the same way as above.

[0316] A solution containing a conjugate of humanized antibody #2, which is one of the anti-CAPRIN-1 antibodies described in Example 2, with the resiquimod derivative (Conjugate 22) was obtained in the same way.

[0317] In the same way as above, a solution containing a conjugate of humanized antibody #3, which is an anti-CAPRIN-1 antibody described in Example 2, with the immune activator (Conjugate 23); a solution containing a conjugate of humanized antibody #4 with the immune activator (Conjugate 24); a solution containing a conjugate of humanized antibody #5 with the immune activator (Conjugate 25); a solution containing a conjugate of humanized antibody #6 with the immune activator (Conjugate 26); a solution containing a conjugate of humanized antibody #7 with the immune activator (Conjugate 27); and a solution containing a conjugate of humanized antibody #8 with the immune activator (Conjugate 28) were prepared.

[0318] In the same way as above, solutions containing conjugates of humanized antibodies #9 to #74 with the immune activator (Conjugates 111 to 176) were each prepared.

[0319] The prepared solutions containing Conjugates 15 to 28, Conjugates 111 to 176, and Control conjugate 2 were each filtered through a 0.22 µm filter (Merck Millipore Corp.) to prepare the conjugates.

Example 5 Specific Reactivity of Conjugate with CAPRIN-1 Protein and CAPRIN-1-Expressing Cancer Cell

[0320] Conjugates 1 to 14 and Conjugates 45 to 110 prepared in Example 3 and Conjugates 15 to 28 and Conjugates 111 to 176 prepared in Example 4 were assayed for their specific reactivity with a CAPRIN-1 protein and their reactivity with the cell membrane surface of human cancer cells and mouse cancer cells which expressing a CAPRIN-1 protein.

[0321] The specific reactivity with the CAPRIN-1 protein was determined by ELISA. A 1 µg/mL CAPRIN-1 protein solution was added at 100 µL/well to a 96-well plate, and the plate was left to stand at 4° C. for 18 hours. Each well was washed with PBS-T three times. Then, a 0.5% bovine serum albumin (BSA) solution was added at 400 µL/well, and the plate was left to stand at room temperature for 3 hours. The solution was removed, and the wells were washed with 400 µL/well of PBS-T three times. Then, each of the solutions containing Conjugates 1 to 6, Conjugates 15 to 20, Control conjugate 1, and Control conjugate 2 was added at 100 µL/well, and the plate was left to stand at room temperature for 2 hours. Each well was washed with PBS-T three times. Then, an HRP-labeled anti-rabbit antibody diluted 5000-fold with PBS was added at 100 µL/well, and left to stand at room temperature for 1 hour. Each well was washed with PBS-T three times. Then, a TMB substrate solution was added at 100 L/well, and left to stand for 15 to 30 minutes for

chromogenic reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well, and the absorbance values at 450 nm and 595 nm were measured using an absorption spectrometer. As a result, Conjugates 1 to 6 and Conjugates 15 to 20 exhibited a higher absorbance value than that of Control conjugates 1 and 2 as negative controls and were found to specifically react with the CAPRIN-1 protein.

[0322] Next, the reactivity with the cell membrane surface of CAPRIN-1-expressing cancer cells was verified by flow cytometry. Human breast cancer cells BT-474 (from ATCC) or mouse breast cancer cells 4T1 (from ATCC) were centrifuged in 1.5 mL microcentrifuge tubes (2×10⁵ cells per tube). 100 µL of the solutions containing each of Conjugates 1 to 6, Conjugates 15 to 20, Control conjugate 1, and Control conjugate 2 was then each added to separate tubes. The tube was left to stand on ice for 1 hour. After washing with PBS, Alexa 488-labeled anti-rabbit IgG (H+L) diluted 100-fold with PBS(-) containing 0.5% FBS (0.5% FBS-PBS(-)) was added thereto, and the tube was left to stand on ice for 1 hour. After washing with 0.5% FBS-PBS(-), the cells were suspended in 0.2 µg/mL propidium iodide and 0.5% FBS-PBS(-), and the fluorescence intensity was measured using FACSVerse™ (Becton, Dickinson and Company). As a result, Conjugates 1 to 6 and Conjugates 15 to 20, which were the conjugates of the anti-CAPRIN-1 polyclonal antibodies and the immune activator, were found to exhibit higher fluorescence intensity than that of Control conjugate 1 and Control conjugate 2 as negative controls, i.e., to strongly react with the cell surface of the human cancer cells BT474 and the mouse cancer cells 4T1 expressing CAPRIN-1.

[0323] The reactivity of the conjugates with the following various human cancer cells and mouse cancer cells was verified in a similar way: breast cancer cells (BT-474), colorectal cancer cells (HT-29), lung cancer cells (QG56 and H1650), stomach cancer cells (NCI-N87), uterine cancer cells (HEC-1-A), prostate cancer cells (22Rv1), pancreatic cancer cells (Panc10.5), liver cancer cells (Hep3B), ovary cancer cells (SKOV3), kidney cancer cells (Caki-2), brain tumor cells (U-87 MG), bladder cancer cells (T24), esophagus cancer cells (OE33), leukemia cells (OCI-AML5), lymphoma cells (Ramos), gallbladder cancer cells (TGBC14TKB), fibrosarcoma cells (HT-1080), and melanoma cells (G-361), which are human cancer cells found to express the CAPRIN-1 gene; and mouse kidney cancer cells (Renca) and mouse breast cancer cells (4T1), which are mouse cancer cells found to express the CAPRIN-1 gene. As a result of the verification, Conjugates 1 to 6 and Conjugates 15 to 20, which were the conjugates of the anti-CAPRIN-1 antibodies and the immune activator, exhibited stronger fluorescence intensities for all of the cancer cells than that of Control conjugate 1 and Control conjugate 2 as negative controls and were thus shown to strongly react with the cell membrane surface of the above cancer cells expressing CAPRIN-1.

[0324] Also, anti-CAPRIN-1 polyclonal antibodies #1 to #6 prepared in Example 1 which are unconjugated with the immune activator were similarly assayed. As a result of assaying their reactivity with the above cancer cells expressing CAPRIN-1 by flow cytometry, these antibodies exhibited fluorescence intensities equivalent to those of Conjugates 1 to 6 and Conjugates 15 to 20.

[0325] Next, Conjugates 7 to 14 and Conjugates 45 to 110, which were the conjugates of the anti-CAPRIN-1 monoclonal antibodies with the immune activator prepared in Example 3, and Conjugates 21 to 28 and Conjugates 111 to 176 prepared in Example 4 were assayed for their specific reactivity with the CAPRIN-1 protein and their reactivity with the cell membrane surface of human cancer cells and mouse cancer cells expressing CAPRIN-1, in the same way as above. As a result, Conjugates 7 to 14 and Conjugates 21 to 28 exhibited significantly higher absorbance values than a negative control with PBS(−) added and were therefore shown to specifically react with the CAPRIN-1 protein.

[0326] Conjugates 7 to 14, Conjugates 45 to 110, Conjugates 21 to 28, and Conjugates 111 to 176 were further evaluated for their reactivity with the cell membrane surface of cancer cells expressing the CAPRIN-1 protein. As a result, these conjugates exhibited significantly stronger reactivity than that of a conjugate of the immune activator and human IgG unreactive with the CAPRIN-1 protein, and also exhibited strong reactivity equivalent to that of anti-CAPRIN-1 monoclonal antibodies #1 to #74 described in Example 2 which are unconjugated with the immune activator.

[0327] These results demonstrated that the conjugates of the anti-CAPRIN-1 antibodies and the immune activator prepared above (Conjugates 7 to 14, Conjugates 45 to 110, Conjugates 21 to 28, and Conjugates 111 to 176) specifically bind to the CAPRIN-1 protein and to the cell membrane surface of CAPRIN-1-expressing cancer cells.

Example 6 Antitumor Effect of Conjugate-1

[0328] Next, Conjugates 1 to 6 and Conjugates 15 to 20 prepared using anti-CAPRIN-1 polyclonal antibodies #1 to #6 and Conjugates 7 to 14 and Conjugates 21 to 28 prepared using anti-CAPRIN-1 monoclonal antibodies in Examples 3 and 4 were evaluated for their in vivo antitumor effects on cancer-bearing mice.

[0329] Specifically, the conjugates of the present invention were examined for their antitumor effect using NOD-SCID mice in which human-derived cancer cells expressing the CAPRIN-1 protein were transplanted. Human breast cancer cells BT474 were mixed with Matrigel (Sigma-Aldrich Corp.) and subcutaneously transplanted at 10 cells/mouse to the mice, which were then grown until tumor became 180 mm³ or larger to prepare cancer-bearing mice. BT474 expresses the CAPRIN-1 protein on the cell membrane surface. As shown in Example 5, Conjugates 1 to 6 and Conjugates 15 to 20 prepared using anti-CAPRIN-1 polyclonal antibodies #1 to #6, and Conjugates 7 to 14 and Conjugates 21 to 28 prepared using anti-CAPRIN-1 monoclonal antibodies specifically bind to the cell membrane surface. Conjugates 1 to 28 were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice.

[0330] A solution containing a conjugate of trastuzumab and resiquimod was prepared by the method described in Example 3 and administered as a comparative control in the same amount as above to the cancer-bearing mice. BT474 expresses HER2 protein, which is a target antigen of trastuzumab, on the cell membrane surface. The conjugate of trastuzumab and resiquimod specifically binds to BT474. The administration to the cancer-bearing mice was carried out once a week.

[0331] PBS(−) was administered to the cancer-bearing mice, for a negative control.

[0332] The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor)×(Length of the minor axis of tumor)²×0.5. As a result of the evaluation, all the mice given Conjugates 1 to 6 prepared in Example 3 and Conjugates 15 to 20 prepared in Example 4 had less than 37% tumor volumes 50 days after the start of the administration relative to the tumor volume of the negative control (100%). All the mice given Conjugates 7 to 14 and Conjugates 21 to 28 had less than 15% tumor volumes. Cancer growth in the mice given Conjugates 11 to 14 and Conjugates 25 to 28 was suppressed early as compared with cancers in the mice given Conjugates 7 to 10 and Conjugates 21 to 24. As a result of similarly evaluating the in vivo antitumor effects of Conjugates 45 to 176 on cancer-bearing mice, all the mice had less than 20% tumor volumes.

[0333] On the other hand, the tumor volume of the mice given the solution containing the conjugate of trastuzumab and resiquimod as a comparative control was 54% relative to the negative control.

[0334] These evaluation results demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 prepared in Examples 3 and 4 using the antibodies against CAPRIN-1 exert a significantly stronger antitumor effect than that of the negative control. These results also demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 have a significantly stronger antitumor effect than that of the conjugate of trastuzumab and resiquimod prepared as a comparative control.

Example 7 Antitumor Effect of Conjugate-2

[0335] The conjugates of the anti-CAPRIN-1 antibodies and the immune activator (Conjugates 1 to 28) prepared in Examples 3 and 4 were evaluated for their in vivo antitumor effects on cancer-bearing mice.

[0336] Specifically, the conjugates of the present invention were examined for their antitumor effect using Balb/c nude mice in which human-derived cancer cells expressing CAPRIN-1 were transplanted. Human lung cancer cells H1650 were subcutaneously transplanted to the ventral regions of the mice, which were then grown until tumor became 180 mm³ or larger to prepare cancer-bearing mice. The lung cancer cells H1650 express the CAPRIN-1 protein on the cell membrane surface. As shown in Example 5, Conjugates 1 to 28 specifically bind to CAPRIN-1 on the cell membrane surface of the lung cancer cells H1650. Conjugates 1 to 14 prepared in Example 3 and Conjugates 15 to 28 prepared in Example 4 were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice.

[0337] A solution containing a conjugate of cetuximab and resiquimod was prepared by the method described in Example 3 and administered as a comparative control in the same amount as above to the cancer-bearing mice. The administration was carried out once a week a total of three times.

[0338] PBS(−) was administered to the cancer-bearing mice, for a negative control.

[0339] The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary

method based on the expression: (Length of the major axis of tumor)×(Length of the minor axis of tumor)²×0.5. As a result, the mice given Conjugates 1 to 6 and Conjugates 15 to 20 had less than 22% tumor volumes 25 days after the start of the administration relative to the tumor volume of the negative control (100%). All the mice given Conjugates 7 to 14 and Conjugates 21 to 28 had less than 12% tumor volumes. Cancer growth in the mice given Conjugates 11 to 14 and Conjugates 25 to 28 was suppressed early as compared with cancers in the mice given Conjugates 7 to 10 and Conjugates 21 to 24. As a result of similarly evaluating the *in vivo* antitumor effects of Conjugates 45 to 176 on cancer-bearing mice, the mice had less than 16% tumor volumes.

[0340] On the other hand, the tumor volume of the mice given the solution containing the conjugate of cetuximab and resiquimod as a comparative control was 32% relative to the negative control.

[0341] These evaluation results demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 exert a significantly stronger antitumor effect than that of the negative control. These results also demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 have a significantly stronger antitumor effect than that of the conjugate of cetuximab and resiquimod as a comparative control.

Example 8 Preparation of Conjugate of Mouse Chimeric Anti-CAPRIN-1 Monoclonal Antibody and Immune Activator

[0342] Mouse chimeric antibodies composed of a heavy chain comprising the heavy chain variable region of each anti-CAPRIN-1 monoclonal antibody and the heavy chain constant region of mouse IgG, and a light chain comprising the light chain variable region of the anti-CAPRIN-1 monoclonal antibody and the light chain constant region of mouse IgG were prepared, and then conjugates of the antibodies with the immune activator resiquimod were prepared in the same way as in Example 3. Also, the mouse chimeric antibodies were prepared, and then conjugates of the antibodies with the resiquimod derivative were prepared in the same way as in Example 4.

[0343] Specifically, the following antibodies were used in this Example as the mouse chimeric antibodies comprising the light chain variable regions of the anti-CAPRIN-1 monoclonal antibodies and the light chain constant region of mouse IgG.

[0344] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 39 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 43 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0345] The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region

consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 47 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 51 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0346] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096519, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 55 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 59 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0347] The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 63 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 67 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0348] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096517, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0349] The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75; the antibody comprises the amino acid sequence of a heavy

the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0362] The mouse chimeric antibodies were prepared by the following method.

[0363] Specifically, an amplification fragment of a gene encoding a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 39 according to the present invention was treated at its both ends with restriction enzymes, then purified, and inserted into a vector already comprising inserts of a human antibody-derived leader sequence and the heavy chain constant region of mouse IgG, according to an ordinary method. Further, an amplification fragment of a gene encoding a light chain variable region having the amino acid sequence represented by SEQ ID NO: 43 was treated at its both ends with restriction enzymes, then purified, and inserted into a vector already comprising inserts of a human antibody-derived leader sequence and the light chain constant region of mouse IgG, according to an ordinary method.

[0364] Next, the recombinant vector having a gene insert of the heavy chain variable region of the antibody against CAPRIN-1 as described above and the recombinant vector having a gene insert of the light chain variable region of the antibody, were transferred to mammalian cells according to an ordinary method, and a solution containing mouse chimeric antibody #1 composed of a heavy chain comprising the heavy chain variable region of the antibody against CAPRIN-1 represented by SEQ ID NO: 39 and the heavy chain constant region of mouse IgG, and a light chain comprising the light chain variable region represented by SEQ ID NO: 43 of the antibody against CAPRIN-1 and the light chain constant region of mouse IgG.

[0365] A solution containing mouse chimeric antibody #2 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 47 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 51 and the light chain constant region of mouse IgG was prepared in a similar way.

[0366] A solution containing mouse chimeric antibody #3 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented

by SEQ ID NO: 55 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 59 and the light chain constant region of mouse IgG was prepared in a similar way.

[0367] A solution containing mouse chimeric antibody #4 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 63 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 67 and the light chain constant region of mouse IgG was prepared in a similar way.

[0368] Solutions containing the following mouse chimeric antibodies #5 to #37 were prepared in a similar way.

[0369] Mouse chimeric antibody #5 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69 and the light chain constant region of mouse IgG.

[0370] Mouse chimeric antibody #6 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71 and the light chain constant region of mouse IgG.

[0371] A solution containing mouse chimeric antibody #7 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73 and the light chain constant region of mouse IgG.

[0372] Mouse chimeric antibody #8 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75 and the light chain constant region of mouse IgG.

[0373] Mouse chimeric antibody #9 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77 and the light chain constant region of mouse IgG.

[0374] Mouse chimeric antibody #10 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79 and the light chain constant region of mouse IgG.

[0391] Mouse chimeric antibody #27 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 112 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 113 and the light chain constant region of mouse IgG.

[0392] Mouse chimeric antibody #28 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 114 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 115 and the light chain constant region of mouse IgG.

[0393] Mouse chimeric antibody #29 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 116 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 117 and the light chain constant region of mouse IgG.

[0394] Mouse chimeric antibody #30 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 118 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 119 and the light chain constant region of mouse IgG.

[0395] Mouse chimeric antibody #31 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 120 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 121 and the light chain constant region of mouse IgG.

[0396] Mouse chimeric antibody #32 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 122 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 123 and the light chain constant region of mouse IgG.

[0397] Mouse chimeric antibody #33 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125 and the light chain constant region of mouse IgG.

[0398] Mouse chimeric antibody #34 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127 and the light chain constant region of mouse IgG.

[0399] Mouse chimeric antibody #35 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129 and the light chain constant region of mouse IgG.

[0400] Mouse chimeric antibody #36 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131 and the light chain constant region of mouse IgG.

[0401] Mouse chimeric antibody #37 composed of a heavy chain having the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the heavy chain constant region of mouse IgG, and a light chain having the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133 and the light chain constant region of mouse IgG.

[0402] The prepared culture supernatant containing each of mouse chimeric antibodies #1 to #37 was purified according to a conventional method using Hitrap Protein A Sepharose FF (GE Healthcare Japan Corp.). The buffer was replaced with PBS(-), and the resultant was filtered through a 0.22 µm filter (Merck Millipore Corp.) to prepare the mouse chimeric antibodies.

[0403] Conjugates with resiquimod were prepared in the same way as the method described in Example 3 using mouse chimeric antibodies #1 to #37 prepared above. Solutions containing a conjugate of mouse chimeric antibody #1 with resiquimod (Conjugate 29), a conjugate of mouse chimeric antibody #2 with resiquimod (Conjugate 30), a conjugate of mouse chimeric antibody #3 with resiquimod (Conjugate 31), a conjugate of mouse chimeric antibody #4 with resiquimod (Conjugate 32), a conjugate of mouse chimeric antibody #5 with resiquimod (Conjugate 177), a conjugate of mouse chimeric antibody #6 with resiquimod (Conjugate 178), a conjugate of mouse chimeric antibody #7 with resiquimod (Conjugate 179), a conjugate of mouse chimeric antibody #8 with resiquimod (Conjugate 180), a conjugate of mouse chimeric antibody #9 (Conjugate 181), a conjugate of mouse chimeric antibody #10 with resiquimod (Conjugate 182), a conjugate of mouse chimeric antibody #11 with resiquimod (Conjugate 183), a conjugate of mouse chimeric antibody #12 with resiquimod (Conjugate 184), a conjugate of mouse chimeric antibody #13 with resiquimod (Conjugate 185), a conjugate of mouse chimeric antibody #14 with resiquimod (Conjugate 186), a conjugate of mouse chimeric antibody #15 with resiquimod (Conjugate 187), a conjugate of mouse chimeric antibody #16 with resiquimod (Conjugate 188), a conjugate of mouse chimeric antibody #17 with resiquimod (Conjugate 189), a conjugate of mouse chimeric antibody #18 with resiquimod (Conjugate 190), a conjugate of mouse chimeric antibody #19 with resiquimod (Conjugate 191), a conjugate of mouse chimeric antibody #20 with resiquimod (Conjugate 192), a conjugate of mouse chimeric antibody #21 with resiquimod (Conjugate 193), a conjugate of mouse chimeric antibody #22 with resiquimod (Conjugate 194), a conjugate of mouse chimeric

antibody #23 with resiquimod (Conjugate 195), a conjugate of mouse chimeric antibody #24 with resiquimod (Conjugate 196), a conjugate of mouse chimeric antibody #25 with resiquimod (Conjugate 197), a conjugate of mouse chimeric antibody #26 with resiquimod (Conjugate 198), a conjugate of mouse chimeric antibody #27 with resiquimod (Conjugate 199), a conjugate of mouse chimeric antibody #28 with resiquimod (Conjugate 200), a conjugate of mouse chimeric antibody #29 with resiquimod (Conjugate 201), a conjugate of mouse chimeric antibody #30 with resiquimod (Conjugate 202), a conjugate of mouse chimeric antibody #31 with resiquimod (Conjugate 203), a conjugate of mouse chimeric antibody #32 with resiquimod (Conjugate 204), a conjugate of mouse chimeric antibody #33 with resiquimod (Conjugate 205), a conjugate of mouse chimeric antibody #34 with resiquimod (Conjugate 206), a conjugate of mouse chimeric antibody #35 with resiquimod (Conjugate 207), a conjugate of mouse chimeric antibody #36 with resiquimod (Conjugate 208), and a conjugate of mouse chimeric antibody #37 with resiquimod (Conjugate 209) were prepared.

[0404] Further, conjugates with the resiquimod derivative were prepared in the same way as the method described in Example 4 using mouse chimeric antibodies #1 to #37 prepared above. Solutions containing a conjugate of mouse chimeric antibody #1 with the resiquimod derivative (Conjugate 33), a conjugate of mouse chimeric antibody #2 with the resiquimod derivative (Conjugate 34), a conjugate of mouse chimeric antibody #3 with the resiquimod derivative (Conjugate 35), and a conjugate of mouse chimeric antibody #4 with the resiquimod derivative (Conjugate 36) were prepared. Solutions containing conjugates of mouse chimeric antibodies #5 to #37 with the resiquimod derivative (Conjugates 210 to 242) were prepared in a similar way.

[0405] The prepared solutions containing Conjugates 29 to 36, Conjugates 177 to 242, and Control conjugate 2 were each filtered through a 0.22 μm filter (manufactured by Merck Millipore Corp.) to prepare the conjugates.

[0406] Conjugates 29 to 36 and Conjugates 177 to 242 were assayed for their specific reactivity with the CAPRIN-1 protein in the same way as in Example 5 using the prepared solutions containing Conjugates 29 to 36 and Conjugates 177 to 242. As a result, the solutions containing Conjugates 29 to 36 and Conjugates 177 to 242 each exhibited specific reactivity with the CAPRIN-1 protein.

[0407] Further, Conjugates 29 to 36 and Conjugates 177 to 242 were assayed for their reactivity with cancer cells by flow cytometry using the cancer cells expressing CAPRIN-1 on the cell membrane surface. As a result, all the conjugates exhibited stronger fluorescence intensity than that of the negative control. Also, the conjugates were found to exhibit strong reactivity equivalent to that of the anti-CAPRIN-1 monoclonal antibodies described in mouse chimeric antibodies #1 to #37 prepared above, unconjugated with the immune activator.

[0408] Example 9 Antitumor effect of conjugate of mouse chimeric anti-CAPRIN-1 monoclonal antibody and immune activator

[0409] The conjugates of the mouse chimeric anti-CAPRIN-1 monoclonal antibodies and the immune activator (Conjugates 29 to 36 and conjugates 177 to 242) prepared in Example 8 were evaluated for their in vivo antitumor effects of the antibodies on cancer-bearing mice.

[0410] Specifically, the conjugates of the present invention were examined for their antitumor effect using Balb/c mice

in which mouse-derived cancer cells expressing CAPRIN-1 were transplanted. Mouse breast cancer cells 4T1 were subcutaneously transplanted at 10^4 cells/mouse to the ventral regions of the mice, which were then grown until tumor became 30 mm³ or larger to prepare cancer-bearing mice. As shown in Example 5, the breast cancer cells 4T1 are cells expressing the CAPRIN-1 protein on the cell membrane surface. The solutions containing Conjugates 29 to 36 prepared in Example 8 each specifically bind to CAPRIN-1 on the cell membrane surface of the breast cancer cells 4T1. Conjugates 29 to 36 prepared in Example 8 were each administered at 8 mg/kg to the tail veins of 10 cancer-bearing mice. Mouse chimeric antibodies #1 to #4 were each administered as a comparative control in the same amount as above to the cancer-bearing mice. The administration was carried out twice a week a total of four times. PBS(–) was administered to cancer-bearing mice, for a negative control. The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) \times (Length of the minor axis of tumor) $\times 0.5$. As a result, all the mice given Conjugates 29 to 36 had 0% tumor volume 20 days after the start of the administration relative to the tumor volume of the negative control (100%). Also, the mice given mouse chimeric antibodies #1 to #4 alone had 69% tumor volume on average relative to the tumor volume of the negative control mice (100%). These evaluation results demonstrated that the conjugates of resiquimod and the mouse chimeric anti-CAPRIN-1 antibodies (mouse chimeric antibodies) (Conjugates 29 to 32) and the conjugates of the resiquimod derivative and these antibodies (Conjugates 33 to 36) prepared in Example 8 exert a stronger antitumor effect as compared with the negative control and the case of administering the anti-CAPRIN-1 antibody alone to cancer-bearing mice. As a result of similarly evaluating Conjugates 177 to 242 for their antitumor effects, all the mice given Conjugates 29 to 36 had 0% tumor volume relative to the tumor volume of the negative control (100%). The mice given mouse chimeric antibodies #5 to #37 alone had 69% tumor volume on average relative to the tumor volume of the negative control (100%).

Example 10 Antitumor Effect of Conjugate-3

[0411] An in vivo antitumor effect on cancer-bearing mice was compared between Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179 prepared in Example 4 using the anti-CAPRIN-1 monoclonal antibodies, and a trastuzumab conjugate prepared in the same way as in Example 4 using the existing antibody drug trastuzumab for a cancer, or trastuzumab.

[0412] The trastuzumab conjugate is a conjugate prepared in the same way as in Example 4 using trastuzumab and the immune activator. The conjugate of trastuzumab and the immune activator was prepared by the following method.

[0413] With reference to J. Med. Chem. 2008, 51, 6916-6926, succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) was condensed with 1-(2-(2-aminoethoxy)-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, a resiquimod derivative made by two-carbon homologation of the tertiary hydroxy group of resiquimod and the addition of an amino group thereto to obtain a condensate of resiquimod bound with SMCC, as the immune activator.

[0414] Meanwhile, trastuzumab was used in the preparation of the conjugate after removing a formulation composition contained in a solution using an ultrafilter, or affinity-purifying only trastuzumab using a protein A carrier and adding the trastuzumab to a phosphate buffer. A conjugate of the condensate of resiquimod with the linker SMCC as described above and an anti-CAPRIN-1 antibody was prepared according to an ordinary method with reference to the methods described in U.S. Pat. No. 8,951,528 and JMD Reports-Case and Research Reports, 2012/5. Using the trastuzumab dissolved in a phosphate buffer, a solution containing SATA-added trastuzumab was obtained in the same way as in Example 4. This solution was further reacted with the condensate prepared above to prepare a solution containing a conjugate of trastuzumab and the resiquimod derivative (trastuzumab conjugate). The obtained trastuzumab conjugate was verified by flow cytometry to exhibit reactivity with human breast cancer cells used in the antitumor effect evaluation. It was further verified by mass spectrometry that the prepared trastuzumab conjugate to be compared, and Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179 prepared in Example 4 using the anti-CAPRIN-1 monoclonal antibodies, have comparable molecule numbers of the immune activator bound therein and the verified conjugates were used in the following evaluation.

[0415] For the comparison of the antitumor effect, human breast cancer cells BT474 were mixed with Matrigel (Sigma-Aldrich Corp.) and subcutaneously transplanted at 10 cells/mouse to the mice, which were then grown until tumor became 150 mm³ or larger to prepare cancer-bearing mice. BT474 has been found to express the CAPRIN-1 protein and HER2, which is a target antigen of trastuzumab, on the cell membrane surface.

[0416] The conjugates of the anti-CAPRIN-1 antibody (Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179) and the trastuzumab conjugate prepared above were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice. The administration was carried out twice a week a total of 13 times. For comparison, the anti-CAPRIN-1 antibodies used in the preparation of the conjugates of the anti-CAPRIN-1 antibody (Conjugates 7 to 14, conjugates 21 to 28, and conjugates 45 to 179), and trastuzumab were administered in the same way as above. PBS(−) was administered to cancer-bearing mice, for a negative control.

[0417] The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor)×(Length of the minor axis of tumor)²×0.5. As a result of the evaluation, all the mice given Conjugates 11 and 25 had less than 15% tumor volumes 45 days after the start of the administration relative to the tumor volume of the negative control (100%). The mice given the unconjugated anti-CAPRIN-1 antibodies to be compared had less than 50% tumor volume. From these results, it was shown that the conjugation of the immune activator to the anti-CAPRIN-1 antibody enhanced the antitumor effect of the antibody by 77%. The rate of enhancement was calculated based on the expression: 1-(Tumor volume determined with conjugate/Tumor volume determined with antibody alone)×100 (%).

[0418] On the other hand, the mice given the trastuzumab conjugate and the mice given the unconjugated trastuzumab

to be compared had 53% and 74% tumor volumes, respectively, relative to the tumor volume of the negative control (100%). Thus, the rate of enhancement in antitumor effect by the conjugation of the immune activator to trastuzumab was only less than 29%.

Example 11 Preparation of Conjugate of Anti-CAPRIN-1 Antibody and Immune Activator and Antitumor Effect of the Conjugate

[0419] Conjugates of humanized antibodies #1 to #8 which were the anti-CAPRIN-1 monoclonal antibodies described in Example 2 with an immune activator DSR-6434 (6-amino-2-(butylamino)-9-[[6-[2-(dimethylamino)ethoxy]-3-pyridinyl]methyl]-7,9-dihydro-8H-purin-8-one) (Conjugate 37 to 44) were prepared. Specifically, a condensate of DSR-6434 with succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) via the amino group of DSR-6434 was first synthesized, and then, solutions containing conjugates of humanized antibodies #1 to #8 and the immune activator RSR-6434 (Conjugates 37 to 44) were prepared basically according to the method described in Example 4.

[0420] The prepared solutions containing Conjugates 37 to 44 were each filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the conjugates. The conjugates were assayed for their specific reactivity with the CAPRIN-1 protein in the same way as in Example 5. As a result, the solutions containing Conjugates 37 to 44 each exhibited specific reactivity with the CAPRIN-1 protein.

[0421] Conjugates 37 to 44 were further assayed for their reactivity with cancer cells by flow cytometry using cancer cells expressing the CAPRIN-1 protein on the cell membrane surface. As a result, all the conjugates exhibited stronger fluorescence intensity than that of the negative control. The conjugates were found to exhibit fluorescence intensity similar to that of the antibodies alone used in the conjugates.

[0422] Conjugates 37 to 44 were evaluated for their antitumor effects on cancer-bearing mice. The conjugates of anti-CAPRIN-1 antibody (Conjugates 37 to 44) were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice in the same way as the method described in Example 10. The administration was carried out twice a week a total of 16 times. The anti-CAPRIN-1 antibodies used in the preparation of the conjugates were administered in the same way as above. PBS(−) was administered to cancer-bearing mice, for a negative control.

[0423] The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor)×(Length of the minor axis of tumor)²×0.5. As a result of the evaluation, all the mice given Conjugates 37 to 44 had less than 32% tumor volumes 50 days after the start of the administration relative to the tumor volume of the negative control (100%). The mice given the unconjugated anti-CAPRIN-1 antibodies to be compared had less than 50% tumor volume. From these results, the conjugation of the immune activator to the anti-CAPRIN-1 antibody was shown to enhance the antitumor effect by more than 35%. The rate of enhancement was calculated based on the expression: 1-(Tumor volume determined with conjugate/Tumor volume determined with antibody alone)×100 (%).

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KKLRNLEKKK GKLDYQERN NKGERLNQDQ LDAVSKYQEV TMNLEFAKEL QRSMALSQD 120
IQTIKKKTAR REQLMREEAE QKRLKTVLEL QYVLDFKLGD DVRTDLKGQI SGVPILSEE 180
LSLLDEFYKL VDPERDMSL LNEQEYEHASI HLWDLLEGKE KPVCGTTYKA LKEIVERVFQ 240
SNYFDSTHNH QNGLCEEEEAA ASAFTVEDQV AEAEPPEPAEE YTEQSEVEST EYVNRFMAE 300
TQFSSGEKEQ VDEWTETVVE VVNSLQQQPO AASPSVPEPH SLTPVAQSDL LVRRORVQDL 360
MAJMQGPYNF IQDSMLDFEN QTLDPAIVSA QPMNPTQNMDF MPQLVCPOVH SESRLAQSNQ 420
VPVQPEATQV PLVSVTSEGY TASQPLYQPS HATEQRQPKE PMDQIATIS LNTDQTTASS 480
SLPAASQPQV FQAGTSKPLH SSGINVNAAAP FQSMQTVFNM NAPVPPANEP ETLKQQSQYQ 540
ATYNQSFSQ PHQVECTELQ QDQLQTVVGT YHGSQDQPHQ VPGNHQQPPQ QNTGFPRSSQ 600
PYYNSRGVSR GGSRGARGLM NGYRGPANGF RGGYDGYRPS FSNTPNSGYS QSQFTAPRDY 660
SGYQRDGYQQ NFKRGSGQSG PRGAPRGNIL WW 692

SEQ ID NO: 29          moltype = DNA  length = 2109
FEATURE
source          Location/Qualifiers
               1..2109
               mol_type = genomic DNA
               organism = Gallus gallus
CDS            1..2109
protein_id = 30
translation = MPSATNGTMASSSGKAGPGGNEQAPAAAAAPQASGGSITSVQTEA
MKQILGVIDKKLRNLEKKSKSLDDYQERMNKGERLNQDQLDAVSKYQEVTNNLEFAKEL
QRSMALSQDIQKTIKKTARREQLMREEEAKQRLKTVLELQFILDKLGDEVRSRSDLKQG
SNGVPVLTTEELTMLDEFYKLVYPERDMNMRLINEQEYQASVHLWDLLEGEKEKPVCGETTY
KALKEVVERILQTSYFDSHTNHQNGLCEEEEAAPTPAVEDTVAEAPDPAEEFTEPTEV
ESTEYVNRFQMAETQFSSSEKQVDEWTVETVEVVNSLQQQTQATSPPVPEPHTLTTVA
QADPLVRRQRVQLMAQMGPYNFMDQSMLEFENQTLDAPIVSAQPMNPAQNLDMPQMV
CPPVHTESRLAOPNQVQVQPEATQVPLVSSTSEGYTASQPMYQPSHTTEQPQKESIDQ
IQASMSLNADQTPSSSSLPTASQPQVFQAGSSKPLHSSGINVNAAFPQSMQTVFNNMAP
VPPVNEPEALKQQNQYQASYNQFSNQPHQVEQSDLQQEQLQTVVGTYHSPDQTHQVA
GNHQOPPQONTFPRNSQPYYNSRGVSRGGSGRTRGLMNGYRGPANGFRGGYDGYRPSF
SNTPNSGTYTQPQFNAPRDYSNYQRDGYQONFKRGSGQSGPRGAPRGRGGPPRNRMQ
MNAQQVN

SEQUENCE: 29
atgcccttcgg ctaccaaacgg caccatggcg acaagcagcg ggaaggccggg cccggggcgc 60
aacgagcagg ccccgccgg ggcagcggcg gccccggcgg cgtcgccgg cagcatcacc 120
tcgggttccaga cggaggccat gaagcagatc ttgggagtgta tcgacaaaaa gctccgcaac 180
ctcgagaaga aaaagagcaa acttgacat taccaggaaac gaatgaacaa gggggaaacgt 240
ctaaatcaag atcaactggta tgcaagtgtca aaataccagg aagtgacaaa taacctggaa 300
ttcgcttaaag aactgcagag gagetttatg gcaactggc agaatatcaca gaaaacacata 360
aaaagacgg ctcgcaggga cgactgtatc agagaagagg ctgagcaggaa gcgttaaag 420
actgtgttag agctgcagtt cattttggac aagttgggtg acgtgaaatg gcgcgatgtac 480
ttgaaacaaag gatcaaatgg agtacccgtt ctgacagagg aggaaactgac atgctggat 540
gaattttaca agctgtttaa ccctgttacaa gacatggaa tgagggttggaa tgacgatgt 600
ggcaagcat ctgttccaccc ttggggactta ctggaaggga aggaaaaacc cggtttggaa 660
acaacctata aaggccctgaa ggagggttgtt gaacgttattc ttcaaacttag ttactttgtat 720
agcacccata accatccatcgggatgtatc gaggaaagaaaggcagcacc cacacccgtca 780
gtagaagaca ctgttagcaga agctgacatc gatccaggaaac aagaatttac tgaacactact 840
gaagttgaat cgactgtatc tgtaaaacaca caatttcatgg cagagactca gttcagcagt 900
agtgagaagg aacaggtaga tgagtggaca gttggaaacgg ttgagggttgtt aaatttactg 960
cagcaacaaa cacaaggatc atctctcataa gttctctgaa ctcataactactactgtg 1020
gctcaagcag atctcttctgt tagaaagacag agatgttacagg acctttaggc ccagatgcag 1080
ggtccatata accatcatgtca ggactctatg ctggggatggtgg agaaccagac acttgcatt 1140
gccattgtat ctgcacagcc catgaatcca gcacagaatt tggacatgcc gcaaatggc 1200
tgcctccatgg ttcactactga gtcaagactt gcccacgttca atcaagttcc tggcaaccca 1260
gaaggttacgcg aggttccctt ggttcatcttca acaagtggatggatatacagc ctcccaggccc 1320
atgtatcagc ctctcttccatc cacaaggatc cggccacagaaggatcatc tgaccaggatt 1380
caggcttcaa tgcactgttca gtcacggacccatccatcatcact tccactgtca 1440
tcccacggc aagttttccaa agctggatct agcaaaacctt tgcacatggcggaaatcaat 1500
gttaatgcg ctccatcttca atccatgtca acagttatccatc acatgttgc acctgttcc 1560
cctgttcaatgcg agcccaatgcg ccttaagcaaaaatcatc accaggccatc ttacaacccag 1620
agtttcttca atcaggccatc ccaatgttacaaatcatc accaggccatc ttacaacccag 1680
acagtgggtt gtacttacca tgggttctccg gaccagacccatcaatgttgc agggaaaccac 1740
cagcaacatcccccacggc aactggatctt ccacgttcaacaa gtcacgttcaatcatc 1800
cgggggatgtt ctgcgttggg atcactgttggat tggatgttgc ttacaggggatgg 1860
cctgttcaatgcg gatgtttagagg aggttcatcttca ggttacccgttccatccatc caacactccg 1920
aacagtgggtt acacgcaccccaatccatc gtcacgttcaatcatc accaggccatc 1980
gatggatatac acacgttgcg aacatccatc gtcacgttcaatcatc accaggccatc 2040
cgaggtcgtg gaggggccccca aagaccaaac agaggatgc ctcaatgttcaacatgttgc 2100
gtgaattaa 2109

SEQ ID NO: 30          moltype = AA  length = 702

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FEATURE	Location/Qualifiers
source	1..702
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 30	
MPSATNGTMA SSSGKAGPGG NEQAPAAAAA APQASGGSIT SVQTEAMKQI LGVIDKKLRN 60	
LEKKKSKLDD YQERMNKGER LNQDQLDAVS KYQEVTNNLE FAKELQRSFM ALSQDIQKTI 120	
KKTARREQLM REEEAEQKRLR TVLELQFILD KLGDEDEVRSR LKQGSNGVPV LTEEELTMLD 180	
EFYKLVYPER DMNMRLNEQY EQASVHLWDL LEGKEKPVCG TTYKALKEVV ERILQTSYFD 240	
STHINHQNGLC EEEEAAPTPA VEDTVAEAEFP DPAAEFTPEPT EVESTEYVN R QFMAETQFSS 300	
SEKEQVQDWET VETVEVNVSL QQQTQATSPP VPEPHTLTTV AQADPLVRRQ RVQDLMAQM 360	
GPYNFMQDSM LEFENQTLDP AIVSAQPMNP AQNLDMPCMV CPPVHTESTRL AQPNCQPVQP 420	
EATQVPLVSS TSEGYTASQP MYQPSHTTEQ RPQKESIDQI QASMSLNADQ TPSSSSLPTA 480	
SQSQVQFQAGS SKPLHSQSGIN VNAAPFQSMQ TVFNMNAPVPP PVNEPEALKQ QNQYQASYNQ 540	
SFSNQPHQVE QSDLQQEQQLQ TVVGTYHGSP DQTHQVAGHN QQPQQNTGF PRNSQPYINS 600	
RGVSRGGSRG TRGLMNGYRG PANGFRGGYD GYRPSFSNTP NSGYTQPFQN APRDYSNYQR 660	
DGYQQNFKRG SGQSGPPRGAP RGRGGPPRPN RGMPQMNAQQ VN 702	
SEQ ID NO: 31	moltype = AA length = 63
FEATURE	Location/Qualifiers
source	1..63
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 31	
EYEYTEQSEVE STEYVNQFM AETQFTSGEK EQVDEWTVET VEVVNSLQQQ PQAASPSVPE 60	
PHS	63
SEQ ID NO: 32	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 32	
VFNMMNAPVPP VNEPETLK	18
SEQ ID NO: 33	moltype = AA length = 16
FEATURE	Location/Qualifiers
source	1..16
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 33	
ATQVPLVSST SEGYTA	16
SEQ ID NO: 34	moltype = AA length = 25
FEATURE	Location/Qualifiers
source	1..25
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 34	
QILGVIDKKL RNLEKKKGKL DDYQE	25
SEQ ID NO: 35	moltype = AA length = 23
FEATURE	Location/Qualifiers
source	1..23
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 35	
PRGRGGPPRP NRGMPQMNTQ QVN	23
SEQ ID NO: 36	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 36	
SYQMN	5
SEQ ID NO: 37	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 37	
AINKFGNSTG HGAAVKG	17
SEQ ID NO: 38	moltype = AA length = 19

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FEATURE	Location/Qualifiers
source	1..19
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 38	
HAYGYCGSGT WCAAGEIDA	19
SEQ ID NO: 39	moltype = AA length = 128
FEATURE	Location/Qualifiers
source	1..128
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 39	
AVTLDESGGG LQMSRGLSL VCKASGFDFSYQMNWIRQA PGKGLEFVAA INKFGNSTGH	60
GAAVKGRVTI SRDNGQSTVR LQLNNLRAED TAIYFCTKHA YGYCGSGTWC AAGEIDAWGH	120
GTEVIVSS	128
SEQ ID NO: 40	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 40	
SGGGSYSYG	9
SEQ ID NO: 41	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 41	
NNKRPSD	7
SEQ ID NO: 42	moltype = AA length = 10
FEATURE	Location/Qualifiers
source	1..10
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 42	
SGDSTDATAVF	10
SEQ ID NO: 43	moltype = AA length = 108
FEATURE	Location/Qualifiers
source	1..108
	mol_type = protein
	organism = Gallus gallus
SEQUENCE: 43	
QAASTQPSSV SANPGETVEI TCSGGGSYSV GWFQQKSPGGS APVTVIYNN KRPSDIPSFR	60
SGSKSGSTGT LTITGVQADD EAVYYCGSGD STDTAVFGAG TTLTVLGQ	108
SEQ ID NO: 44	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Oryctolagus cuniculus
SEQUENCE: 44	
SHSLG	5
SEQ ID NO: 45	moltype = AA length = 16
FEATURE	Location/Qualifiers
source	1..16
	mol_type = protein
	organism = Oryctolagus cuniculus
SEQUENCE: 45	
DIRSGGSAYY ANWAKG	16
SEQ ID NO: 46	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = Oryctolagus cuniculus
SEQUENCE: 46	
TNGPSDLTNR LDL	13
SEQ ID NO: 47	moltype = AA length = 121
FEATURE	Location/Qualifiers

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source          1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 47
EQSLVESGGG LVQPGGSLRL SCAASGFSLS SHSLGWVRQA PGKGLEWIGD IRSGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCTRTNG PSDLTNRLDL WGQQLVTVS 120
S                                         121

SEQ ID NO: 48      moltype = AA length = 13
FEATURE
source
1..13
mol_type = protein
organism = Oryctolagus cuniculus
SEQUENCE: 48
QASQSLYNNE NLA                                         13

SEQ ID NO: 49      moltype = AA length = 7
FEATURE
source
1..7
mol_type = protein
organism = Oryctolagus cuniculus
SEQUENCE: 49
GASTLAS                                         7

SEQ ID NO: 50      moltype = AA length = 13
FEATURE
source
1..13
mol_type = protein
organism = Oryctolagus cuniculus
SEQUENCE: 50
LGEFSCGSAD CFA                                         13

SEQ ID NO: 51      moltype = AA length = 112
FEATURE
source
1..112
mol_type = protein
organism = Homo sapiens
SEQUENCE: 51
QVLTQSPSSL SASVGDRVTI NCQASQSLYN NENLAWFQQK PGKVPKRLIY GASTLASGVS 60
SRFSGSGSGT EFTLTISSLQ CEDFAIYYCL GEFSCGSADC FAFGGGTKE IK           112

SEQ ID NO: 52      moltype = AA length = 4
FEATURE
source
1..4
mol_type = protein
organism = Gallus gallus
SEQUENCE: 52
FDMG                                         4

SEQ ID NO: 53      moltype = AA length = 17
FEATURE
source
1..17
mol_type = protein
organism = Gallus gallus
SEQUENCE: 53
QINDAGSRTW YATAVKG                                         17

SEQ ID NO: 54      moltype = AA length = 12
FEATURE
source
1..12
mol_type = protein
organism = Gallus gallus
SEQUENCE: 54
GSGYVGAGAI DA                                         12

SEQ ID NO: 55      moltype = AA length = 120
FEATURE
source
1..120
mol_type = protein
organism = Gallus gallus
SEQUENCE: 55
AVTLDESGGG LQTPGGGLSL VCKASGFTFS SFDMGWVRQA PGKGLEFVAQ INDAGSRTWY 60
ATAVKGRATI SRDNGQTTRV LQLNNLRAED TGTYYCTRGSS GYVGAGAIDA WGHGTEIVS 120

SEQ ID NO: 56      moltype = AA length = 8
FEATURE

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source          1..8
               mol_type = protein
               organism = Gallus gallus
SEQUENCE: 56
SGGSGYYG                                     8

SEQ ID NO: 57      moltype = AA  length = 7
FEATURE
source          1..7
               mol_type = protein
               organism = Gallus gallus
SEQUENCE: 57
NDKRPSD                                     7

SEQ ID NO: 58      moltype = AA  length = 10
FEATURE
source          1..10
               mol_type = protein
               organism = Gallus gallus
SEQUENCE: 58
RYDSTDSDGIF                                     10

SEQ ID NO: 59      moltype = AA  length = 105
FEATURE
source          1..105
               mol_type = protein
               organism = Gallus gallus
SEQUENCE: 59
AALTQPSSVS ANPGETVKIT CSGGSGYYGW YQQQKSPGSA PVTVIYQNDK RPSDIPSREFS 60
GSGSGSTNTL TITGVQAED AVYFCGRYDS TDSGIFGAGT TLTIVL                         105

SEQ ID NO: 60      moltype = AA  length = 6
FEATURE
source          1..6
               mol_type = protein
               organism = Oryctolagus cuniculus
SEQUENCE: 60
GSYYMS                                     6

SEQ ID NO: 61      moltype = AA  length = 17
FEATURE
source          1..17
               mol_type = protein
               organism = Oryctolagus cuniculus
SEQUENCE: 61
YIYIGDGVT A YANWAKG                                     17

SEQ ID NO: 62      moltype = AA  length = 4
FEATURE
source          1..4
               mol_type = protein
               organism = Oryctolagus cuniculus
SEQUENCE: 62
GNKL                                         4

SEQ ID NO: 63      moltype = AA  length = 112
FEATURE
source          1..112
               mol_type = protein
               organism = Oryctolagus cuniculus
SEQUENCE: 63
QSLEESGGDL VKPGASLTLL CTASGFSFSG SYYMSWVRQA PGKGLEWIAY IYIGDGVTAY 60
ANWAKGRFTI SKASSTTVTL QMTSLTAADT ATYFCARGNK LWPGLVTV SS                         112

SEQ ID NO: 64      moltype = AA  length = 11
FEATURE
source          1..11
               mol_type = protein
               organism = Oryctolagus cuniculus
SEQUENCE: 64
QASQSISSYL A                                     11

SEQ ID NO: 65      moltype = AA  length = 7
FEATURE
source          1..7
               mol_type = protein

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SEQUENCE: 65 DASNLDs	organism = Oryctolagus cuniculus	
SEQ ID NO: 66 FEATURE source	moltype = AA length = 14 Location/Qualifiers 1..14 mol_type = protein organism = Oryctolagus cuniculus	7
SEQUENCE: 66 QCTAVSSATI YGNA		14
SEQ ID NO: 67 FEATURE source	moltype = AA length = 112 Location/Qualifiers 1..112 mol_type = protein organism = Oryctolagus cuniculus	
SEQUENCE: 67 DVVMTQTPAS VEAvggtvt IKCQASQSI SYLAWYQQKP GQPPKRLIY ASNLDGVPS RFKGSGSGTD FTITISDLEC ADAATYYCQ TAVSSATIYG NAFFGGTEVV VK		60 112
SEQ ID NO: 68 FEATURE source	moltype = AA length = 127 Location/Qualifiers 1..127 mol_type = protein organism = Gallus gallus	
SEQUENCE: 68 AVLDESGGG LQTPGGALSL VCKASGFTFS GYDMLWVRQA PGKGLEWVAG IGSTGGGTDY GAAVKGRATI SRDNGQSTVR LQLNNLRAED TATYYCAKVA GGCNSGYCRD SPGSIDAWGH GTEVIVS		60 120 127
SEQ ID NO: 69 FEATURE source	moltype = AA length = 107 Location/Qualifiers 1..107 mol_type = protein organism = Gallus gallus	
SEQUENCE: 69 AVTQQPASVS ANPGETVKIT CGGGGSRNYY GWYQQKSPGS VPVTVIYYDD QRPSNIPSRF SGALSGSTST LTITGVQADD EAVYFCGSAD SNTYEGSFGA GTTLTVL		60 107
SEQ ID NO: 70 FEATURE source	moltype = AA length = 148 Location/Qualifiers 1..148 mol_type = protein organism = Mus musculus	
SEQUENCE: 70 MEWSGVFIFL LSGTAGVLSE VQLHQFGAEL VKPGASVKIS CKASGYTFD YNMDWVKQSH GKSLEWIGDI NPNYDSTSIN QKFKGKATLT VDKSSSTAYM ELRSLTSEDT AVYYCARSR YDYEGFAYWG QTGLTVSAA KTTPPSVY		60 120 148
SEQ ID NO: 71 FEATURE source	moltype = AA length = 105 Location/Qualifiers 1..105 mol_type = protein organism = Mus musculus	
SEQUENCE: 71 GLFCSVERCH YQLQSSQNLL SIVNRHYMS GNPPKLLVYP ALLIYEASIT KSCVPDRFTR SGSGTNFTLT INFVHADDLI FYYCQHNRS FLPSSSVQVP RRRSN		60 105
SEQ ID NO: 72 FEATURE source	moltype = AA length = 109 Location/Qualifiers 1..109 mol_type = protein organism = Mus musculus	
SEQUENCE: 72 PRASLGVSET LLCTSGFTFT DYYMSWVRQP PGKALEWLGF IRNKANGYTT EYSASVKGRF TISRDNQSII LYLMQMTLRA EDSATYYCAR ANWAFDYWGQ GTTVTVSSK		60 109
SEQ ID NO: 73 FEATURE source	moltype = AA length = 94 Location/Qualifiers 1..94 mol_type = protein organism = Mus musculus	
SEQUENCE: 73 SGDRVSLSCR ASQSISSNYLH WYQQKSHESP RLLIKYASQS ISGIPSFRSG SGSGTDFTLS INSVETEDFG MYFCQQSNSW PYTFGGTKL EIKQ		60 94

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SEQ ID NO: 74      moltype = AA length = 118
FEATURE
source
1..118
mol_type = protein
organism = Mus musculus
SEQUENCE: 74
AELVRPGTS VKVSCKASGY AFTNYLIVWI KORPGQGLEW IGVISPGSGG TNYNEKFKGK 60
AILTADKSSS TAYMQLSSLT SDEFAVYFCA REKIYDDYYE GYFDVWGAGP RHLLASLS 118

SEQ ID NO: 75      moltype = AA length = 107
FEATURE
source
1..107
mol_type = protein
organism = Mus musculus
SEQUENCE: 75
GTRCDIRLTO TTSSLASALG DRVTISCSAS LGIGNYLNWY QQKPDGTVKL LIYYTSNLHS 60
GVPSRFSGSG SGTDYSLTIS NLEPEDIATY YCQHYSKLPL TFGAGPS 107

SEQ ID NO: 76      moltype = AA length = 113
FEATURE
source
1..113
mol_type = protein
organism = Mus musculus
SEQUENCE: 76
GAEVLVRSGAS VKMSCKASGY SFTDYNMYWV KOTPGQGLEW IGYIYPGNNG TNYNQFKKGK 60
ATLTADTSSS TAYMQISSLT SEDSAVYFCA RDYDDGGYAM DYWGQGTTVT VSS 113

SEQ ID NO: 77      moltype = AA length = 117
FEATURE
source
1..117
mol_type = protein
organism = Mus musculus
SEQUENCE: 77
LLLWLTGARC DIQMTQSPAS LSASVGETVT ITCRASGNIH NYLTWYQQKQ GKSPQLLVYN 60
AKTLADGVPS RFSGSGSGTQ YSLKINRLQP EDFGSYYCQH FWNIPWTFGG GTKLNSR 117

SEQ ID NO: 78      moltype = AA length = 114
FEATURE
source
1..114
mol_type = protein
organism = Mus musculus
SEQUENCE: 78
DAELVKPGAS VKISCKASGY TFTDHSHIHWV QQKPEQGLEW IGYISPGNGN IKYNEKFKGK 60
ATLTADKSSS TAYMQLNSLT SEDSAVYFCK RSLGRGGPY FDYWGQGTTV TVSS 114

SEQ ID NO: 79      moltype = AA length = 108
FEATURE
source
1..108
mol_type = protein
organism = Mus musculus
SEQUENCE: 79
DIVLTQAAPS LPVTPGESVS ISCRSSKSLL HSNGNTLYW FLQRPGQSPQ LLIYRMSNLA 60
SGVPDRFSGS GSGTAFTLRI SRVEAEDVGV YYCMQHREYP VTFGSGPN 108

SEQ ID NO: 80      moltype = AA length = 111
FEATURE
source
1..111
mol_type = protein
organism = Mus musculus
SEQUENCE: 80
QVQLQQSGAE LMKPGASVKI SCKATGYTFS SYWIEWVKQR PGHGLEWIGE ILPGSGSTNY 60
NEKFKGKATF TADTSSNTAY MQLSSLTSED SAVYYCASYY WYFDVWAQDH V 111

SEQ ID NO: 81      moltype = AA length = 109
FEATURE
source
1..109
mol_type = protein
organism = Mus musculus
SEQUENCE: 81
IVMTQAAFSN PVTLGTSASI SCRSSKNLL SNGITYLYW LQRPGQSPQL LIYRVSNLAS 60
GVPNRFGSE SGTDFTLRIS RVEAEDVGVY YCAQLLELPY TSEGTKRWE 109

SEQ ID NO: 82      moltype = AA length = 109
FEATURE
source
1..109

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mol_type = protein
organism = Mus musculus

SEQUENCE: 82
GGGLVKPGGS LKLSCAAASGF AFSSYDMSWI ROTPEKRLEW VAYISSGAGS TYYPPDTVKGR 60
FTVSRDNNAKN TLYLQMSSLK SEDTAMYYCA RHFYRFDYWG QGTTVTVSS 109

SEQ ID NO: 83      moltype = AA length = 113
FEATURE           Location/Qualifiers
source            1..113
mol_type = protein
organism = Mus musculus

SEQUENCE: 83
LLLCVSGAPG SIVMTQTPKF LLVSAGDRIT ITCKASQSVS NDVAWYQQKP GQSPKLLIYY 60
ASNRYTGVPD RFTGSGYGTG FTFTISTVQA EDLAVYFCQQ DDRFPLTFGA GPS 113

SEQ ID NO: 84      moltype = AA length = 112
FEATURE           Location/Qualifiers
source            1..112
mol_type = protein
organism = Mus musculus

SEQUENCE: 84
QIQLVQSGPE LKKPGETVKI SCKASGYPT NYGMNNWVKQA PGKGLKWMGW INTYTGEPTY 60
ADDFKGRFAF SLETSASTAY LQINNLKNED TATYFCATGA WFAYWAKDSS RH 112

SEQ ID NO: 85      moltype = AA length = 107
FEATURE           Location/Qualifiers
source            1..107
mol_type = protein
organism = Mus musculus

SEQUENCE: 85
GVEGDIVMTO SHKFMSSTVGV DRVSITCKAS QDVGTAVAWY QQKPGQSPKL LIYWASTRHT 60
GVPDRFTGSG SGTDFTLTIS NVQSEDLADY FCQQYSSYPL TFGAGPS 107

SEQ ID NO: 86      moltype = AA length = 118
FEATURE           Location/Qualifiers
source            1..118
mol_type = protein
organism = Mus musculus

SEQUENCE: 86
GGGLVQPGGS MKVSCVASGF SFIDFWMNWV RQSPEKGLEW VAEIRLKSNM YATHYAESVK 60
GRFTISRDDS KSSVYLQMN LRPEDTGIYY CTSLFYYDG TSGFAYWGQG TTVTVLLK 118

SEQ ID NO: 87      moltype = AA length = 109
FEATURE           Location/Qualifiers
source            1..109
mol_type = protein
organism = Mus musculus

SEQUENCE: 87
DIVMTQSPSS LTVTAGEKVT MHCKSSQSLL NSGDQKNYLT WYQQKPGQOPP KLLIYASTR 60
ESGPVPDRFTG SGSGTDFTLT ISSVQAEDLA VYYCQNDYD PLTFGAGPS 109

SEQ ID NO: 88      moltype = AA length = 148
FEATURE           Location/Qualifiers
source            1..148
mol_type = protein
organism = Mus musculus

SEQUENCE: 88
MEWSGVIFIL LSGTAGVLSE VQLHQFGAEL VKPGASVKIS CKASGYTFD YNMDWVKQSH 60
GKSLEWIGDI NPNEYDSTSNT QKFKGKATLT VDKSSSTAYM ELRSLTSEDT AVYYCARSR 120
YDYEGFAYWG QGTLTVSAA KTPPPSVY 148

SEQ ID NO: 89      moltype = AA length = 139
FEATURE           Location/Qualifiers
source            1..139
mol_type = protein
organism = Mus musculus

SEQUENCE: 89
MSVLTQVLGL LLLWLTGARC DIQMTQSPAS LSASVGETVT ITCRASGNIH NYLAWYQQKQ 60
GKSPQLLVYN AKTLADGVPS RFSGSGSGTQ YSLKINSLOP EDFGSYYCQH FWSTLTFGAG 120
TKLELRKADA APTVSNPYD 139

SEQ ID NO: 90      moltype = AA length = 100
FEATURE           Location/Qualifiers
source            1..100
mol_type = protein
organism = Mus musculus

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SEQUENCE: 90
DILQASGYSF TGYTMNWKQ SHGKNLEWIG LINPYNGGTS YNQKFKGKAT LTVDKSSSTA 60
YMELLSLTSE DSAVYYCARW GVWSAMDYWG QGTTVTVSSK 100

SEQ ID NO: 91      moltype = AA length = 90
FEATURE           Location/Qualifiers
source            1..90
mol_type = protein
organism = Mus musculus

SEQUENCE: 91
DRVSIKAS QNVRTAVAWY QQKPRQSPKA LIYLASNRTD GLPDRFFGRG SGTDFTLNIT 60
NVQSEDLEDY PCLQHCNYPN EFRGCKVPI 90

SEQ ID NO: 92      moltype = AA length = 116
FEATURE           Location/Qualifiers
source            1..116
mol_type = protein
organism = Mus musculus

SEQUENCE: 92
LQESGAEALAR PGASVJKLSCK ASGYTFTSYW MOWVKQRPGQ GLEWIGAIYP GDGDTRYTQK 60
FKGKATLTAD KSSSTAYMQL SSLASEDSAV YYCARGEYGN YFAYWGGTT VTVSSN 116

SEQ ID NO: 93      moltype = AA length = 100
FEATURE           Location/Qualifiers
source            1..100
mol_type = protein
organism = Mus musculus

SEQUENCE: 93
TSDASLGERV TITCKASQDI NSYLSWFQQK PGKSPKTLIY RANRLVDGVP SRFSGSGSQ 60
DYSLTISLLE YEDMGIYYCL QYDEFPLTFG GGTKEIKQK 100

SEQ ID NO: 94      moltype = AA length = 108
FEATURE           Location/Qualifiers
source            1..108
mol_type = protein
organism = Mus musculus

SEQUENCE: 94
AWLSQLSCTA SGFNKIDTYM HWVKQRPEQG LEWIGRIDPA NGNTKYDPKF QGKATITADT 60
SSNTAYLQLS SLTSEDTAVY YCARPIHYYY GSSLAYWGGT TTVTVSSK 108

SEQ ID NO: 95      moltype = AA length = 104
FEATURE           Location/Qualifiers
source            1..104
mol_type = protein
organism = Mus musculus

SEQUENCE: 95
EFFHAVSLGQR ATISCRASES VDSYGNNSFMH WYQQKPGQPP KLLIYRASNL ESGIPARFSG 60
SGSRRTDFLT INPVEADDVA TYYCQQSNEP PGRSEVVPSW RSNK 104

SEQ ID NO: 96      moltype = AA length = 109
FEATURE           Location/Qualifiers
source            1..109
mol_type = protein
organism = Mus musculus

SEQUENCE: 96
PRASLGVSET LLCTSGFTFT DYYMSWVRQP PGKALEWLGF IRNKANGYTT EYSASVKGRF 60
TISRDNQSI LYLMQMTLRA EDSATYYCAR ANWAFDYWGQ GTTVTVSSK 109

SEQ ID NO: 97      moltype = AA length = 94
FEATURE           Location/Qualifiers
source            1..94
mol_type = protein
organism = Mus musculus

SEQUENCE: 97
SGDRVSLSCR ASQSISNYLH WYQQKSHESP RLLIKYASQS ISGIPSFRSG SGSGTDFTLS 60
INSVETEDEFG MYFCQQSNSW PYTFGGGTLK EIKQ 94

SEQ ID NO: 98      moltype = AA length = 111
FEATURE           Location/Qualifiers
source            1..111
mol_type = protein
organism = Mus musculus

SEQUENCE: 98
PACLPGGSLR LSCATSGFTF TDYYMSWVRQ PPGKALEWLG FIRNKANGYT TEYSASVKGR 60
FTISRDNQSI ILYLMQMTLRA AEDSATYYCA RAPLILYYAMD YWGQGTTVTV S 111

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SEQ ID NO: 99      moltype = AA length = 102
FEATURE          Location/Qualifiers
source           1..102
mol_type = protein
organism = Mus musculus
SEQUENCE: 99
RLPFYSLEQR ATISYRASKN VSTSGYSYMH WNQQKPGQPP KLLIYLVSNL ESGVPARFSG 60
SGSGTDFTLN IHPVEEEDAA TYYCQHIREL TRSELVPSWK SN               102

SEQ ID NO: 100      moltype = AA length = 101
FEATURE          Location/Qualifiers
source           1..101
mol_type = protein
organism = Mus musculus
SEQUENCE: 100
VSCKASGYTF TSYWMHWVKQ RPGQGLEWIG MIDPSNSETR LNQKFKDKAT LNVDKSSNTA 60
YMQLSSLTSE DSAVYYCARG LRHYWYFDVW GQGTTVTVSS K               101

SEQ ID NO: 101      moltype = AA length = 99
FEATURE          Location/Qualifiers
source           1..99
mol_type = protein
organism = Mus musculus
SEQUENCE: 101
TILWREGPFS YRASKSVSTS GYSYMHWNQQ KPGQPPRLLI YLVSNLESGV PARFSGSGSG 60
TDFTLNIHPV EEEADAATYYC QHIRELTRSE EVPSWRSNK               99

SEQ ID NO: 102      moltype = AA length = 110
FEATURE          Location/Qualifiers
source           1..110
mol_type = protein
organism = Mus musculus
SEQUENCE: 102
GGGLVVKPGGS LKLSCAAASGF TFSSYGMWSW RQTPEKRLEW VATISSGGSY TYYPDVKGR 60
FTISRDNAKN TLYLQMSSLR SEDTAMYYCA SLASYYFDYW GQGTTLTVSS               110

SEQ ID NO: 103      moltype = AA length = 113
FEATURE          Location/Qualifiers
source           1..113
mol_type = protein
organism = Mus musculus
SEQUENCE: 103
GARCDVQMIQ SPSSLSASLG DIVTMTCQAS QGTTSINLNWF QQKPGKAPKL LIYGASSLED 60
GVPSRSGSC FGTDFTLTIS SLEDEDMATY FCLQHSYLPF LTFGAGTKLE LKR               113

SEQ ID NO: 104      moltype = AA length = 111
FEATURE          Location/Qualifiers
source           1..111
mol_type = protein
organism = Mus musculus
SEQUENCE: 104
GPGLVQPSQS LSITCTVSGF SLTTYDLHWV RQSPGKGLEW LGVIWSGGST DYNAAFISRL 60
SISKDNNSKQ VFFKMNSLQA NDTAIYYCAR NYGYSAWPAY WGQGTLTVS A               111

SEQ ID NO: 105      moltype = AA length = 118
FEATURE          Location/Qualifiers
source           1..118
mol_type = protein
organism = Mus musculus
SEQUENCE: 105
PASSSDVLMQ QTPLSLPVSL GDQASISCRS SQSIVHSNGN TYLEWLQKP GQSPKLLIYK 60
VSNRFGSGVPT FTSKISRVEA EDLGVYYCFQ GSHVPLTFGA GTKLELKR               118

SEQ ID NO: 106      moltype = AA length = 114
FEATURE          Location/Qualifiers
source           1..114
mol_type = protein
organism = Mus musculus
SEQUENCE: 106
GFELKKPGET VKISCKASGY TFTAYSMHWV KQTPGKGLKW LGWINTETGE PTYTDDFKGR 60
FTFSLETSAR IAYLQINDLK NEDTATYFC A RRIYYFGRGG FDYWGQGTTV TVSS               114

SEQ ID NO: 107      moltype = AA length = 118
FEATURE          Location/Qualifiers
source           1..118
mol_type = protein

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SEQUENCE: 107
organism = Mus musculus
PASSSDVLMQTPLSLPVRL GDQSSISCRS SQSIVHSNGN TYLEWYLQKP GQSPKLLIYK 60
VSNRFGSGVPD RFSGSGSGTD FTLKISRVEP EDLGVYYCFQ GSHVPYTSEG DQAEIKLA 118

SEQ ID NO: 108      moltype = AA length = 114
FEATURE
source
1..114
mol_type = protein
organism = Mus musculus

SEQUENCE: 108
GGGLVQPGGS MRLSCVASGF TFSNSWFNWV RQSPEKGLEW VAEIRLTSND YAIYYAESVK 60
GRFTISRDDS KSSVYLOMNN LRAEDTGIYY CTRPETARAT FAYWGQGTTV TVSS 114

SEQ ID NO: 109      moltype = AA length = 118
FEATURE
source
1..118
mol_type = protein
organism = Mus musculus

SEQUENCE: 109
PASTSDVLMQTPLSLPVSL GDQASISCRS SQSIVHSNGN TYLEWYLQKP GQSPKVLIYK 60
VFNRFGSGVPD RFSGSGSGTD FTLKISRVEA EDLGVYYCFQ GSHVPRTFGG GTKLNQTG 118

SEQ ID NO: 110      moltype = AA length = 111
FEATURE
source
1..111
mol_type = protein
organism = Mus musculus

SEQUENCE: 110
GPDLVKPGAS VKISCKASGY SFTAYYMHWV KQSHGKSLEW IGRVNPNNGG TTYNQKFKGK 60
AILTVDKSSS TAYMELRSLT FEDSAVYYCA RRIYYGYFDY WGQGTTVTVS S 111

SEQ ID NO: 111      moltype = AA length = 104
FEATURE
source
1..104
mol_type = protein
organism = Mus musculus

SEQUENCE: 111
AFFAVSLGQR ATISCKASQS VDYDGDSYMN WYQQKPGQPP KLLIYVASNL ESGVPARFSG 60
SGSGTDFTLN IHPVEEEDAA TYYCQOSNED PYTFGGTKL EIKQ 104

SEQ ID NO: 112      moltype = AA length = 106
FEATURE
source
1..106
mol_type = protein
organism = Mus musculus

SEQUENCE: 112
GABELVKPGAS VKLSCTASGL NIRDYMHWV KQRPEQGLEW IGKIDPANGN TKYDPKFQGK 60
ATITADTSSN TAYVQLSSLT SEDTAVYYCA GTGDYWGQGT TTVVSS 106

SEQ ID NO: 113      moltype = AA length = 112
FEATURE
source
1..112
mol_type = protein
organism = Mus musculus

SEQUENCE: 113
GTCGDIVMSQ SPSSLAWSAG EKVTMSCKSS QSLLNSRTRK NYLAWVQHKP GQSPRLLIYW 60
ASTRESGVPD RFTGSGSGTD FTLTISSVQA EDLAVYYCRO SYNLVTFGAG PS 112

SEQ ID NO: 114      moltype = AA length = 112
FEATURE
source
1..112
mol_type = protein
organism = Mus musculus

SEQUENCE: 114
GPELVKPGAS VKMSCKASGY TFTSYVMHWV KOKPGQGLEW IGYINPYNDG TKYNEKFKGK 60
ATLTSDKSSS TAYMELSSLT SEDSAVYYCA RRYYYGSSG YFDVWAQDHV RT 112

SEQ ID NO: 115      moltype = AA length = 108
FEATURE
source
1..108
mol_type = protein
organism = Mus musculus

SEQUENCE: 115
DVQITQSPSY LAASPGETIT INCRASKSIS KYLAWYQEKP GKTNKLLIYS GSTLQSGIPS 60
RFSGSGSGTD FTLTISSLEP EDFAMYYCQQ HNEYPYTFGG GTKLEIKR 108

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SEQ ID NO: 116      moltype = AA  length = 113
FEATURE          Location/Qualifiers
source           1..113
mol_type = protein
organism = Mus musculus

SEQUENCE: 116
GPELVKPGAS VKISCKASGY SFTGYFMNWV MQSHGKSLEW IGRINPYNGD TFYNQKFKGK 60
ATLTVDKSSS TAHMELRSLA SEDSAVYYCA RRIHYYYGS YYAMDYWGQE PHH           113

SEQ ID NO: 117      moltype = AA  length = 108
FEATURE          Location/Qualifiers
source           1..108
mol_type = protein
organism = Mus musculus

SEQUENCE: 117
DVQITQSPSY LAASPGETIT INCRASKSIS KYLAWYQEKP GKTNKLIIYS GSTLQSGIPS 60
RFGSGSGSTD FTLTISSSL EDFAMYYCQQ HNEYPWTFGG GTKLEIKR           108

SEQ ID NO: 118      moltype = AA  length = 113
FEATURE          Location/Qualifiers
source           1..113
mol_type = protein
organism = Mus musculus

SEQUENCE: 118
GAGLVKPGAS VKLSCKASGY TFTEYIIHWV KQRSQGGLEW IGWFYPGSGS IKYNEKFKDK 60
ATLTADKSSS TVYMELSRLT SEDSAVYFCA RHEVYYDYDK SMLWTTGVKN LIR           113

SEQ ID NO: 119      moltype = AA  length = 108
FEATURE          Location/Qualifiers
source           1..108
mol_type = protein
organism = Mus musculus

SEQUENCE: 119
SPSSLAWSVG EKVTMSCSKSS QSLLYSSNQK NYLAWYQQKP GQSPKLLIYW ASTRESGVPD 60
RFTGSGSGSTD FTLTISSVKA EDLAVYYCQQ YYSYPPYTFGG GTKLEIKR           108

SEQ ID NO: 120      moltype = AA  length = 113
FEATURE          Location/Qualifiers
source           1..113
mol_type = protein
organism = Mus musculus

SEQUENCE: 120
GAELVRPGTS VKVSCKASVY AFTNYLIEWV KQRPQGGLEW IGVINPKSGG TKYNEKFRGK 60
ATLTADKSSS TAYMQLSSLT SGDSAVYFCA ITGTDYWGQG TTLTVSSAKT TPP           113

SEQ ID NO: 121      moltype = AA  length = 113
FEATURE          Location/Qualifiers
source           1..113
mol_type = protein
organism = Mus musculus

SEQUENCE: 121
QGTRCDIQMT QTTSSLSASL GDRVТИCSA SQGINNNYLW YQQKPDGTVK LLIYYTSSLR 60
SGVPSRFSGS GSGTDYSLTI SNLEPEDVAT YYCQQYSKLP RTFGGGTKLE IKR           113

SEQ ID NO: 122      moltype = AA  length = 121
FEATURE          Location/Qualifiers
source           1..121
mol_type = protein
organism = Homo sapiens

SEQUENCE: 122
EVQLVESGGG LVQPGGSLRL SCAASGFSLS SHSLGWVRQA PGKGLEWIGD IRSGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCTRTNG PSDLTNRSDL WGQGTLVTVS 120
S

SEQ ID NO: 123      moltype = AA  length = 112
FEATURE          Location/Qualifiers
source           1..112
mol_type = protein
organism = Homo sapiens

SEQUENCE: 123
QVLTQSPSSL SASVGDRVTI NCQASQSLYN NENLAWFQQK PGKVPKRILY GASTLASGVS 60
SRFSGSGSGT EFTLTISSLQ CEDFAIYYCL GEFSCGSADC FAFFGGGTKE IK           112

SEQ ID NO: 124      moltype = AA  length = 121
FEATURE          Location/Qualifiers

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source          1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 124
EVQLVESGGG LVQPGGSLRL SCAASGFSL S HSLGWVRQA PGKGLEWIGD IRSIGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYFCTRTNG PSDLTNRLLD W GQGTLVTVS 120
S                                         121

SEQ ID NO: 125      moltype = AA length = 112
FEATURE           Location/Qualifiers
source            1..112
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 125
QVLTQSPSSL SASVGDRVTI NCQASQSLYN NENLAWFQQK PGKVPKRLL YGASTLASGV 60
SRFSGSGSGT EFTLTISNL CEDFAIYYCL GEFSCGSADC CFAFGGGTKVE IK        112

SEQ ID NO: 126      moltype = AA length = 121
FEATURE           Location/Qualifiers
source            1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 126
EVQLVESGGG LVQPGGSLRL SCAASGFSL S HSLGWVRQA PGKGLEWIGD IRSIGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYFCTRTNG PSDLTNRLLD W GQGTLVTVS 120
S                                         121

SEQ ID NO: 127      moltype = AA length = 113
FEATURE           Location/Qualifiers
source            1..113
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 127
EQVLTQSPSS LSASVGDRVT INCQASQSLY NNENLAWFQQ KPGKVPKRLL YGASTLASGV 60
SSRFSGSGSG TEFTLTISNL QPEDFAIYYC LGEFSCGSADC CFAFGGGTKV EIK       113

SEQ ID NO: 128      moltype = AA length = 121
FEATURE           Location/Qualifiers
source            1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 128
EVQLVESGGG LVQPGGSLRL SCAASGFSL S HSLGWVRQA PGKGLEWIGD IRSIGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYFCTRTNG PSDLTNRLLD W GQGTLVTVS 120
S                                         121

SEQ ID NO: 129      moltype = AA length = 113
FEATURE           Location/Qualifiers
source            1..113
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 129
EIVLTQSPSS LSASVGDRVT INCQASQSLY NNENLAWFQQ KPGKVPKRLL YGASTLASGV 60
SSRFSGSGSG TEFTLTISNL QPEDFATYYC LGEFSCGSADC CFAFGGGTKV EIK       113

SEQ ID NO: 130      moltype = AA length = 121
FEATURE           Location/Qualifiers
source            1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 130
EVQLVESGGG LVQPGGSLRL SCAASGFSL S HSLGWVRQA PGKGLEWIGD IRSIGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYFCTRTNG PSDLTNRLLD W GQGTLVTVS 120
S                                         121

SEQ ID NO: 131      moltype = AA length = 113
FEATURE           Location/Qualifiers
source            1..113
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 131
EIVLTQSPSS LSASVGDRVT INCQASQSLY NNENLAWFQQ KPGKVPKRLL YGASTLASGV 60
SSRFSGSGSG TEFTLTISNL QPEDFATYYC LGEFSCGSADC CFAFGGGTKV EIK       113

SEQ ID NO: 132      moltype = AA length = 121
FEATURE           Location/Qualifiers

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source          1..121
               mol_type = protein
               organism = Homo sapiens
SEQUENCE: 132
EVQLVESGGG LVQPGGSLRL SCAASGFSL S HSLGWVRQA PGKGLEWIGD IRSGGSAYYA 60
NWAKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYFCTRTNG PSDLTNRLDL WGQQLVTVS 120
S                                         121

SEQ ID NO: 133      moltype = AA length = 113
FEATURE
source
1..113
mol_type = protein
organism = Homo sapiens
SEQUENCE: 133
EQVLTQSPSS LSASVGDRVT INCQASQSLY NNENLAWFQQ KPGKVPKRLI YGASTLASGV 60
SSRFSGSGSG TEFTLTISNL QPEDFAIYYC LGEFSCGSAD CFAFGGGTKV EIK           113

SEQ ID NO: 134      moltype = AA length = 5
FEATURE
source
1..5
mol_type = protein
organism = Gallus gallus
SEQUENCE: 134
GYDML                           5

SEQ ID NO: 135      moltype = AA length = 17
FEATURE
source
1..17
mol_type = protein
organism = Gallus gallus
SEQUENCE: 135
GIGSTGGGTD YGAAVKG                         17

SEQ ID NO: 136      moltype = AA length = 19
FEATURE
source
1..19
mol_type = protein
organism = Gallus gallus
SEQUENCE: 136
VAGGCNSGYC RDSPGSIDA                         19

SEQ ID NO: 137      moltype = AA length = 10
FEATURE
source
1..10
mol_type = protein
organism = Gallus gallus
SEQUENCE: 137
SGGGSRNYYG                           10

SEQ ID NO: 138      moltype = AA length = 7
FEATURE
source
1..7
mol_type = protein
organism = Gallus gallus
SEQUENCE: 138
DDQRPSN                           7

SEQ ID NO: 139      moltype = AA length = 11
FEATURE
source
1..11
mol_type = protein
organism = Gallus gallus
SEQUENCE: 139
SADSNTYEGS F                           11

SEQ ID NO: 140      moltype = AA length = 5
FEATURE
source
1..5
mol_type = protein
organism = Mus musculus
SEQUENCE: 140
DYNMD                           5

SEQ ID NO: 141      moltype = AA length = 17
FEATURE
source
1..17

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SEQUENCE: 141 DINPNYDSTS YNQKFKG	mol_type = protein organism = Mus musculus	
		17
SEQ ID NO: 142 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 142 SRSYDYEGFA Y		11
SEQ ID NO: 143 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 143 LSIVNRYHYM S		11
SEQ ID NO: 144 FEATURE source	moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = Mus musculus	
SEQUENCE: 144 EASITK		6
SEQ ID NO: 145 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 145 QHNRGGSFLP		9
SEQ ID NO: 146 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 146 DYYMS		5
SEQ ID NO: 147 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 147 RNKANGYTTE YSASVKG		17
SEQ ID NO: 148 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 148 ARANWAFDY		9
SEQ ID NO: 149 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 149 RASQSIISNYL H		11
SEQ ID NO: 150 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 150 YASQSIIS		7

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SEQ ID NO: 151	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 151	
YASQSI	7
SEQ ID NO: 152	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 152	
NYLIV	5
SEQ ID NO: 153	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 153	
VISPGSGGTN YNEKFKG	17
SEQ ID NO: 154	moltype = AA length = 11
FEATURE	Location/Qualifiers
source	1..11
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 154	
EKIYDDYYEG Y	11
SEQ ID NO: 155	moltype = AA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 155	
TISCSASLGI GNYLN	15
SEQ ID NO: 156	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 156	
TSNLHSG	7
SEQ ID NO: 157	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 157	
HYSKLPLTF	9
SEQ ID NO: 158	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 158	
DYNMY	5
SEQ ID NO: 159	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 159	
YIYPGNNGTN YNQKFKG	17
SEQ ID NO: 160	moltype = AA length = 11
FEATURE	Location/Qualifiers
source	1..11

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SEQUENCE: 160 DYDDGGYAMD Y	mol_type = protein organism = Mus musculus	
		11
SEQ ID NO: 161 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15	
SEQUENCE: 161 SVGETVTITC RASGN	mol_type = protein organism = Mus musculus	
		15
SEQ ID NO: 162 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7	
SEQUENCE: 162 NAKTLAD	mol_type = protein organism = Mus musculus	
		7
SEQ ID NO: 163 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9	
SEQUENCE: 163 QHFWNIPWT	mol_type = protein organism = Mus musculus	
		9
SEQ ID NO: 164 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5	
SEQUENCE: 164 DHSIH	mol_type = protein organism = Mus musculus	
		5
SEQ ID NO: 165 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17	
SEQUENCE: 165 YISPGNGNPK YNEKFKG	mol_type = protein organism = Mus musculus	
		17
SEQ ID NO: 166 FEATURE source	moltype = AA length = 12 Location/Qualifiers 1..12	
SEQUENCE: 166 SLGRGGPYFY DY	mol_type = protein organism = Mus musculus	
		12
SEQ ID NO: 167 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16	
SEQUENCE: 167 RSSKSLLHSN GNTYLY	mol_type = protein organism = Mus musculus	
		16
SEQ ID NO: 168 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7	
SEQUENCE: 168 RMSNLAS	mol_type = protein organism = Mus musculus	
		7
SEQ ID NO: 169 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9	
SEQUENCE: 169 MQHREYPVT	mol_type = protein organism = Mus musculus	
		9

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SEQ ID NO: 170 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 170 SYWIE		5
SEQ ID NO: 171 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 171 EILPGSGSTN YNEKFKG		17
SEQ ID NO: 172 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 172 YYWYFDVWAQ D		11
SEQ ID NO: 173 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = Mus musculus	
SEQUENCE: 173 SSKNLLHSNG ITYLY		15
SEQ ID NO: 174 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 174 RVSNLAS		7
SEQ ID NO: 175 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 175 AQLLELPYT		9
SEQ ID NO: 176 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 176 SYDMS		5
SEQ ID NO: 177 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 177 YISSGAGSTY YPDTVKG		17
SEQ ID NO: 178 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 178 HFYRFDYWGQ G		11
SEQ ID NO: 179 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15	

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	mol_type = protein
	organism = Mus musculus
SEQUENCE: 179	
SAGDRITITC KASQS	
SEQ ID NO: 180	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 180	
YASNRYT	
SEQ ID NO: 181	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 181	
QQDDRFPLT	
SEQ ID NO: 182	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 182	
NYGMN	
SEQ ID NO: 183	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 183	
WINTYTGEPT YADDFKG	
SEQ ID NO: 184	moltype = AA length = 11
FEATURE	Location/Qualifiers
source	1..11
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 184	
GAWFAYWAKD S	
SEQ ID NO: 185	moltype = AA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 185	
SITCKASQDV GTAVA	
SEQ ID NO: 186	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 186	
WASTRHT	
SEQ ID NO: 187	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 187	
QQYSSYPLT	
SEQ ID NO: 188	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 188	
DFWMN	

-continued

SEQ ID NO: 189 FEATURE source	moltype = AA length = 19 Location/Qualifiers 1..19 mol_type = protein organism = Mus musculus	
SEQUENCE: 189 EIRLKSNNYA THYAESVKG		19
SEQ ID NO: 190 FEATURE source	moltype = AA length = 13 Location/Qualifiers 1..13 mol_type = protein organism = Mus musculus	
SEQUENCE: 190 LFYYYDGTSG PAY		13
SEQ ID NO: 191 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 191 KSSQSLLNSG DQKNYLT		17
SEQ ID NO: 192 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 192 WASTRES		7
SEQ ID NO: 193 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 193 QNDYDYPLT		9
SEQ ID NO: 194 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 194 DYNMD		5
SEQ ID NO: 195 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 195 DINPNYDSTS YNQKFKG		17
SEQ ID NO: 196 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 196 SRSYDYEGFA Y		11
SEQ ID NO: 197 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 197 RASGNIHNLY A		11
SEQ ID NO: 198 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7	

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SEQUENCE: 198 NAKTLAD	mol_type = protein organism = Mus musculus	7
SEQ ID NO: 199 FEATURE source	moltype = AA length = 8 Location/Qualifiers 1..8 mol_type = protein organism = Mus musculus	
SEQUENCE: 199 QHFWSLT		8
SEQ ID NO: 200 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 200 GYTMN		5
SEQ ID NO: 201 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16 mol_type = protein organism = Mus musculus	
SEQUENCE: 201 NPYNGGTSYN QKFKKGK		16
SEQ ID NO: 202 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 202 WGVWSAMDY		9
SEQ ID NO: 203 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 203 KASQNVRTAV A		11
SEQ ID NO: 204 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 204 LASNRDT		7
SEQ ID NO: 205 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 205 LQHCNYPNE		9
SEQ ID NO: 206 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 206 SYWMQ		5
SEQ ID NO: 207 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 207 AIYPGDGDTR YTQKFKGK		17

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SEQ ID NO: 208 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 208 ARGEYGNFYA Y		11
SEQ ID NO: 209 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 209 KASQDINSYL S		11
SEQ ID NO: 210 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 210 RANRLVD		7
SEQ ID NO: 211 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 211 LQYDEFPLT		9
SEQ ID NO: 212 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 212 DTYMH		5
SEQ ID NO: 213 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 213 RIDPANGNTK YDPKFQG		17
SEQ ID NO: 214 FEATURE source	moltype = AA length = 14 Location/Qualifiers 1..14 mol_type = protein organism = Mus musculus	
SEQUENCE: 214 ARPIHYYYGS SLAY		14
SEQ ID NO: 215 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 215 SVDSYGNSFM H		11
SEQ ID NO: 216 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 216 RASNLES		7
SEQ ID NO: 217 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9	

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	mol_type = protein organism = Mus musculus	
SEQUENCE: 217 QQSNEDPGR		9
SEQ ID NO: 218 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 218 DYYMS		5
SEQ ID NO: 219 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 219 RNKANGYTTE YSASVKG		17
SEQ ID NO: 220 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 220 ARANWAFDY		9
SEQ ID NO: 221 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 221 RASQSiSNYL H		11
SEQ ID NO: 222 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 222 YASQSiS		7
SEQ ID NO: 223 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 223 QQSNWPYT		9
SEQ ID NO: 224 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 224 DYYMS		5
SEQ ID NO: 225 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 225 RNKANGYTTE YSASVKG		17
SEQ ID NO: 226 FEATURE source	moltype = AA length = 12 Location/Qualifiers 1..12 mol_type = protein organism = Mus musculus	
SEQUENCE: 226 ARAPLLYYAM DY		12

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SEQ ID NO: 227 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 227 NVSTSGYSYM H		11
SEQ ID NO: 228 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 228 LVSNLES		7
SEQ ID NO: 229 FEATURE source	moltype = AA length = 8 Location/Qualifiers 1..8 mol_type = protein organism = Mus musculus	
SEQUENCE: 229 QHIRELTR		8
SEQ ID NO: 230 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 230 SYWMH		5
SEQ ID NO: 231 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 231 MIDPSNSETR LNQKFKD		17
SEQ ID NO: 232 FEATURE source	moltype = AA length = 12 Location/Qualifiers 1..12 mol_type = protein organism = Mus musculus	
SEQUENCE: 232 ARGLRHYWYF DV		12
SEQ ID NO: 233 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 233 SVSTSGYSYM H		11
SEQ ID NO: 234 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 234 LVSNLES		7
SEQ ID NO: 235 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 235 QHIRELTRS		9
SEQ ID NO: 236 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5	

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SEQUENCE: 236	mol_type = protein organism = Mus musculus	
SYGMS		5
SEQ ID NO: 237	moltype = AA length = 14 Location/Qualifiers	
FEATURE	1..14	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 237		
WVRQTPEKRL EWVA		14
SEQ ID NO: 238	moltype = AA length = 11 Location/Qualifiers	
FEATURE	1..11	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 238		
LASYYYFDYWG Q		11
SEQ ID NO: 239	moltype = AA length = 15 Location/Qualifiers	
FEATURE	1..15	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 239		
TMTCQASQGT SINLN		15
SEQ ID NO: 240	moltype = AA length = 7 Location/Qualifiers	
FEATURE	1..7	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 240		
GASSLED		7
SEQ ID NO: 241	moltype = AA length = 11 Location/Qualifiers	
FEATURE	1..11	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 241		
LQHSYLPPPLT F		11
SEQ ID NO: 242	moltype = AA length = 5 Location/Qualifiers	
FEATURE	1..5	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 242		
TYDLH		5
SEQ ID NO: 243	moltype = AA length = 16 Location/Qualifiers	
FEATURE	1..16	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 243		
VIWGGGSTDY NAAFIS		16
SEQ ID NO: 244	moltype = AA length = 11 Location/Qualifiers	
FEATURE	1..11	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 244		
NYGYSAWFAY W		11
SEQ ID NO: 245	moltype = AA length = 15 Location/Qualifiers	
FEATURE	1..15	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 245		
ASISCRSSQS IVHSN		15

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SEQ ID NO: 246 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 246 KVSNRFS		7
SEQ ID NO: 247 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 247 FQGSHVPLT		9
SEQ ID NO: 248 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 248 AYSMH		5
SEQ ID NO: 249 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 249 WINTETGEPT YTDDPKG		17
SEQ ID NO: 250 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 250 RIYYFGRGGF D		11
SEQ ID NO: 251 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = Mus musculus	
SEQUENCE: 251 SSISCRSSQS IVHSN		15
SEQ ID NO: 252 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 252 KVSNRFS		7
SEQ ID NO: 253 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 253 FQGSHVPYT		9
SEQ ID NO: 254 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 254 NSWFN		5
SEQ ID NO: 255 FEATURE source	moltype = AA length = 19 Location/Qualifiers 1..19	

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SEQUENCE: 255	mol_type = protein organism = Mus musculus	
EIRLTSNDYA IYYAESVKG		19
SEQ ID NO: 256	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 256		
PETARATFAY W		11
SEQ ID NO: 257	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 257		
ASISCRSSQS IVHSN		15
SEQ ID NO: 258	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 258		
KVFNRF S		7
SEQ ID NO: 259	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 259		
FQGSHVPRT		9
SEQ ID NO: 260	moltype = AA length = 5	
FEATURE	Location/Qualifiers	
source	1..5	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 260		
AYYMH		5
SEQ ID NO: 261	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 261		
RVNPNNGGTT YNQKFKG		17
SEQ ID NO: 262	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 262		
RIYYGYFDYW G		11
SEQ ID NO: 263	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 263		
KASQSVVDYDG DSYMN		15
SEQ ID NO: 264	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = Mus musculus	
SEQUENCE: 264		
VASNLES		7

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SEQ ID NO: 265 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 265 QQSNEDPYT		9
SEQ ID NO: 266 FEATURE source	moltype = AA length = 4 Location/Qualifiers 1..4 mol_type = protein organism = Mus musculus	
SEQUENCE: 266 D1YM		4
SEQ ID NO: 267 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 267 KIDPANGNTK YDPKFQG		17
SEQ ID NO: 268 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 268 TGDYWGQGTT V		11
SEQ ID NO: 269 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = Mus musculus	
SEQUENCE: 269 TMSCKSSQSL LNSRT		15
SEQ ID NO: 270 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 270 WASTRES		7
SEQ ID NO: 271 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 271 RQSYNLVTF		9
SEQ ID NO: 272 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 272 SYVMH		5
SEQ ID NO: 273 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 273 YINPYNDGTK YNEKFKG		17
SEQ ID NO: 274 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11	

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SEQUENCE: 274	mol_type = protein organism = Mus musculus	
RYYYGSSGGY F		11
SEQ ID NO: 275	moltype = AA length = 15 Location/Qualifiers	
FEATURE	1..15	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 275		
RASKSISKYL AWYQE		15
SEQ ID NO: 276	moltype = AA length = 7 Location/Qualifiers	
FEATURE	1..7	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 276		
SGSTLQS		7
SEQ ID NO: 277	moltype = AA length = 9 Location/Qualifiers	
FEATURE	1..9	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 277		
QQHNEYPYT		9
SEQ ID NO: 278	moltype = AA length = 5 Location/Qualifiers	
FEATURE	1..5	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 278		
GYFMN		5
SEQ ID NO: 279	moltype = AA length = 17 Location/Qualifiers	
FEATURE	1..17	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 279		
RINPYNGDTF YNQKFKG		17
SEQ ID NO: 280	moltype = AA length = 11 Location/Qualifiers	
FEATURE	1..11	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 280		
RIHYYYGSSY Y		11
SEQ ID NO: 281	moltype = AA length = 15 Location/Qualifiers	
FEATURE	1..15	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 281		
RASKSISKYL AWYQE		15
SEQ ID NO: 282	moltype = AA length = 7 Location/Qualifiers	
FEATURE	1..7	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 282		
SGSTLQS		7
SEQ ID NO: 283	moltype = AA length = 9 Location/Qualifiers	
FEATURE	1..9	
source	mol_type = protein organism = Mus musculus	
SEQUENCE: 283		
QQHNEYPWT		9

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SEQ ID NO: 284	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 284	
EYIIH	5
SEQ ID NO: 285	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 285	
WFYPGSGSIK YNEKFKD	17
SEQ ID NO: 286	moltype = AA length = 11
FEATURE	Location/Qualifiers
source	1..11
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 286	
HEVYYDYDKS M	11
SEQ ID NO: 287	moltype = AA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 287	
LYSSNQKNYL AWYQQ	15
SEQ ID NO: 288	moltype = AA length = 7
FEATURE	Location/Qualifiers
source	1..7
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 288	
WASTRES	7
SEQ ID NO: 289	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 289	
QQYYSYPYT	9
SEQ ID NO: 290	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 290	
NYLIE	5
SEQ ID NO: 291	moltype = AA length = 19
FEATURE	Location/Qualifiers
source	1..19
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 291	
VINPKSGGTK YNEKFRGKA	19
SEQ ID NO: 292	moltype = AA length = 11
FEATURE	Location/Qualifiers
source	1..11
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 292	
TGTDYWGQGT T	11
SEQ ID NO: 293	moltype = AA length = 10
FEATURE	Location/Qualifiers
source	1..10

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SEQUENCE: 293 VTISCSASQG	mol_type = protein organism = Mus musculus	
		10
SEQ ID NO: 294 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = Mus musculus	
SEQUENCE: 294 YTSSLRS		7
SEQ ID NO: 295 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = Mus musculus	
SEQUENCE: 295 QQYSKLPRT		9
SEQ ID NO: 296 FEATURE source	moltype = AA length = 12 Location/Qualifiers 1..12 mol_type = protein organism = Homo sapiens	
SEQUENCE: 296 FTSGEKEQVD EW		12
SEQ ID NO: 297 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16 mol_type = protein organism = Homo sapiens	
SEQUENCE: 297 AEQKRLKTVL ELQYVL		16
SEQ ID NO: 298 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16 mol_type = protein organism = Homo sapiens	
SEQUENCE: 298 VERVFQSNSYF DSTHNH		16
SEQ ID NO: 299 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16 mol_type = protein organism = Homo sapiens	
SEQUENCE: 299 FQSMQTVFNM NAPVPP		16
SEQ ID NO: 300 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = Mus musculus	
SEQUENCE: 300 TNAMN		5
SEQ ID NO: 301 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = Mus musculus	
SEQUENCE: 301 RIRSKSNNYA TYYADSV		17
SEQ ID NO: 302 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = Mus musculus	
SEQUENCE: 302 DWDGFLYFDY W		11

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SEQ ID NO: 303      moltype = AA length = 112
FEATURE
source
1..112
mol_type = protein
organism = Mus musculus

SEQUENCE: 303
GGGLVQPKGS LKLSCAAASGF TFNTNAMNVW RQAPGKGLEW VARIRSKSNN YATYYADSVK 60
DRFTISRDDS QSMLYLQMNN LKTEDTAMYY CVRDWDGFLY FDYWAKHHLT LF           112

SEQ ID NO: 304      moltype = AA length = 15
FEATURE
source
1..15
mol_type = protein
organism = Mus musculus

SEQUENCE: 304
SVSTSGYSYM HWNQQ                                         15

SEQ ID NO: 305      moltype = AA length = 7
FEATURE
source
1..7
mol_type = protein
organism = Mus musculus

SEQUENCE: 305
LVSNLES                                         7

SEQ ID NO: 306      moltype = AA length = 9
FEATURE
source
1..9
mol_type = protein
organism = Mus musculus

SEQUENCE: 306
QHIRELTRS                                         9

SEQ ID NO: 307      moltype = AA length = 104
FEATURE
source
1..104
mol_type = protein
organism = Mus musculus

SEQUENCE: 307
TQSPASPALAVS LGQRATISYR ASKSVSTSGY SYMHWNQQKP GQPPRLLIYL VSNLESGVPA 60
RFSGSGSGTD FTLNIIHPVEE EDAATYYCQH IRELTRSEGG PSWK                 104

SEQ ID NO: 308      moltype = AA length = 14
FEATURE
source
1..14
mol_type = protein
organism = Homo sapiens

SEQUENCE: 308
PPVNEPETLK QQNQ                                         14

SEQ ID NO: 309      moltype = AA length = 12
FEATURE
source
1..12
mol_type = protein
organism = Homo sapiens

SEQUENCE: 309
ETLKQQNQYQ AS                                         12

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1. A method for treating and/or preventing a cancer expressing a CAPRIN-1 protein on the cell membrane surface, comprising administering an effective amount of a conjugate of an antibody or a fragment thereof linked to an immune activator, wherein the antibody or the fragment thereof has immunological reactivity with a CAPRIN-1 protein of any of even-numbered SEQ ID NOs among SEQ ID NO: 2 to 30 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence of any of even-numbered SEQ ID NOs among SEQ ID NO: 2 to 30, or a pharmaceutical composition comprising the conjugate as an active ingredient and a pharmacologically acceptable carriers or media to a subject in need thereof.

2. The method according to claim 1, wherein the antibody or the fragment thereof has immunological reactivity with a partial polypeptide of the CAPRIN-1 protein, wherein the partial polypeptide consists of any of SEQ ID NO: 31 to 35 and 296 to 299, 308, and 309 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence of any of SEQ ID NO: 31 to 35 and 296 to 299, 308, and 309.

3. The method according to claim 1, wherein the antibody is a monoclonal antibody or a polyclonal antibody.

4. The method according to claim 1, wherein the antibody or the fragment thereof is any of the following (A) to (M):

(A) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complemen-

- tarity-determining regions of SEQ ID NO: 36, 37, and 38 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 40, 41, and 42 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (B) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 44, 45, and 46 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 48, 49, and 50 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (C) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 52, 53, and 54 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 56, 57, and 58 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (D) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 60, 61, and 62 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 64, 65, and 66 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (E) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 170, 171, and 172 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 173, 174, and 175 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (F) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 176, 177, and 178 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 179, 180, and 181 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (G) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 182, 183, and 184 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 185, 186, and 187 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (H) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 188, 189, and 190 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 191, 192,

and 193 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,

- (I) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 146, 147, and 148 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 149, 150, and 151 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (J) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 272, 273, and 274 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 275, 276, and 277 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (K) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 290, 291, and 292 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 293, 294, and 295 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein,
- (L) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein, and
- (M) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NO: 134, 135, and 136 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NO: 137, 138, and 139 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein.
5. The method according to claim 1, wherein the antibody or the fragment thereof is any of the following (a) to (al):
- (a) an antibody or a fragment thereof, comprising 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: 43,
- (b) an antibody or a fragment thereof, comprising 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: 51,
- (c) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid

- sequence of SEQ ID NO: 114 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 115,
- (ac) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 117,
- (ad) an antibody or a fragment thereof, comprising 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: 119,
- (ae) an antibody or a fragment thereof, comprising 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: 121,
- (af) an antibody or a fragment thereof, comprising 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: 123,
- (ag) an antibody or a fragment thereof, comprising 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: 125,
- (ah) an antibody or a fragment thereof, comprising 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: 127,
- (ai) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 129,
- (aj) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 131,
- (ak) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 133, and
- (al) an antibody or a fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.
6. The method according to claim 1, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, or a single-chain antibody.
7. The method according to claim 1, wherein the immune activator is a ligand or an agonist binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR).
8. The method according to claim 1, wherein the Toll-like receptor (TLR) is a ligand or an agonist binding to TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, or TLR10.
9. The method according to claim 7, wherein the ligand or the agonist binding to the Toll-like receptor (TLR) is any of the following (i) to (vii):
- (i) a TLR2-binding ligand or agonist selected from the group consisting of peptidoglycan, lipoprotein, lipopolysaccharide, and zymosan,
 - (ii) a TLR3-binding ligand or agonist selected from the group consisting of poly(I: C) and poly(A: U),
 - (iii) a TLR4-binding ligand or agonist selected from the group consisting of lipopolysaccharide (LPS), HSP60, RS09, and MPLA,
 - (iv) a TLR5-binding ligand or agonist which is flagellin,
 - (v) a TLR7- or TLR8-binding ligand or agonist selected from the group consisting of an imidazoquinoline compound and single-stranded RNA,
 - (vi) a TLR9-binding ligand or agonist selected from the group consisting of bacterial DNA, non-methylated CpG DNA, hemozoin, ODN1585, ODN1668, and ODN1826, and
 - (vii) a TLR10-binding ligand or agonist selected from the group consisting of profilin and a uropathogenic bacterium.
10. The method according to claim 1, wherein the antibody or the fragment thereof is linked to the immune activator via a linker.
11. The method according to claim 1, wherein the cancer is breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer.

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