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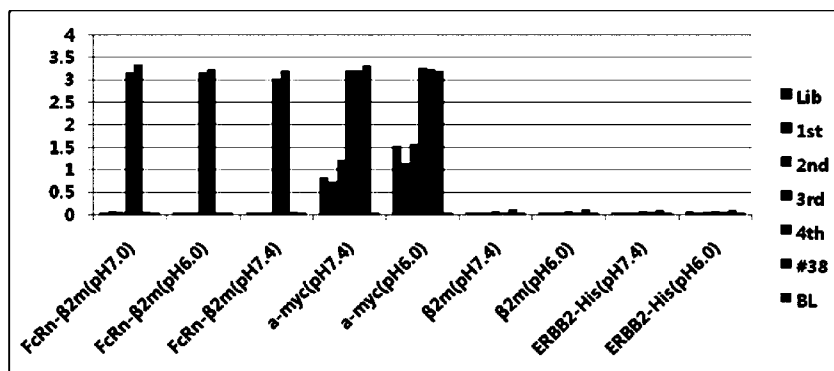
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(54) Title: FCRN-SPECIFIC HUMAN ANTIBODY AND COMPOSITION FOR TREATMENT OF AUTOIMMUNE DISEASES



(57) Abstract: The present invention relates to a human antibody specific for FcRn that is a receptor with a high affinity for IgG, a production method thereof, a composition for treating autoimmune disease, which comprises the antibody, and a method of treating and diagnosing autoimmune disease using the same. The FcRn-specific antibody according to the present invention can bind to FcRn non-competitively with IgG or the like to reduce serum auto-antibody levels, and thus can be used for the treatment of autoimmune diseases.



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Description

Title of Invention: FCRN-SPECIFIC HUMAN ANTIBODY AND COMPOSITION FOR TREATMENT OF AUTOIMMUNE DISEASES

Technical Field

- [1] The present invention relates to a human antibody specific for FcRn (stands for neonatal Fc receptor, also called FcRP, FcRB or Brambell receptor) that is a receptor with a high affinity for IgG, a production method thereof, a composition for treating autoimmune disease, which comprises the antibody, and a method of treating and diagnosing autoimmune disease using the same. The FcRn-specific antibody according to the present invention can bind to FcRn non-competitively with IgG or the like to reduce serum pathogenic auto-antibody levels, and thus can be used for the treatment of autoimmune diseases.

[2]

Background Art

- [3] Antibodies are immunological proteins that bind to a specific antigen. In most animals, including humans and mice, antibodies are constructed from paired heavy and light polypeptide chains. Each chain is made up of two distinct regions, referred to as the variable and constant regions. The light and heavy chain variable regions show significant sequence diversity between antibodies, and are responsible for binding the target antigen. The constant regions show less sequence diversity, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing feature between these antibody classes is their constant regions.
- [4] IgG antibodies are most abundantly present in serum, protect the body from the invasion of pathogens, hasten the recruitment of immune system components, and mediate inflammatory responses in tissues. IgG antibodies are tetrameric proteins composed of two heavy chains and two light chains. The IgG heavy chain is composed of four immunoglobulin domains linked from N- to C-terminus in the order VH-CH1-CH2-CH3, referring to the heavy chain variable domain (VH), heavy chain constant domain 1 (CH1), heavy chain constant domain 2 (CH2), and heavy chain constant domain 3 (CH3), respectively.
- [5] The IgG light chain is composed of two immunoglobulin domains linked from N- to C-terminus in the order of VL-CL, referring to the light chain variable domain (VL) and the light chain constant domain (CL), respectively.
- [6] Under normal conditions, the half-life of most IgG excluding IgG3 isotype in serum is about 22-23 days in humans, which is a prolonged period relative to the serum

half-life of other plasma proteins. With respect to this prolonged serum half-life of IgG, IgG that entered cells by endocytosis can strongly bind to neonatal Fc receptor (FcRn, a kind of Fc gamma receptor) in endosomes at a pH of 6.0 to avoid the degradative lysosomal pathway. When the IgG-FcRn complex cycles to the plasma membrane, IgG dissociates rapidly from FcRn in the bloodstream at slightly basic pH (~7.4). By this receptor-mediated recycling mechanism, FcRn effectively rescues the IgG from degradation in lysosomes, thereby prolonging the half-life of IgG (Roopenian et al. *J. Immunol.* 170:3528, 2003).

- [7] FcRn was identified in the neonatal rat gut, where it functions to mediate the absorption of IgG antibody from the mother's milk and facilitates its transport to the circulatory system. FcRn has also been isolated from human placenta, where it mediates absorption and transport of maternal IgG to the fetal circulation. In adults, FcRn is expressed in a number of tissues, including epithelial tissues of the lung, intestine, kidney, as well as nasal, vaginal, and biliary tree surfaces.
- [8] FcRn is a non-covalent heterodimer that typically resides in the endosomes of endothelial and epithelial cells. FcRn is a membrane bound receptor having three heavy chain alpha domains (#1, #2 and #3) and a single soluble light chain #2-microglobulin (#2m) domain. Structurally, it belongs to a family of major histocompatibility complex class 1 molecules that have #2m as a common light chain. The FcRn chain has a molecular weight of about 46 kD and is composed of an ectodomain containing the #1, #2, and #3 heavy chain domains and a #2m light chain domain and having a single sugar chain, a single-pass transmembrane, and a relatively short cytoplasmic tail (Burmeister et al. *Nature* 372:366, 1994.).
- [9] In order to study the contributions of FcRn to IgG homeostasis, mice have been engineered so that at least part of the genes encoding #2m and FcRn heavy chains have been "knocked out" so that these proteins are not expressed. In these mice, the serum half-life and concentrations of IgG were dramatically reduced (Junghans et al, *Proc. Natl. Acad. Sci.* 93:5512, 1996), suggesting a FcRn-dependent mechanism for IgG homeostasis. It has also been suggested that anti-human FcRn antibodies may be generated in these FcRn knockout mice and that these antibodies may prevent the binding of IgG to FcRn. However, such antibodies have not been generated or tested (WO 02/43658 A).
- [10] The inhibition of IgG binding to FcRn negatively alters IgG serum half-life by preventing IgG recycling, so that autoimmune diseases caused by auto-antibodies can be treated. This possibility was shown in a mouse model of autoimmune cutaneous bullous diseases (Li et al. *J. Clin. Invest.* 115:3440, 2005). Accordingly, agents that block or antagonize the binding of IgG to FcRn may be used in a method for treating or preventing autoimmune and inflammatory diseases, which are mediated by IgG.
- [11] Autoimmune diseases and alloimmune diseases are mediated by pathogenic antibodies, and typical examples thereof include immune neutropenia, Guillain-Barre

syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome, pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, lupus, and idiopathic thrombocytopenic purpura (hereinafter referred to as ITP). ITP is a disease caused by the destruction of peripheral platelets due to the generation of auto-antibodies that bind to a specific platelet membrane glycoprotein. Anti-platelet antibodies opsonize platelets and result in rapid platelet destruction by reticular cells (e.g., macrophages).

[12] In general, attempts to treat ITP include suppressing the immune system, and consequently causing an increase in platelet levels. ITP affects women more frequently than men, and more common in children than adults. The incidence is 1 out of 10,000 people. Chronic ITP is one of the major blood disorders in both adults and children. It is a source of significant hospitalization and treatment cost at specialized hematological departments in the US and around the world. Each year there are approximately 20,000 new cases in the US, and the cost for ITP care and special therapy is extremely high. Most children with ITP have a very low platelet count that causes sudden bleeding, with typical symptoms including bruises, small red dots on the skin, nosebleeds and bleeding gums. Although children can sometimes recover with no treatment, many doctors recommend careful observation and mitigation of bleeding and treatment with intravenous infusions of gamma globulin.

[13] Methods of treating autoimmune diseases by intravenous administration of IgG (IVIG) in large amounts have been widely used (Arnson autoimmunity 42:553 (2009)). IVIG effects are explained by various mechanisms, but are also explained by a mechanism that increases the clearance of pathogenic antibodies by competition with endogenous IgG for FcRn. Intravenous administration of human immunoglobulin (IVIG) in large amounts has been shown to increase platelet counts in children afflicted with immune ITP, and IVIG has shown to be beneficial as a treatment for several other autoimmune conditions. Many studies have investigated the mechanisms by which IVIG achieves effects in the treatment of autoimmune diseases. With regard to ITP, early investigations led to the conclusion that IVIG effects are mainly due to blockade of the Fc receptors responsible for phagocytosis of antibody-opsonized platelets. Subsequent studies showed that Fc-depleted IVIG preparations provided increases in platelet counts in some patients with ITP, and recently it was reported that IVIG effects are due to stimulation of Fc γ RIIb expression on macrophage cells, leading to inhibition of platelet phagocytosis.

[14]

[15] *However, such IVIG treatments have substantial side effects and are very costly to administer. Further, other therapies used for the treatment of autoimmune/alloimmune

conditions other than IVIG include polyclonal anti-D immunoglobulin, corticosteroids, immuno-suppressants (including chemotherapeutics), cytokines, plasmapheresis, extracorporeal antibody adsorption (e.g., using Prosorba columns), surgical interventions such as splenectomy, and others. However, like IVIG, these therapies are also complicated by incomplete efficacy and high cost. Also, very high doses of IVIG are required to produce substantial increases in the clearance of pathogenic antibody due to the putative mechanism of IVIG inhibition of FcRn binding with pathogenic antibody (i.e., competitive inhibition) and due to the fact that IgG shows very low affinity for FcRn at physiologic pH (i.e., pH 7.2-7.4), and the typical clinical dose of IVIG is about 2 g/kg.

[16] The use of an inhibitor that competitively inhibits the binding of IgG to FcRn to treat autoimmune diseases is a promising therapeutic method. However, owing to the high affinity of endogenous IgG for FcRn and to the high concentrations of endogenous IgG in blood, it is likely that competitive inhibition of FcRn would require very high doses, and thus have the same limitations similar to those of the current IVIG treatment.

[17] Accordingly, there is an urgent need for the development of a human antibody that has a high affinity for FcRn, and thus can remove pathogenic antibody even at low doses and reduce immunogenicity.

[18]

[19] DISCLOSURE OF INVENTION

[20] Technical Problem

[21] The present inventors have made extensive efforts to solve the above-described problems and to develop a human antibody that has a high affinity for FcRn, and thus can remove pathogenic antibody even at low doses and reduce immunogenicity. As a result, the present inventors have produced and selected a human antibody, which binds specifically to the FcRn chain in a pH-independent manner, from a human antibody cDNA library. In addition, the present inventors have found that the antibody can be used to prevent or treat autoimmune disease, thereby completing the present invention.

[22] Therefore, it is an object of the present invention to provide a therapeutic agent capable of efficiently and radically treating autoimmune diseases, including ITP, an antibody having the ability to bind specifically to FcRn, and a method for producing the antibody.

[23] The FcRn-specific antibody according to the present invention can bind specifically to FcRn in a pH-independent manner to non-competitively inhibit the binding of the antibody Fc to FcRn to thereby reduce in vivo auto-antibody that is the cause of autoimmune diseases, thereby treating autoimmune diseases.

[24] Another object of the present invention is to provide a pharmaceutical composition for treating autoimmune diseases, including ITP, immune neutropenia, Guillain-Barre syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome,

pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, and lupus, the composition containing the FcRn-specific antibody.

[25] Still another object of the present invention is to provide methods for preventing or treating and diagnosing autoimmune diseases, including ITP, immune neutropenia, Guillain-Barre syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome, pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, and lupus, the method comprising using the FcRn-specific antibody.

[26]

[27] Technical Solution

[28] To achieve the above objects, the present inventors have developed a complete human antibody, which can bind specifically to FcRn with high affinity in a pH-independent manner and is composed of a human-derived sequence, and thus causes little or no immune response when being administered in vivo. The present inventors have also developed an antibody having a higher affinity by affinity maturation of this complete human antibody.

[29] The antibody according to the present invention is a polyclonal or monoclonal antibody having binding specificity to FcRn. Preferably, it is in the form of monoclonal antibody, particularly human monoclonal antibody, for human FcRn, and acts as a non-competitive inhibitor of IgG in binding to FcRn. The binding of the antibody of the present invention to FcRn results in the inhibition of pathogenic antibody to FcRn, which promotes the clearance (i.e., removal) of pathogenic antibody from the body of the subject to reduce the half-life of the pathogenic antibody.

[30] As used herein, the term "pathogenic antibody" means antibodies that cause pathological conditions or diseases. Examples of such antibodies include, but are not limited to, anti-platelet antibodies, anti-acetylcholine antibodies, anti-nucleic acid antibodies, anti-phospholipid antibodies, anti-collagen antibodies, anti-ganglioside antibodies, anti-desmoglein antibodies, etc.

[31] The antibody according to the present invention has an advantage in that it makes it possible to non-competitively inhibit the binding of pathogenic antibody to FcRn at physiological pH (i.e., pH 7.0-7.4). US 2002/0138863A and the like describe that an antibody should bind to FcRn at the same site critical for the binding of IgG to Fc so that the binding of IgG to FcRn is inhibited. FcRn binds to its ligand (i.e., IgG) and does not substantially show affinity for IgG at physiological pH rather than acidic pH. Thus, the anti-FcRn antibody that binds specifically to FcRn at physiological pH acts

as a non-competitive inhibitor of the binding of IgG to FcRn, and in this case, the binding of the anti-FcRn antibody to FcRn is not influenced by the presence of IgG. Thus, the inventive antibody that binds to FcRn non-competitively with IgG in a pH-independent manner has an advantage over conventional competitive inhibitors (i.e., antibodies that bind to FcRn competitively with IgG) in that it can treat diseases even at significantly low concentrations by the FcRn-mediated signaling of IgG. In addition, in the procedure of intracellular migration in a state bound to FcRn, the anti-FcRn antibody according to the present invention maintains its binding to FcRn with an affinity higher than IgG in blood, and thus can inhibit the binding of IgG to FcRn even in endosomes that are acidic pH environments in which IgG can bind to FcRn, thereby promoting the clearance of IgG.

- [32] In summary, unlike the antibodies disclosed in prior art documents, the antibody according to the present invention has an affinity for FcRn even in a physiological pH environment (i.e., pH 7.0-7.4) in which IgG does not bind to FcRn. At a pH of 6.0, the antibody of the present invention has a higher affinity for FcRn compared to serum IgG, suggesting that it acts as a non-competitive inhibitor.
- [33] In the present invention, a complete human antibody that binds to FcRn with high affinity and specificity was obtained from a single-chain Fv (scFv) phage library using phage display technology. Phage library preparation and phage display may be performed as described in U.S. Patent No. 7,063,943B, U.S. Patent No. 6,172,197B, and the like. From the library constructed by inducing random mutations in the selected variable region of the complete human antibody, a complete human antibody having increased specificity and affinity was obtained by performing affinity maturation for selecting a human antibody having higher affinity and specificity for FcRn using phage display technology. Affinity maturation may be performed according to the methods described in U.S. Patent No. 5,977,322, U.S. Patent No. 5,994,511, U.S. Patent No. 6,218,149, and the like.
- [34] The inventive antibody that is obtained by the above-described method has any one of the heavy-chain variable regions of FcRn-specific antibody, which comprise CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 2 to 144 (e.g., 2, 4, 66, 128, etc.), or in an amino acid sequence set forth in SEQ ID NO: 289 or 291, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and/or any one of the light-chain variable regions of FcRn-specific antibody, which comprise CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 146 to 288 (e.g., 148, 196, 244, 266, etc.), or in an amino acid sequence set forth in SEQ ID NO: 290 or 292, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%.
- [35] Particularly, the antibody according to the present invention has a heavy-chain

variable region and a light-chain variable region selected from among the following heavy-chain and light-chain variable regions (1) to (74):

- [36] (1) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 2, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 146, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [37] (2) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 4, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 148, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [38] (3) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 6, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 150, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [39] (4) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 8, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 152, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [40] (5) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 10, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 154, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [41] (6) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 12, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 156, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [42] (7) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 14, or a heavy-chain variable

- region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 158, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [43] (8) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 16, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 160, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [44] (9) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 18, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 162, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [45] (10) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 20, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 164, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [46] (11) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 22, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 166, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [47] (12) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 24, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 168, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [48] (13) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 26, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 170, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;

- [49] (14) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 28, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 172, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [50] (15) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 30, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 174, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [51] (16) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 32, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 176, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [52] (17) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 34, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 178, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [53] (18) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 36, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 180, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [54] (19) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 38, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 182, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [55] (20) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 40, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained

- in an amino acid sequence of SEQ ID NO: 184, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [56] (21) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 42, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 186, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [57] (22) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 44, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 188, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [58] (23) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 46, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 190, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [59] (24) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 48, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 192, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [60] (25) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 50, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 194, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [61] (26) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 52, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 196, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [62] (27) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 54, or a heavy-chain variable

- region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 198, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [63] (28) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 56, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 200, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [64] (29) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 58, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 202, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [65] (30) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 60, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 204, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [66] (31) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 62, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 206, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [67] (32) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 64, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 208, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [68] (33) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 66, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 210, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;

- [69] (34) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 68, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 212, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [70] (35) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 70, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 214, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [71] (36) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 72, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 216, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [72] (37) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 74, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 218, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [73] (38) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 76, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 220, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [74] (39) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 78, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 222, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [75] (40) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 80, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained

- in an amino acid sequence of SEQ ID NO: 224, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [76] (41) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 82, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 226, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [77] (42) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 84, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 228, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [78] (43) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 86, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 230, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [79] (44) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 88, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 232, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [80] (45) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 90, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 234, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [81] (46) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 92, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 236, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [82] (47) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 94, or a heavy-chain variable

- region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 238, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [83] (48) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 96, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 240, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [84] (49) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 98, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 242, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [85] (50) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 100, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 244, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [86] (51) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 102, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 246, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [87] (52) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 104, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 248, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [88] (53) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 106, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 250, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;

- [89] (54) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 108, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 252, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [90] (55) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 110, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 254, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [91] (56) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 112, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 256, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [92] (57) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 114, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 258, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [93] (58) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 116, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 260, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [94] (59) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 118 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 262 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [95] (60) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 120 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained

- in an amino acid sequence of SEQ ID NO: 264 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [96] (61) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 122 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 266 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [97] (62) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 124 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 268 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [98] (63) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 126 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 270 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [99] (64) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 128 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 272 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [100] (65) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 130 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 274 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [101] (66) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 132 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 276 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [102] (67) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 134 or a heavy-chain variable

- region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 278 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [103] (68) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 136 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 280 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [104] (69) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 138 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 282 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [105] (70) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 140 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 284 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [106] (71) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 142 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 286 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [107] (72) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 144 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 288 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [108] (73) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 289 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 290 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%; and

- [109] (74) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 291 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 292 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%.
- [110] More preferably, the antibody according to the present invention has a heavy-chain variable region and a light-chain variable region selected from among the following heavy-chain and light-chain variable regions (1) to (74):
- [111] (1) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 2, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 146, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [112] (2) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 4, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 148, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [113] (3) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 6, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 150, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [114] (4) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 8, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 152, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [115] (5) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 10, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 154, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [116] (6) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 12, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 156, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [117] (7) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 14,

- or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 158, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [118] (8) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 16, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 160, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [119] (9) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 18, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 162, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [120] (10) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 20, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 164, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [121] (11) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 22, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 166, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [122] (12) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 24, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 168, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [123] (13) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 26, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 170, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [124] (14) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 28, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 172, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [125] (15) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 30, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 174, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [126] (16) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 32, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 176, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [127] (17) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 34, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 178, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [128] (18) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 36, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 180, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [129] (19) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 38, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 182, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [130] (20) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 40, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 184, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [131] (21) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 42, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 186, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [132] (22) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 44, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 188, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [133] (23) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 46, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 190, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [134] (24) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 48, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 192, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [135] (25) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 50, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 194, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [136] (26) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 52, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 196, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [137] (27) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 54, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 198, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [138] (28) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 56, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 200, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [139] (29) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 58, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 202, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [140] (30) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 60, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 204, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [141] (31) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 62, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 206, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [142] (32) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 64, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 208, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [143] (33) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 66, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 210, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [144] (34) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 68, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 212, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [145] (35) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 70, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 214, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [146] (36) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 72, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 216, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [147] (37) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 74, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 218, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [148] (38) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 76, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 220, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [149] (39) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 78, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 222, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [150] (40) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 80, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 224, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [151] (41) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 82, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 226, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [152] (42) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 84, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 228, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [153] (43) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 86, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 230, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [154] (44) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 88, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 232, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [155] (45) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 90, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 234, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [156] (46) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 92, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 236, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [157] (47) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 94, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 238, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [158] (48) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 96, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 240, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [159] (49) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 98, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 242, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [160] (50) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 100, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 244, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [161] (51) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 102, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 246, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [162] (52) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 104, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 248, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [163] (53) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 106, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 250, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [164] (54) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 108, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 252, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [165] (55) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 110, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 254, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [166] (56) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 112, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 256, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [167] (57) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 114, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 258, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [168] (58) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 116, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 260, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [169] (59) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 118 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 262 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [170] (60) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 120 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 264 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [171] (61) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 122 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 266 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [172] (62) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 124 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 268 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [173] (63) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 126 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 270 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [174] (64) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 128 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 272 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [175] (65) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 130 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 274 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [176] (66) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 132 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 276 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [177] (67) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 134 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 278 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [178] (68) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 136 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 280 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [179] (69) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 138 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 282 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [180] (70) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 140 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 284 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [181] (71) a heavy-chain variable region having an amino acid sequence of SEQ ID NO:

- 142 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 286 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [182] (72) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 144 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 288 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;
- [183] (73) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 289 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 290 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%; and
- [184]
- [185] *(74) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 291 or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 292 or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%.
- [186] The antibodies according to the present invention also include fragments of the antibody. Fragments of the antibody according to the present invention include, but are not limited to, single-chain antibodies, diabodies, triabodies, tetrabodies, Fab fragments, F(ab#)2 fragments, Fd, scFv, domain antibodies, dual-specific antibodies, minibodies, scap, IgD antibodies, IgE antibodies, IgM antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies, derivatives in antibody constant regions, and synthetic antibodies based on protein scaffolds, which have the ability to bind to FcRn. It will be obvious to those skilled in the art that any fragment of the antibody according to the present invention will show the same properties as those of the antibody of the present invention, as long as its ability to bind to FcRn is maintained.
- [187] In addition, antibodies having a mutation in the variable region are included in the scope of the present invention, as long as they retain the properties of the antibody of the present invention. Examples of such antibodies include antibodies having a conservative substitution of an amino acid residue in the variable region. As used herein, the term "conservative substitution" refers to substitution with another amino acid residue having properties similar to those of the original amino acid residue. For example, lysine, arginine and histidine have similar properties in that they have a basic side-chain, and aspartic acid and glutamic acid have similar properties in that they have an acidic side chain. In addition, glycine, asparagin, glutamine, serine, threonine,

tyrosine, cysteine and tryptophan have similar properties in that they have an uncharged polar side-chain, and alanine, valine, leucine, threonine, isoleucine, proline, phenylalanine and methionine have similar properties in that they have a non-polar side-chain. Also, tyrosine, phenylalanine, tryptophan and histidine have similar properties in that they have an aromatic side-chain. Thus, it will be obvious to those skilled in the art that, even when substitution of amino acid residues in groups showing similar properties as described above occurs; it will show no particular change in the properties. Accordingly, antibodies having a mutation caused by conservative substitution in the variable region are included in the scope of the present invention, as long as they retain the properties of the antibody of the present invention.

[188] In addition, the antibody according to the present invention or its fragment may be used as a conjugate with another substance. Substances that may be used as conjugates with the antibody according to the present invention or its fragment include therapeutic agents that is generally used for the treatment of autoimmune diseases, substances capable of inhibiting the activity of FcRn, and a moiety that is physically associated with the antibody to improve its stabilization and/or retention in circulation, for example, in blood, serum, lymph, or other tissues. For example, the FcRn-binding antibody can be associated with a polymer, e.g., a non-antigenic polymer such as polyalkylene oxide or polyethylene oxide. Suitable polymers will vary substantially by weight. Polymers having molecular number average weights ranging from about 200 to about 35,000 (or about 1,000 to about 15,000, and 2,000 to about 12,500) can be used. For example, the FcRn-binding antibody can be conjugated to water soluble polymers, e.g., hydrophilic polyvinyl polymers, e.g. polyvinylalcohol and polyvinylpyrrolidone. A non-limiting list of such polymers includes, but is not limited to, polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained.

[189] The present invention also provides a pharmaceutical composition comprising the antibody of the present invention or a fragment thereof. The pharmaceutical composition may comprise a pharmaceutically acceptable carrier, excipient, and the like, which are well known in the art. The pharmaceutically acceptable carrier that may be used in the present invention should be compatible with the active ingredient such as the antibody according to the present invention and may be physiological saline, sterile water, Ringer's solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, ethanol, or a mixture of two or more thereof. In addition, the pharmaceutical composition of the present invention may, if necessary, comprise other conventional additives, including antioxidants, buffers, and bacteriostatic agents. Further, the pharmaceutical composition of the present invention may be formulated as injectable forms such as aqueous solutions, suspensions or emulsions with the aid of diluents, dis-

persants, surfactants, binders and lubricants. In addition, the pharmaceutical composition of the present invention may be provided by formulating into a various form such as powder, tablet, capsule, liquid, inject, ointment, syrup etc, and single-dosage or multi-dosage container such as sealed ample or vial.

- [190] The pharmaceutical composition of the present invention may be applied to all autoimmune diseases that are mediated by IgG and FcRn, and typical examples of such autoimmune diseases include, but are not limited to, immune neutropenia, Guillain-Barre syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome, pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, lupus, and idiopathic thrombocytopenic purpura (ITP).
- [191] The present invention also provides a method for ameliorating an autoimmune or alloimmune condition, the method comprising administering the antibody of the present invention or a fragment of the antibody to a subject in need of treatment. The present invention also provides a specific anti-FcRn therapy.
- [192] The inventive method for ameliorating an autoimmune or alloimmune condition or the inventive anti-FcRn therapy can be achieved by administering the pharmaceutical composition of the present invention to a subject. The pharmaceutical composition of the present invention can be administered orally or parenterally. The pharmaceutical composition according to the present invention can be administered by various routes, including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intradural, intracardial, transdermal, subcutaneous, intraperitoneal, gastrointestinal, sublingual, and local routes. The dose of the composition of the present invention may vary depending on various factors, such as a patient's body weight, age, sex, health condition and diet, the time and method of administration, excretion rate, and severity of a disease, and may be easily determined by a person of ordinary skill in the art. Generally, 1-200 mg/kg, and preferably, 1-40 mg/kg of the composition may be administered to patients afflicted with autoimmune or alloimmune conditions, and these regimens are preferably designed to reduce the serum endogenous IgG concentration to less than 75% of pretreatment values. Intermittent and/or chronic (continuous) dosing strategies may be applied in view of the conditions of patients.
- [193] The present invention also provides a diagnostic composition comprising the antibody of the present invention or a fragment thereof, and a diagnostic method that uses the diagnostic composition. In other words, the antibody of the present invention or a fragment thereof, which binds to FcRn, have in vitro and in vivo diagnostic utilities.
- [194] In one aspect, the present invention provides a method for detecting the presence of FcRn in vitro and in vivo.

- [195] The in vitro detection method may, for example, comprise the steps of: (1) bringing a sample into contact with the FcRn-binding antibody; (2) detecting the formation of a complex between the FcRn-binding antibody and the sample; and/or (3) bringing a reference sample (e.g., a control sample) into contact with the antibody; and (4) determining the degree of formation of the complex between the antibody and the sample by comparison with that in the reference sample. A change (e.g., a statistically significant change) in the formation of the complex in the sample or the subject as compared to that in the control sample or subject may mean the presence of FcRn in the sample.
- [196] The in vivo detection method may comprise the steps of: (1) administering the FcRn-binding antibody to a subject; and (2) detecting the formation of a complex between the FcRn-binding antibody and the subject. The detecting may include determining location or time of formation of the complex. The FcRn-binding antibody can be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, and radioactive materials. The formation of a complex between the FcRn-binding antibody and FcRn can be detected by measuring or visualizing the antibody bound or not bound to FcRn. A conventional detection assay, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) or tissue immunohistochemistry may be used. In addition to labeling of the FcRn-binding antibody, the presence of FcRn can be assayed in a sample by competition immunoassay using a standard labeled with a detectable substance and an unlabeled FcRn-binding antibody. In one example of this assay, the biological sample, the labeled standard and the FcRn-binding antibody are combined and the amount of labeled standard unbound to FcRn is determined. The amount of FcRn in the biological sample is inversely proportional to the amount of labeled standard unbound to FcRn.
- [197] For use for therapeutic purposes, the antibody of the present invention or a fragment thereof can be labeled with a fluorophore and a chromophore. Because antibodies and other proteins absorb light having wavelengths up to about 310 nm, the fluorescent moieties should be selected to have substantial absorption at wavelengths above 310 nm and preferably above 400 nm. The antibody of the present invention or a fragment thereof can be labeled with a variety of suitable fluorescers and chromophores. One group of fluorescers is xanthene dyes, which include fluoresceins and rhodamines. Another group of fluorescent compounds are naphthylamines. Once labeled with a fluorophore or chromophore, the antibody can be used to detect the presence or localization of the FcRn in a sample, e.g., using fluorescent microscopy (such as confocal or deconvolution microscopy).
- [198] Detection of the presence or localization of FcRn using the antibody of the present invention or a fragment thereof can be performed by various methods as described

below.

- [199] Histological Analysis: The antibody of the present invention or a fragment thereof can be synthesized with a label (such as a purification or epitope tag), or can be detectably labeled, e.g., by conjugating a label or label-binding group. The antibody is then contacted to a histological preparation, e.g., a fixed section of tissue that is on a microscope slide. After incubation for binding, the preparation is washed to remove unbound antibody. The preparation is then analyzed, e.g., using microscopy, to identify if the antibody bound to the preparation. Of course, the antibody can be unlabeled at the time of binding. After binding and washing, the antibody is labeled in order to render it detectable.
- [200] Protein Arrays: The antibody of the present invention or a fragment thereof can be immobilized on a protein array. The protein array can be used as a diagnostic tool, e.g., to screen medical samples (such as isolated cells, blood, sera, biopsies, and the like). Of course, the protein array can also include other ligands, e.g., that bind to FcRn or to other target molecules. Polypeptides for the array can be spotted at high speed using commercially available robotic apparatus, e.g., from Genetic Microsystems or BioRobotics. The array substrate can be, for example, nitrocellulose, plastic, glass, e.g., surface-modified glass. The array can also include a porous matrix, e.g., acrylamide, agarose, or another polymer.
- [201] FACS (Fluorescence Activated Cell Sorting): The antibody of the present invention or a fragment thereof can be used to label cells, e.g., cells in a sample (e.g., a patient sample). The antibody is also attached to a fluorescent compound. The cells can then be sorted using fluorescence activated cell sorter (e.g., using a sorter available from Becton Dickinson). As cells pass through the sorter, a laser beam excites the fluorescent compound while a detector counts cells that pass through and determines whether a fluorescent compound is attached to the cell by detecting fluorescence. The amount of label bound to each cell can be quantified and analyzed to characterize the sample.
- [202] In the present invention, the presence of FcRn or FcRn-expressing tissue in vivo can be performed by an in vivo Imaging method. The method includes (i) administering to a subject (e.g., a patient having an autoimmune disorder) an anti-FcRn antibody, conjugated to a detectable marker; and (ii) exposing the subject to a means for detecting said detectable marker to the FcRn-expressing tissues or cells. For example, the subject is imaged, e.g., by NMR or other tomographic means. Examples of labels useful for diagnostic imaging include radiolabels, fluorescent labels, positron emitting isotopes, chemiluminescers, and enzymatic markers. A radiolabeled antibody can also be used for in vitro diagnostic tests. The specific activity of a isotopically-labeled antibody depends upon the half life, the isotopic purity of the radioactive label, and how the label is incorporated into the antibody.
- [203] The present invention also provides a kit comprising an antibody that binds to FcRn

and instructions for diagnostic use, e.g., the use of the FcRn-binding antibody or antigen-binding fragment thereof, to detect FcRn, in vitro, e.g., in a sample, e.g., a biopsy or cells from a patient having an autoimmune disorder, or in vivo, e.g., by imaging a subject. The kit can further contain at least one additional reagent, such as a label or additional diagnostic agent. For in vivo use, the antibody can be formulated as a pharmaceutical composition.

- [204] The present invention also provides polynucleotide sequences that encode the variable regions of the antibody of the present invention or a fragment thereof.
- [205] Specifically, a polynucleotide sequence that encodes the heavy-chain variable region of the antibody of the present invention or a fragment thereof is a sequence that encodes either any one of the heavy-chain variable regions of FcRn-specific antibody, which comprise CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 2 to 144 (e.g., 2, 4, 66, 128, etc.) or in an amino acid sequence set forth in SEQ ID NO: 289 or 291, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%.
- [206] A polynucleotide sequence that encodes the light-chain variable region of the antibody of the present invention or a fragment thereof is a sequence that encodes either any one of the light-chain variable regions of FcRn-specific antibody, which comprise CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 146 to 288 (e.g., 148, 196, 244, 266, etc.) or in an amino acid sequence set forth in SEQ ID NO: 290 or 292, or a heavy-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%.
- [207] Preferably, the polynucleotide sequence that encodes the heavy-chain variable region of the antibody of the present invention or a fragment thereof has either any one sequence selected from the group consisting of uneven numbers between SEQ ID NOS: 1 to 143 (e.g., 1, 3, 87, 121, etc.), or a sequence homology thereto of at least 90%, preferably at least 95%, and the polynucleotide sequence that encodes the light-chain variable region has either any one sequence selected from the group consisting of uneven numbers between SEQ ID NOS: 145 to 287 (e.g., 147, 193, 267, 283, etc.), or a sequence homology thereto of at least 90%, preferably at least 95%.
- [208] More preferably, the polynucleotide sequences that encode the heavy-chain or light-chain variable regions of the antibody of the present invention or a fragment thereof may be selected from the following sequences:
- [209] (1) a sequence of SEQ ID NO: 1 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 145 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [210] (2) a sequence of SEQ ID NO: 3 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 147 or a sequence

- having a sequence homology thereto of at least 90%, preferably 95%;
- [211] (3) a sequence of SEQ ID NO: 5 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 149 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [212] (4) a sequence of SEQ ID NO: 7 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 151 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [213] (5) a sequence of SEQ ID NO: 9 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 153 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [214] (6) a sequence of SEQ ID NO: 11 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 155 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [215] (7) a sequence of SEQ ID NO: 13 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 157 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [216] (8) a sequence of SEQ ID NO: 15 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 159 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [217] (9) a sequence of SEQ ID NO: 17 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 161 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [218] (10) a sequence of SEQ ID NO: 19 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 163 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [219] (11) a sequence of SEQ ID NO: 21 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 165 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [220] (12) a sequence of SEQ ID NO: 23 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 167 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [221] (13) a sequence of SEQ ID NO: 25 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 169 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [222] (14) a sequence of SEQ ID NO: 27 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 171 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [223] (15) a sequence of SEQ ID NO: 29 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 173 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;

- [224] (16) a sequence of SEQ ID NO: 31 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 175 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [225] (17) a sequence of SEQ ID NO: 33 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 177 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [226] (18) a sequence of SEQ ID NO: 35 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 179 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [227] (19) a sequence of SEQ ID NO: 37 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 181 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [228] (20) a sequence of SEQ ID NO: 39 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 183 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [229] (21) a sequence of SEQ ID NO: 41 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 185 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [230] (22) a sequence of SEQ ID NO: 43 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 187 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [231] (23) a sequence of SEQ ID NO: 45 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 189 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [232] (24) a sequence of SEQ ID NO: 47 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 191 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [233] (25) a sequence of SEQ ID NO: 49 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 193 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [234] (26) a sequence of SEQ ID NO: 51 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 195 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [235] (27) a sequence of SEQ ID NO: 53 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 197 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [236] (28) a sequence of SEQ ID NO: 55 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 199 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [237] (29) a sequence of SEQ ID NO: 57 or a sequence having a sequence homology

- thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 201 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [238] (30) a sequence of SEQ ID NO: 59 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 203 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [239] (31) a sequence of SEQ ID NO: 61 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 205 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [240] (32) a sequence of SEQ ID NO: 63 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 207 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [241] (33) a sequence of SEQ ID NO: 65 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 209 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [242] (34) a sequence of SEQ ID NO: 67 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 211 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [243] (35) a sequence of SEQ ID NO: 69 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 213 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [244] (36) a sequence of SEQ ID NO: 71 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 215 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [245] (37) a sequence of SEQ ID NO: 73 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 217 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [246] (38) a sequence of SEQ ID NO: 75 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 219 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [247] (39) a sequence of SEQ ID NO: 77 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 221 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [248] (40) a sequence of SEQ ID NO: 79 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 223 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [249] (41) a sequence of SEQ ID NO: 81 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 225 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [250] (42) a sequence of SEQ ID NO: 83 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 227 or a

- sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [251] (43) a sequence of SEQ ID NO: 85 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 229 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [252] (44) a sequence of SEQ ID NO: 87 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 231 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [253] (45) a sequence of SEQ ID NO: 89 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 233 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [254] (46) a sequence of SEQ ID NO: 91 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 235 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [255] (47) a sequence of SEQ ID NO: 93 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 237 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [256] (48) a sequence of SEQ ID NO: 95 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 239 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [257] (49) a sequence of SEQ ID NO: 97 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 241 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [258] (50) a sequence of SEQ ID NO: 99 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 243 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [259] (51) a sequence of SEQ ID NO: 101 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 245 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [260] (52) a sequence of SEQ ID NO: 103 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 247 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [261] (53) a sequence of SEQ ID NO: 105 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 249 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [262] (54) a sequence of SEQ ID NO: 107 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 251 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [263] (55) a sequence of SEQ ID NO: 109 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 253 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;

- [264] (56) a sequence of SEQ ID NO: 111 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 255 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [265] (57) a sequence of SEQ ID NO: 113 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 257 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [266] (58) a sequence of SEQ ID NO: 115 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 259 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [267] (59) a sequence of SEQ ID NO: 117 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 261 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [268] (60) a sequence of SEQ ID NO: 119 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 263 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [269] (61) a sequence of SEQ ID NO: 121 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 265 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [270] (62) a sequence of SEQ ID NO: 123 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 267 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [271] (63) a sequence of SEQ ID NO: 125 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 269 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [272] (64) a sequence of SEQ ID NO: 127 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 271 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [273] (65) a sequence of SEQ ID NO: 129 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 273 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [274] (66) a sequence of SEQ ID NO: 131 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 275 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [275] (67) a sequence of SEQ ID NO: 133 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 277 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [276] (68) a sequence of SEQ ID NO: 135 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 279 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [277] (69) a sequence of SEQ ID NO: 137 or a sequence having a sequence homology

- thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 281 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [278] (70) a sequence of SEQ ID NO: 139 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 283 or a sequence having a sequence homology thereto of at least 90%, preferably 95%;
- [279] (71) a sequence of SEQ ID NO: 141 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 285 or a sequence having a sequence homology thereto of at least 90%, preferably 95%; and
- [280] (72) a sequence of SEQ ID NO: 143 or a sequence having a sequence homology thereto of at least 90%, preferably 95%, and a sequence of SEQ ID NO: 287 or a sequence having a sequence homology thereto of at least 90%, preferably 95%.
- [281] The present invention also provides a recombinant vector comprising the above-described nucleotide sequence, a host cell comprising the recombinant vector, and a method of producing the inventive antibody, which binds specifically to FcRn, using the above recombinant vector or host cell. Particularly, the antibody of the present invention is preferably produced by expression and purification using a gene recombination method. Specifically, the variable regions that encode the inventive antibody that binds specifically to FcRn are preferably produced by being expressed in separate host cells or simultaneously in a single host cell.
- [282] As used herein, the term "recombinant vector" refers to an expression vector capable of expressing the protein of interest in a suitable host cell and means a DNA construct including essential regulatory elements operably linked to express a nucleic acid insert. As used herein, the term "operably linked" means that a nucleic acid expression control sequence is functionally linked to a nucleic acid sequence encoding the protein of interest so as to execute general functions. Operable linkage with the recombinant vector can be performed using a gene recombination technique well known in the art, and site-specific DNA cleavage and ligation can be easily performed using enzymes generally known in the art.
- [283] A suitable expression vector that may be used in the present invention may comprise expression regulatory elements such as a promoter, an operator, an initiation codon, a stop codon, a polyadenylation signal, and an enhancer, as well as a signal sequence for membrane targeting or secretion. The initiation and stop codons are generally considered as part of a nucleotide sequence encoding the immunogenic target protein, and are necessary to be functional in an individual to whom a genetic construct has been administered, and must be in frame with the coding sequence. Promoters may generally be constitutive or inducible. Prokaryotic promoters include, but are not limited to, lac, tac, T3 and T7 promoters. Eukaryotic promoters include, but are not limited to, simian virus 40 (SV40) promoter, mouse mammary tumor virus (MMTV) promoter, human immunodeficiency virus (HIV) promoter such as the HIV Long Terminal Repeat (LTR) promoter, moloney virus promoter, cytomegalovirus (CMV)

promoter, epstein barr virus (EBV) promoter, rous sarcoma virus (RSV) promoter, as well as promoters from human genes such as human β -actin, human hemoglobin, human muscle creatine and human metallothionein. The expression vector may include a selectable marker that allows selection of host cells containing the vector. Genes coding for products that confer selectable phenotypes, such as resistance to drugs, nutrient requirement, resistance to cytotoxic agents or expression of surface proteins, are used as general selectable markers. Since only cells expressing a selectable marker survive in the environment treated with a selective agent, transformed cells can be selected. Also, a replicable expression vector may include a replication origin, a specific nucleic acid sequence that initiates replication. Recombinant expression vectors that may be used in the present invention include various vectors such as plasmids, viruses and cosmids. The kind of recombinant vector is not specifically limited, as long as it functions to express a desired gene and produce a desired protein in various host cells such as prokaryotic and eukaryotic cells. However, it is preferred to use a vector that can produce a large amount of a foreign protein similar to a natural protein while having strong expression ability with a promoter showing strong activity.

[284] In the present invention, a variety of expression host/vector combinations may be used to express the antibody or an antibody fragment of the present invention. For example, expression vectors suitable for the eukaryotic host include, but are not limited to, SV40, bovine papillomavirus, adenovirus, adeno-associated virus, cytomegalovirus, and retrovirus. Expression vectors that may be used for bacterial hosts include bacterial plasmids such as pET, pRSET, pBluescript, pGEX2T, pUC, col E1, pCR1, pBR322, pMB9 and derivatives thereof, a plasmid such as RP4 having a wider host range, phage DNA represented as various phage lambda derivatives such as gt10, gt11 and NM989, and other DNA phages such as M13 and filamentous single-stranded DNA phage. Expression vectors useful in yeast cells include 2 μ m plasmid and derivatives thereof. A vector useful in insect cells is pVL941.

[285] The recombinant vector is introduced into a host cell to form a transformant. Host cells suitable for use in the present invention include prokaryotic cells such as *E. coli*, *Bacillus subtilis*, *Streptomyces* sp., *Pseudomonas* sp., *Proteus mirabilis* and *Staphylococcus* sp., fungi such as *Aspergillus* sp., yeasts such as *Pichia pastoris*, *Saccharomyces cerevisiae*, *Schizosaccharomyces* sp., and *Neurospora crassa*, and eukaryotic cells such as lower eukaryotic cells, and higher other eukaryotic cells such as insect cells.

[286] Host cells that may be used in the present invention are preferably derived from plants and mammals, and examples thereof include, but are not limited to, monkey kidney cells (COS7), NSO cells, SP2/0, Chinese hamster ovary (CHO) cells, W138, baby hamster kidney (BHK) cells, MDCK, myeloma cells, HuT 78 cells and HEK293 cells. Preferably, CHO cells are used.

[287] In the present invention, transfection or transformation into a host cell includes any

method by which nucleic acids can be introduced into organisms, cells, tissues or organs, and, as known in the art, may be performed using a suitable standard technique selected according to the kind of host cell. These methods include, but are not limited to, electroporation, protoplast fusion, calcium phosphate (CaPO₄) precipitation, calcium chloride (CaCl₂) precipitation, agitation with silicon carbide fiber, and agrobacterium-, PEG-, dextran sulfate-, lipofectamine- and desiccation/inhibition-mediated transformation.

- [288] The FcRn-specific antibody according to the present invention can be produced in large amounts by culturing the transformant comprising the recombinant vector in nutrient medium, and the medium and culture conditions that are used in the present invention can be suitable selected depending on the kind of host cell. During culture, conditions, including temperature, the pH of medium, and culture time, can be controlled so as to be suitable for the growth of cells and the mass production of protein. The antibody or antibody fragment produced by the recombination method as described can be collected from the medium or cell lysate and can be isolated and purified by conventional biochemical isolation techniques (Sambrook et al., *Molecular Cloning: A laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press(1989); Deuschler, M., *Guide to Protein Purification Methods Enzymology*, Vol. 182. Academic Press. Inc., San Diego, CA(1990)). These techniques include, but are not limited to, electrophoresis, centrifugation, gel filtration, precipitation, dialysis, chromatography (ion exchange chromatography, affinity chromatography, immunosorbent chromatography, size exclusion chromatography, etc.), isoelectric point focusing, and various modifications and combinations thereof. Preferably, the antibody or the antibody fragment is isolated and purified using protein A.

[289]

[290] Advantageous Effects

- [291] The inventive human antibody specific for FcRn that is a receptor having a high affinity for IgG has high affinity and specificity, causes little or no immunogenicity-related problems, and binds to FcRn non-competitively with IgG or the like to reduce serum auto-antibody levels. By virtue of such properties, the antibody is useful for the treatment and diagnosis of autoimmune diseases.

[292]

Brief Description of Drawings

- [293] FIG. 1 shows the results of selecting antibody variable domains that bind only to the #FcRn of human FcRn protein without binding to #2m. The results in FIG. 1 were obtained by treating #FcRn (heavy chain)-, #2m- and #?Myc-coated 96-well plates with phages constructed from a human antibody cDNA library and panning phages, which bind to #FcRn (heavy chain) at a pH of 6.0 and a pH of 7.4 without binding to #2m, by ELISA.

- [294] FIG. 2 shows the ability of HIT antibodies to bind to human FcRn (hFcRn) on the

cell surface. The results in FIG. 2 were obtained by treating human FcRn-overexpressing HEK293 cells with 8 different antibodies that bind to human FcRn on the cell surface and confirming antibodies that bind to the cell surface FcRn at a pH of 6.0 and a pH of 7.4. The binding of the antibody to FcRn was measured by treating cells with the antibody at each pH, and then analyzing the cells by fluorescent activated cell sorter (FACS) using Alexa488-labeled anti-human goat antibody, and measurement results for the ability of the HIT antibodies to bind to the cell surface were expressed as values relative to the MFI of human IgG1 (hIgG1).

[295] FIG. 3 shows the results of observing whether HIT antibodies that bind to human FcRn on the cell surface can inhibit the binding of human IgG to human FcRn, at the cellular level. Human FcRn-overexpressing HEK293 cells were treated with 8 HIT antibodies confirmed to bind to the cells and 250 nM, 500 nM and 1000 nM of human IgG1, and the ability of the antibodies to inhibit the binding of human IgG to human FcRn was measured based on a decrease in the binding of Alexa488-labeled human IgG1 to the cell surface.

[296] FIG. 4 shows the results of examining whether antibodies that bind to human FcRn also bind to FcRn of other species, by cross-reactivity with mice, rats and monkeys. The results in FIG. 4 were obtained by treating NIH3T3L1, Rat-2 and Cos7 cells, which overexpress mouse FcRn, rat FcRn and monkey FcRn, with various IgG antibodies, treating the cells with FITC-labeled anti-mouse, anti-rat and anti-human goat antibodies that recognize the antibodies, and analyzing the fluorescence intensity of each antibody bound to the cell surface by FACS. The fluorescence intensities were expressed as the ratios of the MFI values of three HIT antibodies, anti-mouse and anti-rat FcRn antibodies and cynomolgus IgG antibody relative to the MFI of human IgG1.

[297] FIG. 5 shows the results of examining the effects of the HIT antibodies HL161_1A and HL161_11H, selected from the human FcRn-expressing transgenic mice Tg276 (hFcRn^{+/+}, h[#]2m^{+/+}, mFcRn^{-/-}, m[#]2m^{-/-}) on the catabolism of hIgG1. The results in FIG. 5 were obtained by intraperitoneally injecting 5 mg/kg of biotinylated human IgG1 into Tg276 mice, and after 24, 48, 72 and 96 hours, intraperitoneally injecting 10 mg/kg of human IgG1, HL161_1A, HL161_11H or PBS into the mice. Sampling was performed at 6, 12, 24, 48, 72, 96, 120 and 168 hours after injection of biotin-IgG and analyzed by ELISA to determine the level of the remaining biotin-IgG. The results were expressed as the ratio of the level of biotin-IgG remaining at each time point relative to 100% for the level of biotin-IgG remaining at 6 hours.

[298] FIG. 6 is a schematic view of a pComb3X vector cloned with a gene encoding a scFv-type fragment of HL161-1A or HL161-11H to achieve affinity maturation.

[299]

[300] EXAMPLES

[301] Hereinafter, the present invention will be described in further detail with reference to examples. It will be obvious to a person having ordinary skill in the art that these

examples are illustrative purposes only and are not to be construed to limit the scope of the present invention.

[302]

[303] Part I: Development of FcRn-specific human antibody

[304] Example 1: Construction of soluble FcRn expression vector

[305] FcRn is a non-covalently associated heterodimeric protein composed of a trans-membrane anchored- # heavy chain (#FcRn) and a # chain (#2m), in which are linked by non-covalent bond. Thus, to construct a soluble FcRn expression vector, the two genes were constructed in a single expression vector using the multisite gateway system. The #FcRn and #2m genes having the signal sequences of human growth hormone were amplified by PCR using the primers, shown in Table 1 below and comprised of the restriction enzyme sequences of #FcRn 5-end NheI/3-end XhoI and #2m 5-end NheI/3-end XbaI in addition to the genes, respectively. The amplification products were cloned into a pcDNA3.1(#) vector.

[306] Specifically, a clone (#FcRn: hMU008093/#2m: hMU005156) was purchased from the Korea Research Institute of Bioscience and Biotechnology, and plasmid DNA was extracted from the clone. 2 # of 200 ng template, 2 # of 10 pmole N-primer, 2 # of 10 pmole C-primer, 25 # of 2X Solgent mixture and 19 # of distilled water were mixed with each other to make 50 # of a reaction solution.

[307] The PCR reaction was performed under the following conditions: initial denaturation at 95# for 2 min, and then 25 cycles of denaturation at 95# at 20 sec, primer annealing at 60# for 40 sec and elongation at 72# for 1 min, followed by final enzymatic reaction at 72# for 5 min. The amplification of the hGH signaling sequence was performed using the same composition as above, and after completion of each PCR reaction, DNA was extracted from the PCR band on agarose gel and used as a template for the next PCR reaction. The hGH leader #FcRn gene amplification product was treated with NheI and XhoI enzymes at 37# for at least 4 hours, and the hGH leader #2m gene amplification product was treated with NheI and XbaI enzymes at 37# for at least 4 hours, and the pcDNA3.1(#) vector was treated with NheI/XhoI and NheI/XbaI enzymes at 37# for at least 4 hours, followed by electrophoresis.

[308] Each of the DNA fragments was electrophoresed on agarose gel to confirm its size and recovered using an agarose gel extraction kit. The DNA fragment and the vector fragment were mixed with each other at a ratio of 1:5 to form a total of 10 # of a mixture, and 10 # of NEB ligase buffer and 1 # of ligase were added thereto, followed by incubation at room temperature for 2 hours. 5 # of the ligation mixture was added to DH5# competent cells and transformed into the cells by heat shock at 42# for 1 minute, and the cells were stationary cultured in ampicillin-containing LB solid medium to obtain colonies. The colonies were cultured in ampicillin-containing LB liquid medium at 37# for 24 hours, and plasmid DNA was isolated therefrom and sequenced. The results of the sequencing indicated that each of natural leader #FcRn,

hGH leader #FcRn, natural leader #2m and hGH leader #2m genes was cloned into pcDNA3.1(+).

[309] PCR was performed using the two plasmid DNAs cloned into the pcDNA3.1(+) vector as a template together with PCR primers having an attB site inserted into the 5' and 3' ends, using a Jump-In™ fast gateway cloning kit according to the manufacturer's instructions, thereby constructing an expression vector comprising the hGH leader #FcRn/#2m cloned into the pJTI™FastDEST vector. The genes in the constructed expression vector were sequenced.

[310]

[311] Table 1

[Table 1]

			Forward-primer	Reverse-primer
Common primer	Leader sequence	1st	5'-CTCTGCCTGCCCTG GCTTCAAGAGGGCAG TGCC-3'	
		2nd	5'-TGGCTTTTGGCCTG CTCTGCCTGCCCTGGC TTCAAG-3'	
		3rd	5'-GGACGTCCCTGCTC CTGGCTTTTGGCCTGC TCTGCC-3'	
		4th	5'-ACCATGGCTACAG GCTCCCGGACGTCCCT GCTCCTGGCT-3'	
Human FcRn	Soluble FcRn	#FcRn	5'-TTC AAG AGG GCA GTG CCG CAG AAA GCC ACC TCT CCC TC- 3'	5'-GCT CGA GTC AGG CGG TGG CTG GAA TC-3'
		#2M	5'-TTC AAG AGG GCA GTG CCA TCC AGC GTA CTC CAA AGA TT-3'	5'-GTC TAG ATT ACA TGT CTC GAT CCC ACT T-3'
	Full length FcRn	#FcRn	5'-GGC TAG CAT GGG GGT CCC GCG-3'	5'-GCT CGA GTC AGG CGG TGG CTG GAA TC-3'
		#2M	5'-GGC TAG CAT GTC TCG CTC CGT GGC C- 3'	5'-GTC TAG ATT ACA TGT CTC GAT CCC ACT T-3'

MouseFcRn	Full length FcRn	#FcRn	5'-GGG TAC CAT GGG GAT GCC ACT GCC-3'	5'-GCT CGA GTC AGG AAG TGG CTG GAA A-3'
		#2M	5'-GGG TAC CAT GGC TCG CTC GGT GAC-3'	5'-GCT CGA GTC ACA TGT CTC GAT CCC A-3'
RatFcRn	Full length FcRn	#FcRn	5'-GGG TAC CAT GGG GAT GTC CCA GCC-3'	5'-GCT CGA GTC AGG AAG TGG CCG GAA A-3'
		#2M	5'-GGG TAC CAT GGC TCG CTC GGT GAC-3'	5'-GCT CGA GTT ACA TGT CTC GGT CCC AG-3'
Monkey FcRn	Full length FcRn	#FcRn	5'-GGG ATC CAT GAG GGT CCC GCG G-3'	5'-GCT CGA GTC AGG CAG TGG CTG GG-3'
		#2M	5'-GGG TAC CAT GTC TCC CTC AGT GGC-3'	5'-GCT CGA GTT ACA TGT CTC GAT CCC A-3'
Common primer	pJTI™FASTD EST vector	#FcRn	5'-GGG GAC AAG TTT GTA CAA AAA AGC AGG CTC CGT TGA CAT TGA TTA TTG ACT AGT T-3'	5'-GGG GAC AAC TTT TGT ATA CAA AGT TGT CCA TAG AGC CCA CCG CAT CCC CAG-3'
		#2M	5'-GGG GAC AAC TTT GTA TAC AAA AGT TGC CGT TGA CAT TGA TTA TTG ACT AGT T-3'	5'-GGG GAC CAC TTT GTA CAA GAA AGC TGG GTA CCA TAG AGC CCA CCG CAT CCC CAG-3'

[312]

[313] Example 2: Construction of cell line expressing soluble FcRn

[314] Because plasmid DNA to be used for transfection should have high concentration and purity, QIAGEN plasmid purification was performed. The bacterial clone of the sequenced hGH leader FcRn pJTI™FastDEST vector was inoculated into a 100-ml LB flask containing ampicillin. The bacterial cells were recovered by centrifugation at 3600 rpm for 15 minutes. After removal of the medium, the pellet was completely dissolved in 10 ml of P1 solution by vortexing, and then 10 ml of P2 solution was added thereto. The mixture was gently inverted five times and incubated at room temperature for 5 minutes. Then, 10 ml of P3 solution was added to the mixture, which was then inverted five times and incubated on ice for 30 minutes. After completion of incubation, the solution was centrifuged at 4# and 15,000 rpm for 30 minutes. The supernatant was transferred into a 50-ml fresh centrifuge tube and additionally centrifuged for 15 minutes. The supernatant was loaded into a column equilibrated with 10 ml of QBT solution. When loading of the solution by gravity was completed, the column was washed twice with 30 ml of QC solution. A 50-ml centrifuge tube was placed below the column, and then elution with 15 ml of QF solution was performed. 10.5 ml of isopropanol was added to the eluate and centrifuged at 4# and 15,000 rpm for 30 minutes. After the DNA pellet was visually observed, the supernatant was carefully removed, and 5 ml of 70% ethanol was added to the pellet. Then, the solution was centrifuged for 15 minutes, and the supernatant was removed so that the pellet was not detached, after which the pellet was dissolved in 150 # of LAR water. After the pellet was completely dissolved, the solution was filtered through a 0.22 # filter. The DNA concentration was analyzed by a Nanodrop spectrophotometer, and the DNA measured to have a purity corresponding to an A260 value of 0.1-1.0 was used for transfection.

[315] 24 hours before transfection, $6-7 \times 10^5$ cells/ml were inoculated. After 24 hours, the cell viability and number were measured. To remove a cell clump, the cells were transferred into a 50 ml tube and vortexed at 20# for 30 seconds. Then, the cells were transferred to 28 ml of medium in a fresh flask at a concentration of 3×10^7 viable cells.

[316] 20 µg of each of an FcRn DEST vector having the hGH leader sequence and a phiC31 integrase vector was diluted in 1 ml of OptiMEM® medium. Then, 80 µg of 293 fectin was diluted in 1 ml of OptiMEM® medium and allowed to stand at room temperature for 5 minutes. When fectin is allowed to stand for 5 minutes or longer, the activity of fectin will decrease, and for this reason, fectin was not allowed to stand for a long period of time. Next, 1 ml of the diluted vector was mixed with 1 ml of the diluted fectin, and the mixture was allowed to stand at room temperature for 30 minutes so that a complex of DNA and fectin could be formed. Next, the mixture was added to the flask containing 3×10^7 viable cells. The flask was mounted in an orbital shaker in an 8% CO₂ incubator at 37#, and then shaken at 125 rpm. After 24 hours of

transfection, the medium was replaced with fresh 293 medium, and the cells were cultured.

[317] The expression level of FcRn could be increased by selectively killing non-integrated cells using a process for selecting cells comprising the FcRn expression vector permanently integrated into the chromosome. After 48 hours of transfection, hygromycin B was added to the cells, and selection of cells was started. Medium replacement and antibiotic treatment were performed once at 3-day intervals during culture, and the cell viability and number were measured as a function of time, thereby constructing an expression cell line.

[318] The expression of FcRn in the constructed stable cell line was analyzed by Western blotting using primary antibodies against #FcRn and #2m. Quantitative analysis was performed using commercially available human #2-microglobulin as a standard, and the results were analyzed by imaging.

[319] During culture of the FcRn stable cell line, the medium was sampled and centrifuged at 15,000 rpm for 10 minutes. 20 # of the supernatant was collected, and 4 # of 5X reducing sample loading dye was added thereto and allowed to stand at 95# for 5 minutes. 12 # of the resulting sample was loaded onto 12% NuPAGE Bis-Tris gel. The human #2-microglobulin standard was loaded in amounts of 5 ng and 10 ng. The PAGE gel was run at 250 volt for 35 minutes and transferred to a PVDF membrane at 30 volt for 90 minutes. Blocking was performed with 10% skim milk for 1 hour. Primary antibody against each of #FcRn and #2m was diluted at 1: 1,000 in TBST solution and incubated at room temperature for 1 hour, and secondary antibody was diluted at 1: 5,000 in TBST solution and incubated at room temperature for 30 minutes. Next, the membrane was washed with TBST solution for 30 minutes more. ECL solutions A and B were mixed with each other at a ratio of 1:1, applied to the membrane, and then allowed to react for 1 minute. Color was developed with manual increment at 10-sec intervals, and the results were imaged.

[320]

[321] Example 3: Expression and purification of soluble FcRn

[322] FcRn expressed in the constructed stable cell line is secreted from the medium. An experiment was performed to determine the time when soluble FcRn is collected from the culture of the stable cell line. 30-ml flasks containing 30×10^4 cells/ml and 60×10^4 cells/ml were prepared, and samples were collected for 7 days from the day of inoculation of cells. The samples were analyzed by WB (Western blotting), and the day at which the expression of soluble FcRn reached the highest after inoculation was determined as the time for collecting the sample medium. After inoculation and culture of the cells, the medium was centrifuged at 4# and 3,600 rpm for 10 minutes. Only the supernatant medium was collected in such a manner that the cell pellet was not detached, and then the supernatant was filtered through a 0.22 # filter. To purify 800-1,000 ml of the collected sample, a buffer change and concentration process by

UF (ultra filtration) was performed. In order to remove NaOH from the filter, about 2 L of distilled water was allowed to flow through the filter, and the filter was sufficiently washed with distilled water, and then 200 ml or more of a buffer comprising 20 mM Bis-Tris and 150 mM NaCl (pH 6.0) was allowed to flow through the filter. The degree of removal of NaOH from the filter could be determined by measuring and comparing the pH of the buffer added to the feed reservoir and the pH of the permeate. When the pH of the permeate reached pH 6.0, the sample was injected into the feed reservoir and concentrated to 200 ml. To change the buffer of the medium sample into a buffer comprising 20 mM Bis-Tris and 150 mM NaCl (pH 6.0), about 2 L (corresponding to about 10 times or more) was filtered. The pressure sensor used was connected to the feed/inlet P1 and operated in a manual mode. The trans-membrane pressure (TMP) was between 0.15 and 0.20 and did not exceed 0.5. After completion of buffer change, 200 ml of the sample medium was concentrated to 50 ml. The concentrated sample was centrifuged at 4#, 3,600 rpm for 15 minutes, and the supernatant was collected.

[323] About 50 ml of the sample prepared by UF was purified by affinity chromatography using IgG Sepharose 6 Fast Flow. IgG Sepharose 6 Fast Flow was packed into an XK16 column and used in a column volume of 8 ml, and affinity chromatography was performed at a linear velocity of 150 cm/hr (5 ml/min). After 50 ml of the concentrated sample was injected at a flow rate of 2 ml/min, the column was washed with about 5 CV or more of washing buffer (20 mM Bis-Tris, 150 mM NaCl pH 5.8) until the baseline was restored. Next, elution buffer (50 mM Tris-Cl, pH8.0) was allowed to flow through the column at a flow rate of 4 ml/min, and the eluate was collected as 2-ml fractions. Protein concentrations were measured by the Bradford quantification method, and purity analysis was performed by Coomassie staining after electrophoresis.

[324]

[325] Example 4: Selection of polyphages and monophages by phage display method

[326] Using the isolated and purified shFcRn (soluble human FcRn) as an antigen, polyphages that bind to the FcRn # chain at a pH between 6.0 and 7.4 in a pH-independent manner without binding to #2m were selected from a human antibody cDNA library (see FIG. 1), and among them, 8 monophages were used in the analysis of hit gene.

[327] Specifically, a library having a diversity of 2.7×10^{10} was cultured at 30# for 16 hours, concentrated in PEG (polyethyleneglycol), and then added to PBS buffer. Three-round panning was performed using shFcRn as an antigen, and in round 3, it was shown that the colony titer of the phages against the antigen was amplified by about 10-100 times. A group of monoclonal phage antibodies was prepared from a group of polyclonal phage antibodies resulting from round 3. The ability of each of the antibodies to bind to the antigen was analyzed, and monoclonal phage antibodies were obtained by fin-

gerprinting and sequencing. The cells obtained from the library cells by the three-round panning were transfected with a helper phage and cultured, and poly ScFv-phages present in the supernatant were analyzed by ELSIA using an immuno-plate reader. As a result, it was found that the poly ScFv-phages had an enhanced ability to bind to the antigen (see FIG. 1).

[328] To sequence each of the monophage clones confirmed by fingerprinting with BstN1, DNA was isolated from the monoclonal cells and sequenced. The V_H and V_L CDR regions of the selected antibodies were analyzed, and the similarity between these antibodies and a germ line antibody group was examined using the Ig BLAST program of NCBI (<http://www.ncbi.nlm.nih.gov/igblast/>). As a result, 8 kinds of shFcRn-specific phage antibodies could be selected. The variable region sequences of the 8 selected antibodies and the nucleotide sequences that encode the variable region sequences are shown in Tables 2 and 3 below. In addition, the CDR sequences in each of the variable regions are shown in Table 4 below.

[329]

[330] Table 2

[Table 2]

Antibody name	Sequences of heavy-chain variable regions		Sequences of light-chain variable regions	
	SEQ ID NO:	Amino acid sequences	SEQ ID NO:	Amino acid sequences
HL161-1A	2	QVQLVQSGGG LVQPGRSLRL SCAASGFSFG EYGMHWVRQA PGKGLEWVSG VSWNSGSIAY ADSVRGRFTI SRDNSKNSLY LQMNSLRAED TAVYYCARGR SMDVWGQGT VTVSS	146	NFMLTQPASV SGSPGQTITI SCTGSSSDVG GY- NYVSWYQQ HPGKAPQLII YD- VTKRPSGV SNRFSGSKSG NSASLTISGL QAEDADYYC SSYSSSTFYV FGTGTKVTVL
HL161-2A	4	QMQLVQSGAE VKKPGSSVKV SCKASGGTFN NYAVSWVRQA PGQGLEWMGR IIPILGIANY AQTFQGRVTI TADKSTTTAY MELSSLRSED TAVYYCARDR YG- MDVWGQGT TVTVSS	148	QLVLTQPPST SETPGQRVTI SC- SGSSSNIG SNYVYWYQQL PG- TAPKLLIY RN- NQRPSGVP DRFSGSKSGT SASLAISGLR SEDEADYYCA SWDDSLSGVV FGGGTKLTVL
HL161-2D	6	QVQLVESGGG LVQPGRSLRL SC- TASGFTFG DYAMSWVRQA PGKGLEWVGF IRSKAYGGTT EYAASVKGRF TISRDDSKSI AYLQMNSLRA ED- TAVYYCAR	150	NFMLTQPHSV SESPGKTVTI SC- TRSSGSIA ANYVHWYQQR PGSPPTTVIY ND- NQRPSGVP DRFSGSIDRS SNSASLTISG LK- TEDEADYY CQSYDSTTYA

		EGLFLPLGGF DL- WGLGTMVT VSS		FGGGTKLTVL
HL161-6C	8	QVQLVESGAE VKKPGASVKV SCKASGYTFT SYVMHWVRQA PGQGLEWMGI INPSGGSTSY AQKFQGRVTM TRDTSTSTVY MELSSLRSED TAVYYCARGG GAFDIWGQGT MVTVSS	152	DIQMTQSPSS VSASVGDRV ITCRASQGIS NWVAWYQQK GKAPKLLIYA ASSLQSGVPS RF- SGSGSGTD FTLTISLQP ED- FAIYYCQQ GHSFPYTFGQ GTKVEIK
HL161-9F	10	QVQLVESGGG LVQSGRSLRL SC- TASGFTFG DYAMSWVRQA PGKGLEWVGF IRSKAYGGTT EYAASVKGRF TISRDDSKI AYLQMNSLRA ED- TAVYYCAR EGLFLPLGGF DL- WGLGTMVT VSS	154	NFMLTQPHSV SESPGKTVTI SC- TRSSGSIA ANYVHWYQQR PGSPPTTVIY ND- NQRPSGVP DRFSGSIDRS SNSASLTISG LK- TEDEADYY CQSYDSTTYA FGGGTKLTVL
HL161 10E	12	QVQLVESGGG LVQPGGSLRL SCAASGFRFS NFAMTWVRQA PGKGLEWVST LS- GSGGSIHH ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKGP LRGQPAYLDP WGQGTLVTVS S	156	SYELTQPLSV SM- SPGQTARI TC- SGDALSKQ YASWYQLKPG QAPVVVMYKD TERPSGIPDR FS- GSSSGTTV TLTISGVQAE DEADYYCQSI TD- KSGTDVIF GGGTKLTVL
HL161-11G	14	QMQLVESGGG	158	NFMLTQPASV

		VVQPGRSLRL SCVGSGFNFN SY- GIHWVRQA PGKGLEWVGG IFYDGSQVKY ADSVKGRVSI SRDNSKNTAY LQMNSLRAED TAVYYCARRN LLDYWGQGTV VTVSS		SGSPGQSITI SCTGSSSDVG GY- NYVSWYQQ HPGKAPQLII YD- VTKRPSGV SNRFSGSKSG NSASLTISGL QAEDEADYYC SSYSSSTFYV FGTGTKVTVL
HL161-11H	16	QMQLVESGGG LVQPGRSLRL SCAASGFTFS SYAMHWVRQA PGKGLEWVAV ISYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRSED TAVYYCSRGS GGRDAFDVWG QGTMITVSS	160	DIQMTQSPST LSASVGDRV ITCRASQSI SR- LAWYQQK GKAPKLLIYK ASSLETGVPS RF- SGSGSGTE FTLTISLQ DDFATYYCQ TNSFPLTFGG GTKVEIK

[331]

[332] Table 3

[Table 3]

Antibody name	Sequences of heavy-chain variable regions		Sequences of light-chain variable regions	
	SEQ ID NO:	Polynucleotide sequences	SEQ ID NO:	Polynucleotide sequences
HL161-1A	1	CAGGTGCAGC TG- GTGCAGTC TGGGGGAGGC TTGGTACAGC CTGGCAGGTC CCTGAGACTC TC- CTGTGCAG CCTCTGGTTT CAGTTTGGT GAATATGGCA TG- CACTGGGT CCGGCAAGCT CCAGGGAAGG GC- CTGGAGTG GGTCTCAGGT GT- TAGTTGGA ACAGTGGTAG CATTGCCTAT GCGGACTCTG TGAGGGGCCG ATTCACCATC TCCAGAGACA ACAGCAAAAA CTCCCTGTAT CT- GCAAATGA ACAGTCTGAG AGCCGAGGAC ACGGCCGTGT AT- TACTGTGC GAGAGGTAGA AGTATGGACG TCTGGGGCCAA GGGACCACG GT- CACCGTCT CCTCA	145	AATTTTATGC TGA CTCAGCC CGCCTCCGTG TCTGGGTCTC CTGGACAGAC GATCACCATC TC- CTGCACTG GAAGCAGCAG CGACGTTGGT GGTATAACT AT- GTCTCCTG GTACCAACAG CACCCAGGCA AAGCCCCCA ACTCATCATT TATGATGTCA CTAAGCGGCC CTCAGGGGTT TC- TAATCGCT TCTCCGGCTC CAAGTCTGGC AACTCGGCCT CC- CTGACCAT CTCTGGACTC CAGGCTGAGG AC- GAGGCTGA TTATTACTGC AGCTCATACA GCAGCAGCAC TTTTACGTC TTCGGAAGTG GGACCAAGGT CACCGTCCTA

HL161-2A	3	CAGATGCAGC TG- GTGCAGTC TGGGGCTGAG GT- GAAGAAGC CTGGGTCCTC GGTGAAGGTC TC- CTGCAAGG CTTCTGGAGG CACCTTCAAC AACTATGCTG TCAGCTGGGT GC- GACAGGCC CCTGGACAAG GGCTTGAGTG GATGGGAAGG AT- CATCCCTA TC- CTTGGTAT AG- CAAACCTAC GCACAGACAT TCCAGGGCAG AGTCACGATT AC- CGCGGACA AATCCACGAC CACAGCCTAC ATGGAGCTGA GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT AT- TACTGTGC AA- GAGATCGT TACGGTATGG ACGTCTGGGG CCAAGGGACC ACGGTCACCG TCTCCTCA	147	CAGCTCGTGC TGA CTCAGCC AC- CCTCAACG TCTGAGACCC CCGGGCAGAG GTCACCATC TCTTGTTCTG GAAGCAGCTC CAACATCGGA AG- TAATTATG TATACTGGTA CCAGCAACTC CCAGGAACGG CC- CCCAAACCT CCTCATCTAT AG- GAATAATC AGCGGCCCTC AGGGGTCCCT GACCGATTCT CTGGCTCCAA GTCTGGCACT TCAGCCTCCC TG- GCCATCAG TGGGCTCCGG TC- CGAGGATG AG- GCTGATTA TTACTGTGCA TCATGGGATG ACAGCCTGAG TG- GTGTGGTT TTCGGCGGAG GGACCAAGCT GACCGTCCTA
HL161-2D	5	CAGGTGCAGC TG- GTGGAGTC TGGGGGAGGC TTGGTACAGC CAGGGCGGTC	149	AATTTTATGC TGA CTCAGCC CCACTCTGTG TCGGAGTCTC CGGGGAAGAC

		CCTGAGACTC TC- CTGTACAG CTTCTGGATT CACCTTTGGT GATTATGCTA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTAGGTTTC ATTAGAAGCA AAGCTTATGG TGGGACAACA GAATACGCCG CGTCTGTGAA AG- GCAGATTC AC- CATCTCAA GAGATGATTC CAAAGCATC GC- CTATCTGC AAATGAACAG TCTGAGAGCC GAGGACACGG CCGTGTATTA CT- GTGCGAGA GAGGGGCTGT TC- CTGCCCCT GGGAGGTTTT GATTTATGGG GC- CTAGGGAC AATGGTCACC GTCTCCTCA		GGTCACCATC TC- CTGCACCC GCAGCAGTGG CAGCATTGCC GC- CAACTATG TG- CACTGGTA CCAACAGCGC CCGGGCAGTC CC- CCCACCAC TGTCATCTAT AACGATAACC AAAGACCCTC TG- GAGTCCCT GATCGGTTCT CTGGGTCCAT CGACAGGTCC TC- CAACTCTG CCTCCCTCAC CATCTCTGGA CT- GAAGACTG AG- GACGAGGC TGACTACTAC TGTCAGTCCT AC- GATAGTAC CACTTATGCA TTCGGCGGAG GGACCAAGCT GACCGTCCTA
HL161-6C	7	CAGGTGCAGC TG- GTGGAGTC TGGGGCTGAG GT- GAAGAAGC CTGGGGCCTC AGTGAAGGTT TC- CTGCAAGG CATCTGGATA	151	GACATCCAGA TGACCCAGTC TC- CATCTTCC GT- GTCTGCAT CT- GTAGGAGA CA- GAGTCACC AT- CACTTGTC GGGCGAGTCA

		CACCTTCACC AGCTACTATA TG- CACTGGGT GC- GACAGGCC CCTGGACAAG GGCTTGAGTG GATGGGAATA AT- CAACCCTA GTGGTGGTAG CA- CAAGCTAC GCACAGAAAGT TCCAGGGCAG AGTCACCATG ACCAGGGACA CGTCCACGAG CACAGTCTAC ATGGAGCTGA GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT AT- TACTGTGC AA- GAGGGGGG GGGGCTTTTG ATATCTGGGG CCAAGGGACA ATGGTCACCG TCTCCTCA		GGGTATCAGC AACTGGGTAG CCTGGTATCA GCAGAAACCA GGCAAAGCCC CTAAGCTCCT GATCTATGCT GCATCCAGTT TG- CAAAGTGG GGTCCCATCA AG- GTTCAGCG GCAGTGGATC TGGGACAGAC TTCCTCTCA CCATCAGCAG CCTGCAGCCT GAAGATTTTG CAATTTACTA TTGTCAACAG GGTCACAGTT TC- CCGTACAC TTTTGGCCAA GGGACCAAGG TG- GAAATCAA A
HL161-9F	9	CAGGTGCAGC TG- GTGGAGTC TGGGGGAGGC TTGGTACAGT CAGGGCGGTC CCTGAGACTC TC- CTGTACAG CTTCTGGATT CACCTTTGGT GATTATGCTA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	153	AATTTTATGC TGACTCAGCC CCTCTGTG TCGGAGTCTC CGGGGAAGAC GGTCACCATC TC- CTGCACCC GCAGCAGTGG CAGCATTGCC GC- CAACTATG TG- CACTGGTA CCAACAGCGC CCGGGCAGTC CC-

		GGCTGGAGTG GGTAGGTTTC ATTAGAAGCA AAGCTTATGG TGGGACAACA GAATACGCCG CGTCTGTGAA AG- GCAGATTC AC- CATCTCAA GAGATGATTC CAAAAGCATC GC- CTATCTGC AAATGAACAG TCTGAGAGCC GAGGACACGG CCGTGTATTA CT- GTGCGAGA GAGGGGCTGT TC- CTGCCCCT GGGAGGTTTT GATTTATGGG GC- CTAGGGAC AATGGTCACC GTCTCCTCA		CCCACCAC TGTCATCTAT AACGATAACC AAAGACCCTC TG- GAGTCCCT GATCGGTTCT CTGGGTCCAT CGACAGGTCC TC- CAACTCTG CCTCCCTCAC CATCTCTGGA CT- GAAGACTG AG- GACGAGGC TGACTACTAC TGTCAGTCCT AC- GATAGTAC CACTTATGCA TTCGGCGGAG GGACCAAGCT GACCGTCCTA
HL161 10E	11	CAGGTGCAGC TG- GTGGAGTC TGGGGGAGGC TTAGTACAGC CTGGGGGGTC CCTGAGACTC TC- CTGTGCAG CCTCTGGCTT CA- GATTCAGC AACTTTGCCA TGACCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTCTCAACT CT- TAGTGGTA	155	TCCTATGAGC TGACACAGCC ACTCTCGGTG TCAATGTCCC CAGGACAAAC GGCCAGGATC AC- CTGTTCTG GAGATGCTTT GT- CAAAGCAA TATGCTTCTT GGTACCAGCT GAAGCCAGGC CAGGCCCTG TG- GTGGTGAT GTATAAAGAC ACTGAGAGGC

		GTGGTGGTAG TATACACCAC GCAGACTCCG TGAAGGGCCG ATTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CT- GCAAATGA ACAGTCTGAG AGCCGAGGAC ACGGCCGTGT AT- TACTGTGC GAAAGGGCCC TTGAGGGGAC AGCCGGCCTA CCTTGACCCC TGGGGCCAGG GAACCCTGGT CACCGTCTCC TCA		CCTCAGGGAT CC- CTGACCGA TTCTCTGGCT CCAGCTCCGG GACAACAGTC ACGTTGACCA TCAGTGGAGT CCAGGCAGAA GACGAGGCTG AT- TATTACTG TCAATCAATA ACAGACAAGA GTGGTACTGA TGTGATCTTC GGCGGAGGGA CCAAGCTGAC CGTCCTA
HL161-11G	13	CAGATGCAGC TG- GTGGAGTC GGGGGGAGGC GTGGTCCAGC CTGGGAGGTC TCTGAGACTC TC- CTGTGTAG GGTCTGGATT CAACTTCAAC AGTTATGGCA TACACTGGGT CCGCCAGGCT CCAGGCAAGG GGCTGGAGTG GGTGGGAGGA ATATTTTATG ATGGAAGTCA AG- TAAAGTAT GCAGACTCCG	157	AATTTTATGC TGA CTCAGCC CGCCTCCGTG TCTGGGTCCC CTGGACAGTC GATCACCATC TC- CTGCACTG GAAGCAGCAG CGACGTTGGT GGTTATAACT AT- GTCTCCTG GTACCAACAG CACCCAGGCA AAGCCCCCA ACTCATCATT TATGATGTCA CTAAGCGGCC CTCAGGGGTT TC- TAATCGAT

		TGAAGGGCCG AGTCTCCATC TATGCCATGA ATTCCAAGAA CACAGCGTAT CT- GCAAATGA ACAGTCTGAG AGCCGAGGAC ACGGCCGTGT AT- TACTGTGC GC- GACGAAAC CTCCTGGACT ACTGGGGCCA GGGAACGGTG GT- CACCGTCT CCTCA		TCTCCGGCTC CAAGTCTGGC AACTCGGCCT CC- CTGACCAT CTCTGGACTC CAGGCTGAGG AC- GAGGCTGA TTATTACTGC AGCTCATACA GCAGCAGCAC TTTTTACGTC TTCGGAAGT GGACCAAGGT CACCGTCCTA
HL161-11H	15	CAGATGCAGC TG- GTAGAGTC TGGGGGAGGT TTGGTACAGC CGGGCAGGTC CCTGAGACTC TC- CTGTGCAG CCTCTGGATT CACCTTCAGT AGCTATGCTA TG- CACTGGGT CCGCCAGGCT CCAGGCAAGG GGCTGGAGTG GGTGGCAGTT ATATCATATG ATGGAAGCAA TAAATACTAC GCAGACTCCG TGAAGGGCCG ATTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CT-	159	GACATCCAGA TGACCCAGTC TC- CTTCCACC CT- GTCTGCAT CT- GTAGGAGA CA- GAGTCACC AT- CACTTGCC GGGCCAGTCA GAGTATTAGT AGCCGGTTGG CCTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATAAG GCATCTAGCT TAGAACTGG GGTCCCATCA AG- GTTCAGCG GCAGTGGATC TGGGACAGAA TTCCTCTCA CCATCAGCAG CCTGCAGCCT

		GCAAATGA ACAGCCTGAG ATCTGAGGAC ACGGCCGTGT AT- TACTGTGC GAGAGGTAGT GGTGGTCGTG ACGCTTTTGA TGTCTGGGGC CAAGGAACAA TGATCACCGT CTCCTCA		GATGATTTTG CAACTTACTA TTGTCAACAG AC- GAACAGTT TC- CCTCTCAC TTTCGGCGGA GGGACCAAGG TG- GAGATCAA A
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[333]

[334] Table 4

[Table 4]

Antibody name	CDR sequences of heavy-chain variable regions				CDR sequences of light-chain variable regions			
	SEQ ID NO:	CDR1	CDR2	CDR3	SEQ ID NO:	CDR1	CDR2	CDR3
HL161-1A	2	EYGMH	GVSW NSGSI AYADS VRG	GRSM DV	146	GPLRG QPAYL DP	DVTK RPS	SSYSSS TFYV
HL161-2A	4	NYAVS	RIIPIL GIAN Y AQTFQ G	DRYG MDV	148	SGSSS NIGSN YVY	RNNQ RPS	ASWD DSLGS VV
HL161-2D	6	DYAMS	FIRSK AYGGT TEYAA SVKG	EGLFL PLGGF DL	150	TRSSG SIAAN YVH	NDNQ RPS	QSYDS TTYAF GGGTK LTVLG
HL161-6C	8	SYMH	IINPSG GSTSY AQKFQ G	GGGAF DI	152	RASQG ISNWV A	AASSL QS	QQGHS FPYT
HL161-9F	10	DYAMS	FIRSK AYGGT TEYAA SVKG	EGLFL PLGGF DL	154	TRSSG SIAAN YVH	NDNQ RPS	QSYDS TTYA
HL161-10E	12	NFAMT	TLSGS GGSIH HADSV KG	GPLRG QPAYL DP	156	TRSSG SIAAN YVH	DNQRP S	QSYDS TTYA
HL161-11G	14	SYGIH	GIFYD GSQVK YADSV KG	RNLLD Y	158	TGSSS DVGGY NYVS	DVTK RPS	SSYSSS TFYV
HL161-11H	16	SYAMH	VISYD GSNKY YADSV KG	GSGGR DAFDV	160	RASQSI SSRLA	KASSL ET	QQTNS FPLT

[335]

[336] Example 5: Construction and production of human antibodies

[337] Each of the heavy-chain and light-chain variable regions from the selected monoclonal scFv phages was amplified by PCR, and then cloned into a pNATAB vector for human antibody expression. The pNATAB vector for heavy-chain expression had Fc gene already constructed therein, and the pNATAB vector for light-chain expression had a light-chain constant region already constructed therein, and thus the Fc gene and the light-chain constant region were ligated with the cloned variable region gene and expressed in the form of whole human IgG. A human antibody was obtained by transiently transfecting 293E cells with two kinds of plasmids, which express the heavy chain region and the light chain region, and purifying an antibody secreted into the medium using a protein A column.

[338] Specifically, before a day of transfection, 5×10^6 293E cells were seeded into a 100-mm culture dish. When the cells reached a confluence of 90%, transfection was performed. 5 μ g of each of heavy-chain and light-chain plasmid DNAs was prepared and added to 500 μ l of serum-free DMEM medium. 20 μ g of polyethylenimine (polyscience, cat#. 23966) as a transfection reagent was added to the plasmid DNA-containing medium and well mixed with a pipette, followed by incubation at room temperature for 15 minutes. Next, a DNA/transfection reagent mixture was added to the medium in which 293E cells have grown. The next day, the medium was replaced with fresh serum-free medium, and then the medium was harvested while the medium was replaced at 2-day intervals. The antibody-containing medium was concentrated using a Pellicon 3 filter (Millipore, cat#. P3C030C01), and then the human antibody was purified using a Hi-Trap protein A FF column (GE healthcare, cat#. 17-5079-01) in an AKTA purifier system. The antibody eluted with 100 mM glycine-HCl (pH 3.3) buffer was dialyzed with PBS and quantified by measuring the absorbance at a wavelength of 280 nm.

[339]

[340] Example 6: Measurement of binding ability of antibody by SPR

[341] Measurement of the binding ability of antibody by SPR was performed by immobilizing shFcRn as a ligand onto a Proteon GLC chip (Bio-Rad) and measuring affinity.

[342] To determine the K_D of anti-FcRn 161 antibody that bind to FcRn, SPR analysis was performed using Proteon XPR36 (Bio-Rad). The analysis of ligand and analyte was performed using a Proteon GLC chip, and the interaction was analyzed at a pH of 6.0 and a pH of 7.4. Immobilization of the ligand was activated by injecting a 1:1 mixture of 1X EDAC (EDC) and 1X Surfo-NHS for 5 minutes. shFcRn was diluted in 10 mM sodium acetate (pH 4.5) at a concentration of 25 μ g/ml and added to the ligand at a flow rate of 30 μ l/min for 5 minutes. Deactivation was performed with ethanolamine HCl at a flow rate of 30 μ l/min for 5 minutes, and it could be seen that shFcRn was im-

mobilized at a level of about 1200-1500 RU. The analyte antibody was allowed to flow on the immobilized chip at a flow rate of 30 μ l/min. The analyte antibody was diluted in 0.05% Tween 20/PBS (pH 6.0 or pH 7.4) at concentrations of 100 nM, 50 nM, 20 nM, 10 nM, 5 nM and 2.5 nM before injection. The association time of the analyte antibody was 240 seconds, and the dissociation time was 600 seconds. Regeneration of the chip was performed by injecting 10 mM glycine (pH 2.5) at a flow rate of 100 μ l/min for 18 seconds. Based on sensorgrams resulting from six concentrations of the analyte, kinetics analysis was performed using Proteon XPR36 software. The kinetic parameters of the antibody, obtained by the SPR analysis, are shown in Table 5 below.

[343]

[344] Table 5

[Table 5]

Antibody name	shFcRn immobilization						
	SPR (pH6.0)				SPR (pH7.4)		
	$k_{on}(M^{-1}s^{-1})$	$k_{off}(s^{-1})$	$K_D (M)$		$k_{on}(M^{-1}s^{-1})$	$k_{off}(s^{-1})$	$K_D (M)$
HL161-1 A	4.0×10^6	3.2×10^{-3}	8.0×10^{-10}		1.1×10^6	9.3×10^{-3}	8.5×10^{-9}
HL161-2 A	6.9×10^5	1.1×10^{-3}	1.6×10^{-9}		4.2×10^5	6.7×10^{-4}	1.6×10^{-9}
HL161-2 D	6.9×10^5	6.8×10^{-4}	9.8×10^{-10}		3.8×10^5	1.7×10^{-3}	4.5×10^{-9}
HL161-6 C	1.0×10^6	1.9×10^{-3}	1.9×10^{-9}		4.7×10^5	3.1×10^{-3}	6.6×10^{-9}
HL161-9 F	7.5×10^5	7.0×10^{-4}	9.3×10^{-10}		4.5×10^5	1.6×10^{-3}	3.6×10^{-9}
HL161-1 0E	1.2×10^6	4.6×10^{-3}	3.8×10^{-9}		3.1×10^5	8.2×10^{-3}	2.6×10^{-8}
HL161-1 1G	1.2×10^6	1.9×10^{-4}	1.6×10^{-10}		5.2×10^5	1.2×10^{-4}	2.3×10^{-10}
HL161-1 1H	9.7×10^5	3.4×10^{-4}	3.5×10^{-10}		5.0×10^5	4.5×10^{-4}	9.0×10^{-10}
hIgG ₁	3.2×10^5	4.6×10^{-4}	1.4×10^{-9}		No binding	No binding	No binding

[345]

[346] Example 7: Construction of Full-length FcRn expression vector

- [347] In order to examine whether the eight antibodies bind to hFcRn on the human cell surface and inhibit the interaction between hFcRn and IgG Fc and to examine the cross-reactivity of the antibodies with FcRn of each of humans, monkeys, mice and rats, an expression vector for constructing a cell line of each species that overexpresses FcRn on the cell surface was constructed.
- [348] 1) Human FcRn
- [349] A clone (#FcRn: hMU008093/#2m: hMU005156) was purchased from the Korea Research Institute of Bioscience and Biotechnology, and plasmid DNA was extracted from the clone. 2 # of 200 ng template, 2 # of 10 pmole N-primer, 2 # of 10 pmole C-primer, 25 # of 2X Solgent mixture and 19 # of distilled water were mixed with each other to make 50 # of a reaction solution. The primer sequences used in the experiment are shown in Table 1. The PCR reaction was performed under the following conditions: initial denaturation at 95# for 2 min, and then 25 cycles of denaturation at 95# at 20 sec, primer annealing at 60# for 40 sec and elongation at 72# for 1 min, followed by final enzymatic reaction at 72# for 5 min. The #FcRn gene amplification product was treated with NheI and XhoI enzymes at 37# for at least 4 hours, and the #2m gene amplification product was treated with NheI and XbaI enzymes at 37# for at least 4 hours, and the pcDNA3.1(#) vector was treated with each of NheI/XhoI and NheI/XbaI enzymes at 37# for at least 4 hours, followed by electrophoresis. Each of the DNA fragments was electrophoresed on agarose gel to confirm its size and recovered using an agarose gel extraction kit. The DNA fragment and the vector fragment were mixed with each other at a ratio of 1:5 to form a total of 10 ul of a mixture, and 10 # of NEB ligase buffer and 1 # of ligase were added thereto, followed by incubation at room temperature for 2 hours. 5 # of the ligation mixture was added to DH5# competent cells and transformed into the cells by heat shock at 42# for 1 minute, and the cells were stationary cultured in ampicillin-containing LB solid medium to obtain colonies. The colonies were cultured in ampicillin-containing LB liquid medium at 37# for 24 hours, and plasmid DNA was isolated therefrom and sequenced. The results of the DNA sequencing indicated that each of the #FcRn and #2m genes was cloned into pcDNA3.1(#).
- [350] PCR was performed using the two plasmid DNAs cloned into the pcDNA3.1(#) vector as a template together with PCR primers having an attB site inserted into the 5' and 3' ends, using a Jump-In™ fast gateway cloning kit according to the manufacturer's instructions, thereby constructing an expression vector comprising the hGH leader #FcRn/#2m cloned into the pJTI™ FastDEST vector. The genes in the constructed expression vector were sequenced.
- [351] 2) Construction of mouse, rat and monkey full-length FcRn expression vectors
- [352] Mouse, rat and monkey cDNA libraries used in this Example were purchased from BioChain. Mouse cDNA (C1334149), rat cDNA (C1434149) and monkey cDNA (C1534150-cy) were used as templates. 1 # of template, 2 # of 10 pmole N-primer

shown in Table 1, 2 # of 10 pmole C-primer shown in Table 1, 25 # of 2X Solgent mixture and 20 # of distilled water were mixed with each other to make 50 # of a reaction solution. The nucleotide sequences of the primers used in the experiment are shown in Table 1. PCR reaction was performed under the following conditions: initial denaturation at 95# for 2 min, and then 25 cycles of denaturation at 95# for 20 sec, primer annealing at 56# for 40 sec and extension at 72# for 1 min, followed by final enzymatic reaction at 72# for 5 min. The #FcRn and #2m gene amplification products were treated with Kpn and Xho enzymes at 37# for at least 4 hours, and the pcDNA3.1(#) vector was treated with Kpn/Xho enzymes, followed by electrophoresis. Each of the DNA fragments was electrophoresed on agarose gel to confirm its size and recovered using an agarose gel extraction kit. The DNA fragment and the vector fragment were mixed with each other at a ratio of 1:5 to form a total of 10 ul of a mixture, and 10 # of NEB ligase buffer and 1 # of ligase were added thereto, followed by incubation at room temperature for 2 hours. 5 # of the ligation mixture was added to DH5# competent cells and transformed into the cells by heat shock at 42# for 1 minute, and the cells were stationary cultured in ampicillin-containing LB solid medium to obtain colonies. The colonies were cultured in ampicillin-containing LB liquid medium at 37# for 24 hours, and plasmid DNA was isolated therefrom and sequenced. The results of the DNA sequencing indicated that each of the #FcRn and #2m genes was cloned into pcDNA3.1(#). PCR was performed using the two plasmid DNAs cloned into the pcDNA3.1(#) vector as a template together with PCR primers having an attB site inserted into the 5' and 3' ends, using a Jump-In™ fast gateway cloning kit according to the manufacturer's instructions. In this way, expression vectors having the hGH leader and the #FcRn/#2m genes of different species in pJTI™FastDEST vector were constructed. The genes in the constructed expression vectors were sequenced.

[353]

[354] Example 8: Construction of cell lines expressing full-length FcRn

[355] Because plasmid DNA to be used for transfection should have high concentration and purity, QIAGEN plasmid purification was performed. The bacterial clone of the sequenced hGH leader FcRn pJTI™ FastDEST vector was inoculated into a 100-ml LB flask containing ampicillin. The bacterial cells were recovered by centrifugation at 3600 rpm for 15 minutes. After removal of the medium, the pellet was completely dissolved in 10 ml of P1 solution by vortexing, and then 10 ml of P2 solution was added thereto. The mixture was gently inverted five times and incubated at room temperature for 5 minutes. Then, 10 ml of P3 solution was added to the mixture, which was then inverted five times and incubated on ice for 30 minutes. After completion of incubation, the solution was centrifuged at 4# and 15,000 rpm for 30 minutes. The supernatant was transferred into a 50-ml fresh centrifuge tube and additionally centrifuged for 15 minutes. The supernatant was loaded into a column equilibrated with 10

ml of QBT solution. When loading of the solution by gravity was completed, the column was washed twice with 30 ml of QC solution. A 50-ml centrifuge tube was placed below the column, and then elution with 15 ml of QF solution was performed. 10.5 ml of isopropanol was added to the eluate and centrifuged at 4# and 15,000 rpm for 30 minutes. After the DNA pellet was visually observed, the supernatant was carefully removed, and 5 ml of 70# ethanol was added to the pellet. Then, the solution was centrifuged for 15 minutes, and the supernatant was removed in such a manner that the pellet was not detached, after which the pellet was dissolved in 150 # of LAR water. After the pellet was completely dissolved, the solution was filtered through a 0.22 # filter. The DNA concentration was analyzed by a Nanodrop spectrophotometer, and the DNA measured to have a purity corresponding to an A260 value of 0.1-1.0 was used for transfection.

- [356] Cell lines, which express human FcRn, rat FcRn and monkey FcRn, respectively, were constructed in the following manner. The HEK293 cell line for human FcRn, the 3T3L1 cell line for mouse FcRn, Rat-2 fibroblasts for rat FcRn, and the COS-7 cell line for monkey FcRn were used. 24 hours before transfection, each of the cell lines was seeded into T75 flask and grown to a confluence of 80#. After 24 hours, the medium was replaced with fresh medium.
- [357] 5 µg of each of a FcRn DEST vector and a phiC31 Integrase vector was diluted in 500 # of OptiMEM medium. Then, 20 # of Lipofectamine 2000 was diluted in 500 # of OptiMEM medium, and allowed to stand at room temperature for 5 minutes. Next, the two dilutions were mixed with each other and allowed to stand at room temperature for 30 minutes so that a complex of DNA and Lipofectamine could be formed. Next, the mixture was added to a flask containing cells. The cells were cultured in a 5% CO₂ incubator at 37# for 6 hours, and then the medium was replaced with refresh 10% FBS/DMEM medium, and the cells were further cultured.
- [358] To select cells comprising the FcRn expression vector permanently integrated into the chromosome, the following process was performed. Through this process, the expression level of FcRn could be increased by selectively killing non-integrated cells. After 48 hours of transfection, hygromycin B was added to the cells to perform selection. Medium replacement and antibiotic treatment were performed at 3-day intervals during cell culture, and the formed colonies were detached at various time points and cultured. From the selected cell groups, stable monoclonal cell lines were selected by clonal selection.
- [359] Confirmation of the selected stable cell lines was performed by FACS analysis. Alexa488-labeled hIgG1 was bound to the human FcRn-expressing stable cell line at a pH of 6.0 to measure a shift in population. Likewise, Alexa488-labeled Cynomolgus monkey IgG1 was bound to the monkey FcRn-expressing stable cell line at a pH of 6.0 to measure a shift in population. In the case of the mouse FcRn-expressing stable cell line, mouse IgG1 was bound to the cell line at a pH of 6.0 for 1 hour, the level of

bound mouse IgG1 was measured by FACS using FITC-labeled anti-mouse IgG1, thereby measuring a shift in population. In the case of the rat FcRn-expressing stable cell line, anti-rat FcRn mouse antibody was bound to the cell line at a pH of 7.4 for 1 hour, and then the level of bound rat IgG was measured by FACS using FITC-labeled anti-rat IgG antibody, thereby measuring a shift in population.

[360]

[361] Example 9: Analysis of binding of antibody to FcRn by FACS

[362] In stable HEK293 cells expressing human FcRn, the degrees of binding of antibody to FcRn at various pHs were analyzed using a FACS system. Specifically, 100,000 stable HEK293 cells were washed with PBS and centrifuged in a table top micro-centrifuge at 4500 rpm for 5 minutes to obtain pellets. 1 µg of antibody was added to 100 # of pH 6.0 or pH 7.4PBS/10 mM EDTA. The cell pellets were resuspended in 100 # of the antibody solution and incubated on ice for 60 minutes. The cells were washed once with 150 # of buffer having pH difference, and then pellets were obtained therefrom. Alexa488-labeled anti-human antibody goat antibody (1 mg/ml) was diluted at 1: 20 in buffer having pH difference, and the pellets were resuspended in 100 # of the buffer, and then cultured on ice for 60 minutes. The cells were washed once with 150 # of buffer having pH difference, and pellets were obtained therefrom and re-suspended in buffer having pH difference. The suspension was transferred into a tube for FACS analysis. These cells were analyzed by FACS using BD FACSDiva™ v6.1.3 software (BD Bioscience). The results of the analysis were expressed as Mean Fluorescence Intensity (MFI) (see FIG. 2). It was shown that, among the eight selected antibodies, HL161-1A, HL161-11G and HL161-11H did strongly bind to hFcRn on the cell surface compared to the comparative substance IgG1.

[363]

[364] Example 10: Analysis of blocking function of antibody by FACS

[365] HEK293 cells expressing hFcRn on the surface were treated with the eight antibodies confirmed to have the ability to bind to hFcRn on the cell surface, and whether the binding of Alexa-Fluo-488-labeled hIgG1 decreased was analyzed to examine the blocking function of the antibodies.

[366] The analysis process was performed in the following manner.

[367] 1) Labeling of human IgG1 with Alexa-Fluor-488

[368] Human IgG1 (Calbiochem, cat#.400120) was labeled by a Alexa Fluor 488 labeling kit (Molecular Probed/Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. Specifically, 50 # of 1 M sodium bicarbonate (pH 9.0) was added to 500 # of 2 mg/ml solution of IgG in PBS. This protein solution was added to Alexa-Fluor-488 succinimidyl ester (dry powder) and incubated with stirring at room temperature for 1 hour. The protein was purified by size-exclusion chromatography using the kit component column (Bio-Rad BioGel P-30 Fine size exclusion purification resin). The sample was loaded onto the column and eluted with PBS. The first colored band

contained the labeled protein. The degree of labeling was determined by measuring the absorbance of the eluted IgG at A280 (absorbance at 280 nm) and A494 (absorbance at 494 nm). The protein molar concentration was determined using the following formula:

[369] $(M) = [A280 - (A494 \times 0.11) \times \text{dilution factor}] / 203,000.$

[370] In addition, the formula used to derive the moles of dye per mole of protein was as follows:

[371] $(M) = A494 \times \text{dilution factor} / 71,000 \times \text{protein concentration}.$

[372] Typically, 4-5 moles of Alexa-Fluor 488 were incorporated per mole of IgG.

[373] 2) Cell competition assay using FcRn-expressing cells

[374] In stable HEK293 cells expressing human FcRn, the blocking of the antibody against FcRn was analyzed by FACS. The antibody was diluted in binding buffer (PBS pH 6.0, 10 mM EDTA) at concentrations of 2,000 nM, 400 nM and 80 nM to make 50 # of dilutions, which were dispensed into tubes. To each of the tubes, 10 # of 1uM Alexa488-labeled hIgG1 (pH 6.0) was added. Stable HEK293 cells were diluted in binding buffer at a concentration of 2,500,000 cells/ml, and 40 # of the cell dilution was added to each of the labeled antibody-containing tubes. Thus, a final volume of 100 # contained 100,000 cells, 100 nM labeled antibody and 1000 nM, 500 nM or 250 nM competitor antibody. The cells were washed once with 150 # of buffer (pH 6.0), and pellets were obtained therefrom and resuspended in 150 # of buffer having pH difference. The suspension was transferred into a tube for FACS analysis. The cells were analyzed by FACS using BD FACSDiva™ v6.1.3 software (BD Bioscience). The results of the analysis were expressed as mean fluorescence intensity (MFI).

[375] The MFI of the test group was processed after subtracting the MFI (background signal) measured in cells alone. The ratio of the MFI of the competitor-containing tube relative to the MFI (taken as 100#) of the control tube (Alexa Fluor 488 alone and without competitor) was calculated.

[376] If MFI was lower than the MFI of the human IgG1 competitor-containing tube, it was determined that the binding of the competitor antibody was high. The results in FIG. 3 indicated that HL161-1A, HL161-11G and HL161-11H have blocking functions.

[377]

[378] Example 11: Analysis of cross-reactivity by FACS

[379] In order to examine whether the three human antibodies having blocking functions bind to FcRn of other species to block the binding of IgG to FcRn of each species, cross-reactivity between species was analyzed in the following manner.

[380] 1) Analysis of cross-reactivity with mouse FcRn

[381] 3T3-L1 cells stably expressing mouse FcRn were cultured in 10# FCS DMEM medium, and then detached from the culture plate by trypsin treatment. The cells were washed three times with cold binding buffer (PBS, pH 6.0 10 mM EDTA), and then

diluted in binding buffer at a concentration of 105 cells/ml. 100 # of the cell dilution was dispensed into each 1.5-ml tube in such a manner that each tube contained 104 cells, and 1 # of HL161 antibody (1 mg/ml) was added to the dispensed cells. Next, the cells were incubated on ice. As control antibodies, 1 # of each of rabbit antibody (SantaCruz, sc-66893) and human IgG (Abcam, cat#. 409120), which bind to mouse FcRn, was used. The cells were recovered by centrifugation at 4# and 4000 rpm for 5 minutes, after which the cells were washed once with binding buffer and resuspended in 100 # of binding buffer. As FITC-conjugated secondary antibody, 1 # of anti-human IgG goat antibody (Invitrogen, Cat#. A11013) was added to the cells. In the case of the experiment using anti-mouse FcRn rabbit antibody, the anti-rabbit antibody was incubated with the cells on ice for 1 hour, and then the cells were recovered by centrifugation at 4# and 700 g for 5 minutes, washed once with binding buffer, re-suspended in 400 ul of binding buffer and analyzed by FACS to examine the cross-reactivity of the HL161 antibodies with mouse FcRn (see FIG. 4). An experiment at a pH of 7.4 was performed using binding buffer at a pH of 7.4 in the same manner as the experiment using binding buffer at a pH of 6.0. The degree of the binding of each antibody to mouse FcRn was presented as relative MFI based on human IgG. At both a pH of 6.0 and a pH of 7.4, the HL161-1A and hl161-11G antibodies did bind to mouse FcRn, but HL161-11H did not bind to mouse FcRn (see FIG. 4).

[382] 2) Analysis of cross-reactivity with rat FcRn

[383] Rat-2 (KCTC #AC28203), rat fibroblasts stably expressing rat FcRn, were cultured in 10% FBS DMEM medium, and then detached from the culture plate by trypsin treatment. The cells were washed three times with cold binding buffer (PBS pH 6.0, 10 mM EDTA), and then diluted in binding buffer at a concentration of 105 cells/ml. 100 # of the cell dilution was dispensed into each 1.5-ml tube in such a manner that each tube contained 104 cells, and 1 # of HL161 antibody (1 mg/ml) was added to the dispensed cells. Next, the cells were incubated on ice. As control antibodies, 1 # of each of mouse 1G3 antibody and human IgG antibody (Abcam, cat#. 409120), which bind to rat FcRn, was used. The 1G3 antibody was produced and purified from mouse hybridoma cells (ATCC #. CRL2434). The cells were recovered by centrifugation at 4# and 4000 rpm for 5 minutes, after which the cells were washed once with binding buffer and resuspended in 100 # of binding buffer. As FITC-conjugated secondary antibody, 1 # of anti-human IgG goat antibody (Invitrogen, cat#. A11013) was added to the cells. In the case of the experiment using anti-rat FcRn mouse antibody, the anti-mouse IgG goat antibody (Invitrogen, cat#. A11001) was incubated with the cells on ice for 1 hour, and then the cells were recovered by centrifugation at 4# and 4000 rpm for 5 minutes, washed once with binding buffer, resuspended in 400 # of binding buffer and analyzed by FACS to examine the cross-reactivity of the HL161 antibodies with rat FcRn (see FIG. 4). An experiment at a pH of 7.4 was performed using binding buffer at a pH of 7.4 in the same manner as the experiment using binding buffer at a

pH of 6.0. The degree of the binding of each antibody to rat FcRn was presented as relative MFI based on human IgG. At both a pH of 6.0 and a pH of 7.4, the HL161-1A and h161-11G antibodies did bind to rat FcRn, but HL161-11H did not bind to rat FcRn (see FIG. 4).

[384] 3) Analysis of cross-reactivity with monkey FcRn

[385] Cos-7 cells stably expressing monkey FcRn were cultured in 10% FBS DMEM medium, and then detached from the culture plate by trypsin treatment. The cells were washed three times with cold binding buffer (PBS pH 6.0, 10 mM EDTA), and then diluted in binding buffer at a concentration of 105 cells/ml. 100 # of the cell dilution was dispensed into each 1.5-ml tube in such a manner that each tube contained 104 cells, and 1 # of each HL161 antibody (1 mg/ml) was added to the dispensed cells. Next, the cells were incubated on ice. As control antibodies, 1 # of each of Cynomolgus monkey IgG (Equitech-Bio Inc, cat#. SLCM66 0100) and human IgG (Abcam, cat#. 409120) was used. The cells were recovered by centrifugation at 4# and 700 g for 5 minutes, after which the cells were washed once with binding buffer and resuspended in 100 # of binding buffer. As FITC-conjugated secondary antibody, 1 # of anti-human IgG goat antibody (Invitrogen, cat#. A11013) was added to the cells, which were then incubated with on ice for 1 hour. Next, the cells were recovered by centrifugation at 4# and 700 g for 5 minutes, washed once with binding buffer, re-suspended in 400 # of binding buffer, and then analyzed by FACS to examine the cross-reactivity of the HL161 antibodies with monkey FcRn (see FIG. 4). An experiment at a pH of 7.4 was performed using binding buffer at a pH of 7.4 in the same manner as the experiment using binding buffer at a pH of 6.0. The degree of the binding of each antibody to monkey FcRn was presented as relative MFI based on human IgG. At both a pH of 6.0 and a pH of 7.4, the HL161-1A, h161-11G and HL161-11H antibodies did bind to monkey FcRn (see FIG. 4).

[386]

[387] Example 12: Test for effect of human antibody in mFcRn -/- hFCRN transgenic 276 mice

[388] Among the three human antibodies determined by FACS analysis to bind to hFcRn to block the binding of hIgG1, two antibodies were selected. Tg276 (hFcRn##, h2m##, mFcRn-/-, m2m-/-) mice (Jackson Laboratory) expressing hFcRn were injected with human IgG, and then HL161_1A or HL161_11H and human IgG were administered to the mice to examine whether the antibody influences the catabolism of human IgG. Each of two HL161 candidates (HL161_1A and HL161_11H) and human IgG (Greencross, IVglobulinS) was diluted at a concentration of 1 mg/mL, and each dilution was dispensed and stored for 4-day administration. As a vehicle, PBS (phosphate buffered saline; pH 7.4) was used. hFcRn Tg276 mice were acclimated for about 7 days and allowed access to water and feed ad libitum and housed at a temperature of $23 \pm 2^\circ$ and a humidity of $(55 \pm 5\%)$ with a 12-hr light/12-hr dark cycle.

The mice were grouped into three test groups, each consisting of three mice, and a vehicle group consisting of one mouse. In order to use human IgG as a tracer, biotin-conjugated hIgG was prepared using a kit (Pierce, Cat No. 21327) according to the manufacturer's protocol. The prepared biotin-IgG was injected intraperitoneally into the mice at a dose of 5 mg/kg. At 24, 48, 72 and 96 hours after injection of biotin-IgG, the antibody was injected intraperitoneally into the mice at a dose of 10 mg/kg. The mice were gently anesthetized with Forane (Isoflurane, JW pharmaceutical), and then blood was collected from the Retro-orbital plexus using a heparinized micro-hematocrit capillary tube (Fisher) at 6, 12, 24, 48, 72, 96, 120 and 168 hours after injection of biotin-IgG. At 24, 48, 72 and 96 hours after blood collection, the antibody was administered after blood collection. 0.1 mL of the whole blood was received in an Eppendorf tube, and then immediately, plasma was separated by centrifugation and stored in a deep freezer (Thermo) at -70# until use in analysis.

[389] The level of biotin-hIgG1 in the collected blood was analyzed by an ELISA assay in the following manner. 100 # of neutravidin (Pierce, 31000) was seeded into each well of a 96-well plate (Costar, Cat. No: 2592) at a concentration of 1.0 g/ml, and then immobilized at 4# for 16 hours. The plate was washed three times with buffer A (0.05# Tween-20, 10 mM PBS, pH 7.4), and then incubated in 1# BSA-containing PBS (pH 7.4) at room temperature for 2 hours. After washing the plate three times with buffer A, a neutravidin plate was prepared at a concentration of 1 µg/ml using 0.5% BSA-containing PBS (pH 7.4). The blood sample was 500-1000-fold serially diluted with buffer B (100 mM MES, 150 mM NaCl, 0.5# BSA IgG-free, 0.05 % Tween-20, pH 6.0), and 150 # of each of the dilutions was injected into each well. The injected sample was allowed to react at room temperature for 1 hour. The plate was washed three times with buffer A, and then 200 # of 1 nM HRP-conjugated anti-human IgG goat antibody was injected into each well and allowed to react at 37# for 2 hours. The plate was washed three times with ice-cold buffer B, and then 100 # of 3,3',5,5'-tetramethylbenzidine (RnD, Cat. No: DY999) as a substrate was injected into each well and allowed to react at room temperature for 15 minutes. 50 # of 1.0M sulfuric acid solution (Samjeon, Cat. No: S2129) was injected into each well to stop the reaction, and then the absorbance at 450 nm was measured.

[390] The concentration of biotin-IgG at 6 hours (approximate Tmax of biotin-IgG in mice, before the catabolism of biotin-IgG occurred) was set at 100%, and the ratios (#) of biotin-IgG concentrations at other time points relative to the concentration at 6 hours. The results are shown in FIG. 5.

[391] The half-life of the vehicle group was 97.55 hours, and the half-life of the hIgG group used to examine the IVIG effect was 75 hours. The half-lives of the two HL161 candidates HL161-1A and HL161-11H were 72 hours and 57 hours, respectively. The half-life of HL161-1A was shorter than that of the vehicle group by at least 25 hours, but was similar to that of the hIgG group. The half-life of HL161-11H was shorter than

that of the vehicle group by at least 40 hours and shorter than that of the hIgG group by about 20 hours or more. These results indicate that the pH-independent, Fc-competitive antibody specific for hFcRn has the effect of increasing the catabolism of endogenous antibody.

[392]

[393] Part II: Optimization of FcRn-specific antibody by affinity maturation

[394] Example 13: Optimization of candidate antibody by affinity maturation

[395] 13-1: Primary affinity maturation

[396] In order to perform primary affinity maturation, HL161-1A and HL161-11H determined to have the best effect in Examples 1 to 12 using the isolated and purified shFcRn (soluble human FcRn) as an antigen were used as antibodies for affinity maturation. In addition, primary affinity maturation was performed based on 1Ag and 11Hg obtained by modifying the amino acid sequences of HL161-1A and HL161-11H into amino acid sequences that are frequently found in human germ lines. 1Ag and 11Hg have the variable region sequences and CDR sequences shown in Tables 6 and 7 below.

[397]

[398] Table 6

[Table 6]

Clone name	Heavy-chain variable regions		Light-chain variable regions	
	SEQ ID NO:	Amino acid sequences	SEQ ID NO:	Amino acid sequences
1Ag	289	EVQLVESGGGLV QPGKSLRLSCAAS GFTFDEYGMHWV RQAPGKGLEWVS GVSWNSGSIAYA DSVRGRFTISRDN AKNSLYLQMNSL RAEDTALYYCAK GRSMDVWGQGT VTVSSASTKGPSV FPLAPSSKSTSGGT AALGCLVKDYFPE PVTVSWNSGALTS GVHTFPAVLQSSG LYSLSSVTVPSST LGTQTYICNVNHK PSNTKVDKKVEPK SCDKTHTCPPCA PELLGGPSVFLFPP KPKDTLMISRTPE VTCVVVDVSHED PEVKFNWYVDGV EVHNAKTKPREE QYNSTYRVVSVLT VLHQDWLNGKEY KCKVSNKALPAPI EKTISKAKGQPRE PQVYTLPPSREEM TKNQVSLTCLVK GFYPSDIAVEWES NGQPENNYKTTPP VLDSFGSFLYSK LTVDKSRWQQGN VFSCSVMEALH NHYTQKSLSLSPG K	290	QSALTQPASVSGSPGQSITIS CTGSSSDVGGYNYVSWYQQ HPGKAPKLMYDVTKRPSG VSNRFGSGKSGNTASLTISGL QAEDEADYYCSSYSSSTFYV FGTGTKVTVLGRSVAAPSVF IFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC

11Hg	291	QVQLVESGGGVV QPGRSLRLSCAAS GFTFSSYAMHWV RQAPGKGLEWVA VISYDGSNKYYAD SVKGRFTISRDN KNTLYLQMNSLR AEDTAVYYCARG SGGRDAFDVWGQ GTMITVSSASTKG PSVFPLAPSSKSTS GGTAALGCLVKD YFPEPVTVSWNSG ALTSGVHTFPAVL QSSGLYSLSSVVT VPSSSLGTQTYICN VNHKPSNTKV KVEPKSCDKTHTC PPCPAPPELLGGPS VFLFPPKPKDTLM ISRTPEVTCVVVD VSHEDPEVKFNW YVDGVEVHNAKT KPREEQYNSTYRV VSVLTVLHQDWL NGKEYKCKVSNK ALPAPIEKTISKAK GQPREPQVYTLPP SREEMTKNQVSLT CLVKGFYPSDIAV EWESNGQPENNY KTTTPVLDSDGSF FLYSKLTVDKSR WQQGNVFSCSVM HEALHNHYTQKS LSLSPGK	292	DIQMTQSPSTLSASVGDRV TCRASQSISSRLAWYQQKPG KAPKLLIYKASSLETGVPSRF SGSGSGTEFTLTISLQPD ATYYCQQTNSFPLTFGGG VEIKRSVAAPSVFIFPPSDE LKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESV TEQDSKDSSTLSSTLTLSK ADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
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[399]

[400]

Table 7

[Table 7]

Clone name	Heavy-chain variable regions				Light-chain variable regions			
	SEQ ID NO:	CDR1	CDR2	CDR3	SEQ ID NO:	CDR1	CDR2	CDR3
1Ag	289	EYGMH	GVSWNSG SIAYADSV RG	GRSM DV	290	TGSSSD VGGYN YVS	DVTKR PS	SSYSSS TFYV
11Hg	291	SYAMH	VISYDGSN KYYADSV KG	GSGGR DAFDV	292	RASQSIG SRLA	KASSL ET	QQTNS FPLT

[401]

[402] For affinity maturation, antibodies that bind in a pH-independent manner in the pH range from 6.0 to 7.4 were selected from the scFv format library and sequenced, and then 25 specific antibodies were isolated and purified. Next, the affinities of the antibodies were measured by SPR, and antibodies determined to have enhanced affinity and specificity were selected as templates for use in secondary affinity maturation. A detailed method for affinity maturation is as follows.

[403]

[404] (1) Construction of library

[405] The CDR-H3 of each of 1Ag and 11Hg was subjected to saturated randomization at one position in order to minimize the activity of binding to antigen or a change in surface protein in the randomization process. Some residues that are frequently found were not modified or were randomized in a limited manner. The CDR-L3 was subjected to randomization so that it could contain amino acids that were frequently found at positions as a result of analysis of human germ line antibody genes. Oligonucleotides for randomized sites were synthesized, and randomized scFv genes were obtained by PCR. The scFv genes were ligated into pComb3X vectors using a Sfi-I restriction enzyme, and then transformed into an E. coli ER2537, thereby constructing a library having a diversity of 8.0×10^6 for 1Ag and a diversity of 5.0×10^6 for 11Hg (see FIG. 6).

[406]

[407] (2) Panning

[408] In a panning strategy, in order to select clones that strongly bind to antigen at a pH of 6.0 (low KD) and are not easily detached at a pH of 7.4 (low K_{off}), biotinylated hFcRn (100 ng) was used as antigen, and hFcRn-expressing HEK293 cells (60-mm, 80% confluence) were used. When HEK293-hFcRn cells were used, the cells were fixed with 3.7% formaldehyde, followed by panning. In the case of 1Ag, fixed soluble cells were used, and in the case of 11Hg, fixed adhesion cells were used. For enhancement

of K_{off} , the washing time was increased and shFcRn was added. When protein was used, shFcRn was added for 24 hours except for 1st round, followed by washing, and when cells were used, washing was performed 15 times (about 2 hours). When output titer increased as panning progressed, it was considered to be enriched.

[409]

[410] (3) ELISA and dot-blot screening

[411] For ELISA and dot-blot screening, each colony was cultured with 0.15 mL of SB medium and induced overnight with 1 mM IPTG, and then a periplasmic extract was obtained therefrom using 0.1 mL of TES. ELISA was performed using TMB reagent after binding periplasmic extract by direct coating with 30 ng, 10 ng and 5 ng of hFcRn and binding anti-HA-HRP. For dot-blot screening, the periplasmic extract was diluted at 1:3 to 1:5 in PBS, and 1 mL of the dilution was dotted onto a nitrocellulose membrane, after which anti-HA-HRP was bound to the membrane which was then analyzed using AbSignal (Abclon, Korea). For numerical comparison with ELISA, a periplasmic extract of parental scFv was serially diluted at 1:2 and used as a standard. For selection of high-affinity binders, based on the dot-blot and ELISA values of parental scFv, clones having lower expression levels and ELISA values higher than parental scFv were selected. In the case of 1Ag, ELISA and dot-blot screening were performed on 855 Strategy-1 4th output colonies, 1425 Strategy-2 3rd output colonies, and 855 Strategy-2 5th output colonies. In order to select binders having high affinity at pH 7.4 and pH 6.0, scFv levels were compared by ELISA for three concentrations of shFcRn. As a result, 40 colonies were selected from Strategy-1 4th outputs, 41 colonies were selected from Strategy-2 3rd outputs, and 40 colonies were selected from Strategy-2 5th outputs.

[412]

[413] (4) Nucleotide sequencing

[414] 121 colonies selected from the library based on 1Ag were sequenced, thereby selecting 74 unique sequence clones. Among these sequence clones, 30 clones having no putative glycosylation site were selected.

[415] 88 colonies selected from the library based on 11Hg were sequenced, thereby selecting 37 unique clones. Among these clones, 25 clones having no putative glycosylation site were selected.

[416]

[417] (5) Purification of 1Ag and 11Hg-derived candidate antibodies having improved affinity

[418] In order to perform ELISA, cELISA and the measurement of SPR K_{off} , scFv was purified. Specifically, cells were incubated in 20-50 mL of SB and then induced overnight with 1 mM IPTG, after which these cells were extracted with 1:5-1:8 volumes of TES buffer to obtain a periplasmic extract. Purification of scFv was performed by affinity chromatography using Ni-NTA. For measurement of K_{off} , 17

clones derived from 1Ag and 8 clones derived from 11Hg were purified.

[419]

[420] (6) Measurement of binding affinity by ELISA and SPR

[421] ELISA was performed at a pH of 6.0 and a pH of 7.4, and all buffers and samples were used at a pH of 6.0 and a pH of 7.4. shFcRn was diluted in PBS (pH 6.0 or pH 7.4) at a concentration of 2 g/mL, and 100 # of the dilution was added to each well of a 96-well plate and coated at room temperature for 2 hours (or O/N coated at 4#). The plate was washed three times with washing buffer (pH 6.0 or pH 7.4), and then solution was removed from each well by suction. Next, 200 # of blocking buffer (pH 6.0 or pH 7.4) was added to each well which was then blocked at room temperature for 2 hours. After completion of blocking, the plate was washed three times with washing buffer, and 100 # of scFv solution at 100 ng/mL for the 1Ag-derived variant or at 150 ng/mL for the 11Hg-derived variant was added to each well of the 96-well plate and incubated for 2 hours. Then, the plate was washed three times with washing buffer. To detect antibody bound to shFcRn, anti-HA-HRP antibody (anti-HA-HRP antibody) (1:2,000, pH 6.0 or pH 7.4) was added to each well and incubated at room temperature for 2 hours. Each well was washed three times with washing buffer (pH 6.0 or pH 7.4), and then 100 # of TMB solution was added to each well and incubated at room temperature for 10 minutes. After 10 minutes, 50 # of stop solution (H2SO4 solution) was added to each well to stop the reaction, and then the absorbance at 450 nm was measured.

[422] The Koff rate of scFv was measured using the Biorad-XPR36 system according to the manual. shFcRn was immobilized on a GLC chip, and scFv was added thereto at one concentration to obtain a sensorgram.

[423]

[424] Table 8

[Table 8]

Clone name	scFv			
	ELISA (OD450)		SPR K_{off} values	
	(pH6.0)	(pH7.4)	(pH6.0)	(pH7.4)
B04	0.22	0.08	3.41E-04	3.10E-04
1Ag (parent)	0.35	0.38	2.22E-04	2.12E-04
A11-A01	1.31	0.86	1.49E-04	2.13E-03
A11-C07	3.50	2.40	3.93E-04	2.48E-03
A11-G06	1.48	0.99	2.25E-04	4.96E-04
A11-A02	0.93	0.80	1.69E-04	8.50E-04
A12-A03	0.60	0.86	3.43E-04	4.81E-04
A12-A05	0.87	0.56	6.57E-05	3.07E-04
A12-B02	1.06	0.74	1.29E-04	3.07E-04
A12-B03	1.03	0.86	1.58E-04	6.07E-04
A12-B04	ND	ND	2.73E-04	3.46E-03
A12-C01	0.59	0.46	2.93E-04	3.52E-04
A12-C04	0.95	0.71	2.88E-04	3.62E-04
A12-C09	1.63	1.30	1.77E-04	9.09E-04
A12-D02	0.64	0.60	1.61E-04	4.70E-04
A12-D04	0.42	0.44	8.51E-05	8.79E-04
A12-D05	1.21	1.16	1.31E-04	9.64E-04
A12-E01	1.71	1.05	5.99E-05	1.15E-03
A12-E04	1.59	1.29	1.32E-04	1.37E-03
A12-E05	2.06	1.80	2.16E-04	2.22E-03
A12-F02	2.17	2.40	3.05E-04	2.25E-04
A12-F05	0.43	0.42	1.29E-04	4.92E-04
A12-F08	1.08	0.74	1.08E-04	9.31E-04
A12-G05	0.68	0.50	7.01E-05	3.72E-04
A12-G07	0.74	0.71	1.05E-04	5.89E-04
A12-G08	0.74	0.64	1.33E-04	4.01E-04
A12-H01	0.49	0.40	3.38E-04	3.31E-04
A12-H04	2.26	1.57	2.20E-04	2.35E-03

A12-H06	1.13	0.99	2.76E-04	5.72E-04
A12-H08	0.93	0.84	2.44E-04	4.79E-04
A12-H09	1.26	1.30	3.88E-04	2.54E-04
A12-H51	0.59	0.68	2.72E-05	1.12E-03

[425]

[426] Table 9

[Table 9]

Clone Name	scFv			
	ELISA (OD450)		SPR K_{off} values	
	(pH6.0)	(pH7.4)	(pH6.0)	(pH7.4)
B04	0.32	0.15	3.41E-04	3.10E-04
11Hg (parent)	.240	0.42	4.34E-04	4.33E-04
H11-A02	0.29	0.36	2.29E-04	4.18E-04
H11-A03	0.38	0.68	2.44E-04	4.17E-04
H11-A05	0.27	0.27	3.45E-04	3.38E-04
H11-A07	0.22	0.70	2.17E-04	5.52E-04
H11-B03	0.28	0.39	4.30E-04	7.81E-04
H11-B04	0.16	0.09	5.43E-04	5.46E-04
H11-B07	0.21	0.45	6.99E-04	6.04E-04
H11-B08	0.19	0.12	1.15E-03	6.57E-04
H11-D07	0.33	0.47	1.60E-04	1.15E-03
H11-D08	0.20	0.62	3.81E-04	5.97E-04
H11-E03	0.17	0.07	3.65E-04	5.13E-04
H11-E05	0.23	0.20	5.46E-04	7.02E-04
H11-E08	0.20	0.80	2.59E-04	5.15E-04
H11-F04	0.18	0.21	9.02E-04	5.93E-04
H11-H05	0.15	0.04	3.01E-04	4.52E-04
H11-H06	0.15	0.09	5.25E-04	5.45E-04
H12-A01	0.26	0.36	4.57E-04	4.23E-04
H12-A09	0.21	0.54	1.50E-04	6.34E-04
H12-A11	0.22	0.24	3.72E-04	5.54E-04
H12-A12	0.14	0.11	2.62E-04	5.27E-04
H12-B01	0.22	0.12	3.24E-04	4.46E-04
H12-B09	0.26	0.49	2.96E-04	3.81E-04
H12-B11	0.15	0.58	3.63E-04	4.54E-04
H12-C09	0.16	0.16	2.83E-04	4.35E-04
H12-C10	ND	ND	ND	3.31E-03
H12-D12	0.17	0.12	5.90E-04	6.79E-04

H12-E12	ND	ND	2.57E-04	3.72E-04
H12-F09	0.40	0.58	1.40E-03	4.18E-04
H12-F10	ND	ND	2.39E-04	4.48E-04

[427]

[428]

As shown in Tables 8 and 9 above, among the randomly mutated CDR-3 clones, eight clones (A11-C07, A11-G06, A12-C09, A12-D55, A12-E01, A12-E04, A12-F02 and A12-H04) were determined to have increased affinity compared to the templates, as a result of the ELISA and SPR tests. Thus, these eight clones were selected as templates for use in secondary affinity maturation. In addition, 11Hg-derived clones showed no increase in affinity compared to the templates, and any of these clones was not selected as a template for use in secondary affinity maturation.

[429]

[430]

Example 13-2: Secondary affinity maturation

[431]

From the scFv format library for secondary affinity maturation of the 1Ag template antibodies and 11Hg selected in Example 13-1 using the isolated and purified shFcRn (soluble human FcRn) as antigen, antibodies that bind to the antigen in a pH-independent manner in the pH range from 6.0 to 7.4 were selected and sequenced. Then, antigen-specific antibodies were isolated and purified, and the binding affinities of the purified antibodies were measured by SPR, thereby selecting 56 optimized complete human antibodies. A detailed method for affinity maturation is as follows.

[432]

(1) Construction of library

[433]

In the case of 1Ag, a sub-library was constructed by randomizing the CDR-1 and CDR-2 of eight clones (A11-C07, A11-G06, A12-C09, A12-D55, A12-E01, A12-E04, A12-F02, and A12-H04) having improved affinity as a result of randomization of CDR-3. In the case of 11Hg, a sub-library was constructed by randomizing three positions of CDR-H3 and CDR-1/2 while maintaining CDR-L3 at the template sequence.

[434]

Amino acids appearing at positions of each of CDR-1 and CDR-2 of the human antibody as a result of sequencing were analyzed, and based on the results of the analysis, CDR-1 and CDR-2 were randomized so as to have a diversity similar to the original diversity. Oligonucleotides for the randomized sites were synthesized, and randomized scFv genes were obtained by PCR and ligated into pComb3X vectors using the restriction enzyme Sfi-I. Next, the vectors were transformed into an E. coli ER2537 strain, thereby obtaining 1.0×10^7 transformants. 83 colonies were sequenced, and as a result, it was found that 29 colonies had the normal scFv sequences and that the diversities of the resulting sub-library were 3.5×10^6 for 1Ag and 1.3×10^7 for 11Hg.

[435]

[436]

(2) Panning

[437]

In a panning strategy, in order to select clones that strongly bind to antigen at a pH of

6.0 (low KD) and are not easily detached at a pH of 7.4 (low K_{off}), biotinylated hFcRn (biotin-hFcRn) and hFcRn-expressing HEK293 cells (293-hFcRn) were used. When HEK293-hFcRn cells were used, these cells were converted to single cells using trypsin-EDTA and fixed with 3.7% formaldehyde, followed by panning.

[438]

[439] (2-a) Panning of 1Ag sub-library

[440] Panning was performed according to the method shown in Table 10 below. In Strategy-1 and Strategy-3, only biotin-shFcRn (100 ng) was used, and in Strategy-4 and Strategy-5, biotin-hFcRn was used in rounds 1 and 2, 293-hFcRn cells (1.0×10^6 cells) were used in rounds 3 and 4. In Strategy-3, Strategy-4 and Strategy-5, soluble parental IgG was used as a competitor in binding. Binding was performed using 1.0×10^{12} phages at a pH of 6.0 at room temperature for 2 hours after quantification using a phage titration kit. To increase the K_{off} rate, the washing time was increased and shFcRn was added. After binding, the cells were washed 10 times with PBS-T to remove unbound phages and cultured with rotation in shFcRn-containing PBS-T at 37°C for 20 hours. Next, the cells were washed 10 times with PBS-T and treated with 100mM TEA (triethylamine) to elute phages. The phages obtained from the sub-library were quantified and analyzed by ELISA, and as a result, it was concluded that the ELISA signal was not lower than that of the template. Thus, parental IgG was used as a competitor in binding from round 1.

[441]

[442] Table 10

[Table 10]

Strategy	Step	Factor	1 st Round	2 nd Round	3 rd Round	4 th Round
Strategy-1	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn
		Competitor	-	-	-	-
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4
Strategy-3	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn
		Competitor	IgG	IgG	IgG	IgG
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4
Strategy-4	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn
		Competitor	IgG	IgG	IgG	IgG
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4
Strategy-5	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	293-hFcRn	293-hFcRn
		Competitor	IgG	IgG	-	-
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4

[443]

[444] The obtained output phages were quantified using a phage titration kit, and then ELISA was performed using the same amount of phages. Among output colonies from round 4 of Strategy-1, Strategy-3 and Strategy-4, 95 colonies were randomly selected, and the activities thereof were analyzed by ELISA, and as a result, it was found that 90% of the colonies in all the strategies had binding activity.

[445]

[446] (2-b) Panning of 11Hg sub-library

[447] Panning was performed according to the method shown in Table 11 below. In Strategy-1 and Strategy-3, only biotin-shFcRn (100 ng) was used, and in Strategy-4 and Strategy-5, biotin-hFcRn was used in rounds 1 and 2, 293-hFcRn cells (1.0×10^6 cells) were used in rounds 3 and 4. In Strategy-3, Strategy-4 and Strategy-5, soluble parental IgG was used as a competitor in binding. Binding was performed using 1.0×10^{12} phages at a pH of 6.0 at room temperature for 2 hours after quantification using a phage titration kit. To increase the Koff rate, the washing time was increased and shFcRn was added. After binding, the cells were washed 10 times with PBS-T to remove unbound phages and cultured with rotation in shFcRn-containing PBS-T at 37# for 20 hours. Next, the cells were washed 10 times with PBS-T and treated with 100mM TEA (triethylamine) to elute phages. The phages obtained from the sub-library were quantified and analyzed by ELISA, and as a result, it was shown that the ELISA signal was not low. Thus, parental IgG was not used as a competitor in round 1 of Strategy-3, Strategy-4 and Strategy-5 and was used from round 2.

[448]

[449] Table 11

[Table 11]

Strategy	Step	Factor	1 st Round	2 nd Round	3 rd Round	4 th Round
Strategy-1	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn
		Competitor				
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.04	7.4	7.4	7.4
Strategy-3	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn	Biotin-hFcRn
		Competitor		IgG	IgG	IgG
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4
Strategy-4	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	293-hFcRn	293-hFcRn
		Competitor		IgG	IgG	IgG
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4
Strategy-5	Binding	Antigen	Biotin-hFcRn	Biotin-hFcRn	293-hFcRn	293-hFcRn
		Competitor		IgG		
		pH	6.0	6.0	6.0	6.0
	Wash	Competitor	shFcRn	shFcRn	shFcRn	shFcRn
		pH	7.4	7.4	7.4	7.4

[450]

[451] The obtained output phages were quantified using a phage titration kit, and then ELISA was performed using the same amount of phages. In strategy-1 and strategy-3 performed using biotin-hFcRn as antigen, the ELISA-positive ratio was shown to be about 80%, and thus colonies resulting from panning were subjected to ELISA screening.

[452]

[453] (3) ELISA screening

[454] scFv in the periplasmic extract was quantified by an ELISA method that recognizes HA, and ELISA was performed using the same amount of scFv. Next, clones having an absorbance value higher than that of the template scFv were selected.

[455]

[456] (3-a) Screening of 1Ag clones

[457] 280 colonies from each of Strategy-1 and Strategy-3 were cultured in 0.15 mL of SB medium and induced with 1 mM IPTG, after which the cells were treated with 0.1 mL of TES to obtain a periplasmic extract. scFv in the periplasmic extract was quantified by ELISA, and scFv was diluted in PBS-T (pH 7.4 or pH 6.0) to final concentrations of 1000 ng/mL and 3000 ng/mL, and shFcRn was coated at a concentration of 1 µg/mL. In this way, ELISA was performed.

[458] As a result of ELISA, colonies having an absorbance higher than that of the template scFv at a pH of 7.4 and a pH of 6.0 were selected. The clones having an absorbance higher than that of the template at a pH of 6.0 mostly showed an absorbance higher than that of the template at a pH of 7.4. Based on the ELISA values for a total of 456 colonies, 200 higher-ranked colonies having an ELISA signal higher than that of the template at a pH of 7.4 were sequenced, and as a result, 77 unique clones were selected. The 77 selected clones had the same H-CDR3 sequence (A11-C07), and L-CDR3 from the template clones had various sequences.

[459]

[460] (3-b) Screening of 11Hg-derived clones

[461] Screening of 11Hg-derived clones was performed in the same manner as described above with respect to ELISA screening of 1Ag-derived clones. As a result of ELISA screening, the number of colonies having an absorbance higher than that of the template scFv at a pH of 7.4 was 64/456 (14.0%), and the number of colonies having an absorbance higher than that of the template scFv at a pH of 6.0 was 32 (7.0%). Based on the ELISA values for a total of 456 colonies, the colonies were ranked based on folds of the ELISA signal compared to the template at a pH of 7.4, and 50 higher-ranked colonies were sequenced. As a result, 10 unique sequence clones were selected.

[462]

[463] (4) Purification of improved 1Ag- and 11Hg-derived candidate antibodies

[464] (4-a) Purification of 1Ag-derived clones

- [465] Among 77 unique clones, scFv for 48 clones excluding 29 clones having a putative N-glycosylation site (derived from the template) was purified from periplasmic extracts. Specifically, cells were cultured in 100-400 mL of SB medium and then induced overnight with 1 mM IPTG, after the cells treated with treated with a 1:5 volume of TES buffer to obtain periplasmic extracts. scFv was purified from the periplasmic extracts using Ni-NTA resin, and then concentrated with PBS, and the buffer was replaced. The scFv was quantified by the Bradford assay, and 1 g of the scFv was separated by SDS-PAGE and stained with Coomassie blue, thereby determining the concentration and purity of the scFv.
- [466]
- [467] (4-b) Purification of 11Hg-derived clones
- [468] scFvs for 7 clones among 10 unique clones and for 1Ag, 11Hg and H11-B04 were purified from periplasmic extracts in the same manner as described above with respect to purification of 1Ag.
- [469]
- [470] (5) Measurement of binding affinity by ELISA and SPR
- [471] Binding affinity was measured according to the above-described Example, and the results of the measurement are shown in Tables 12 and 13.
- [472]
- [473] Table 12

[Table 12]

Clone name	Partially purified scFv			
	ELISA (fold)		K _{off} values (fold)	
	pH 6.0	pH 7.4	pH 6.0	pH 7.4
			Two state	Two state
			kd1	kd1
B04	1.7	1.5	10.7	33.7
1Ag	1.0	1.0	1.0	1.0
A23-3H04	25.4	25.8	27.3	11.6
A21-4C03	21.8	18.8	41.65	14.6
A24-1G10	18.0	26.2	37.7	16.7
A24-1F07	17.5	24.7	29.2	16.5
A21-4B10	17.4	25.9	36.3	19.9
A21-4G04	17.1	24.0	11.2	5.7
A23-3H05	15.0	20.1	20.9	10.0
A21-3A09	14.2	25.2	18.8	10.8
A21-4B06	13.7	17.4	7.2	3.8
A24-1B05	12.8	20.8	26.2	11.6
A23-3A08	11.1	24.0	32.6	18.3
A21-4C08	10.5	19.6	12.1	6.9
A23-4D09	10.4	15.5	24.1	10.5
A23-3D03	10.1	19.8	21.3	9.3
A21-4B03	9.1	16.1	11.2	6.7
A21-3D10	8.5	18.3	19.5	13.1
A21-3A10	7.9	25.6	23.3	14.5
A21-4H04	7.2	23.8	11.8	8.1
A21-4F11	5.7	19.6	13.1	5.9
A23-3G05	5.5	25.0	53.2	22.7
A23-3A10	5.0	15.9	9.3	5.4
A25-1H04	5.0	20.4	47.0	2.6
A23-3B06	4.8	22.8	41.8	10.5
A23-4A09	4.7	17.1	28.4	7.2

A25-1D09	4.5	26.6	42.1	43.0
A21-4E10	4.0	24.3	21.9	12.0
A23-3C04	3.8	20.3	24.8	7.7
A23-3G06	3.1	6.0	12.9	4.6
A24-1E09	3.1	14.8	11.2	5.9
A23-3F03	3.1	20.7	17.9	11.2
A21-4F07	2.9	16.2	8.7	4.1
A24-1A03	2.8	11.5	5.9	3.8
A24-1H11	2.7	21.7	19.5	10.5
A21-3D09	2.5	16.9*	11.8	7.2
A24-1D10	2.3	18.6	32.6	8.9
A21-4B04	2.3	9.3	24.5	8.0
A23-4C12	2.2	23.8	16.7	9.5
A21-4G06	2.1	17.3	9.4	5.4
A23-3E04	2.0	12.9	10.4	5.4
A24-1C09	2.0	13.1	5.1	2.8
A24-1C04	2.0	8.9	3.4	2.9
A25-1H10	1.9	15.1	11.9	6.5
A21-4D08	1.6	5.5	9.0	4.8
A24-1D08	1.4	9.4	5.9	5.0
A24-1A08	1.4	4.1	5.1	2.3
A21-4A07	1.3	9.1	7.0	3.9
A24-1B09	1.2	9.6	5.8	3.7
A24-1E07	1.2	3.3	4.8	2.2

[474]

[475] Table 13

[Table 13]

Clone name	Partially purified scFv			
	ELISA (fold)		K _{off} values (fold)	
	pH 6.0	pH 7.4	pH 6.0	pH 7.4
			Two state	Two state
			kd1	kd1
H11-B04	1.3	1.6	1.372	9.611
11Hg	1.0	1.0	1.000	1.000
H21-3A07	1.0	4.2	1.075	1.499
H21-4D11	0.7	3.6	0.001	0.000
H21-3C11	1.9	10.9	1.363	1.468
H21-3A09	0.7	0.2	0.174	0.002
H21-4H04	0.9	5.7	0.893	1.233
H23-3D08	3.7	7.0	2.891	1.893
H21-4D09	ND	ND	NA	NA
H24-1D11	1.0	1.0	NA	NA

[476]

[477] The amino acid sequences of the variable regions of the antibodies, selected by the above-described primary and secondary affinity maturation and having increased affinity and specificity for FcRn, and nucleotide sequences encoding the amino acid sequences, are shown in Tables 14 and 15 below. In addition, the CDR sequences of the variable regions are shown in Tables 16 and 17 below.

[478]

[479] Table 14

[Table 14]

Antibody name	Heavy-chain variable regions		Light-chain variable regions	
	SEQ ID NO:	Amino acid sequences	SEQ ID NO:	Amino acid sequences
A11-C07	18	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRY SDVWGQGTT VTVSS	162	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYASY SSNTFYVFG TGTKVTVLG
A11-G06	20	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRL MDVWGQGT TVTVSS	164	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYGSY NNNTFYVFG TGTKVTVLG
A12-C09	22	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN	166	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA

		AKNSLYLQM NSLRAEDTA LYYCAKGRT MDVWGQGT TVTVSS		SLTISGLQAE DEADYYGSY SSNTFYVFG TGTKVTVLG
A12-E05	24	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRIL DVWGQGTTV TVSS	168	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYGSY NNSTFYVFG TGTKVTVLG
A12-E01	26	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKSRS MDVWGQGT TVTVSS	170	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYGSY SNNNFYVFG TGTKVTVLG
A12-E04	28	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM	172	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE

		NSLRAEDTA LYYCAKGRL FDVWGQGTT VTVSS		DEADYYGSY SNSNFYVFG TGTKVTVLG
A12-F02	30	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRY LDVWGQGTT VTVSS	174	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYGSY DSNTFYVFG TGTKVTVLG
A12-H04	32	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRL LDVWGQGTT VTVSS	176	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYGA YSNTNFYVF GTGTVTVL G
A23-3H04	34	EVQLVESGG GLVQPGRSL RLSCAASGFT FDYGMNW VRQAPGKGL EWVSGISYN GGTTAYADS VRGRFTISR NAKNSLYLQ MNSLRAEDT	178	QSALTQPAS VSGSPGQSIT ISCGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS

		ALYYCAKGR SMDVWGQG TTVTVSS		YDSNTFYVF GTGTKVTVL G
A21-4C03	36	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYNS GTIAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	180	QSALTQPAS VSGSPGQSIT ISCTGSSSDI GGYNYVSW YQQHPGKAP KLMIYDVSD RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A24-1G10	38	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYNS GTKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	182	QSALTQPAS VSGSPGQSIT ISCGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSNSNFYVF GTGTKVTVL G
A24-1F07	40	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGVSYN SGTTAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR	184	QSALTQPAS VSGSPGQSIT ISCSGSSSNV GSYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF

		SMDVWGQG TTVTVSS		GTGTKVTVL G
A21-4B10	42	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGISYNS GNKAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TTVTVSS	186	QSALTQPAS VSGSPGQSIT ISCSGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A21-4G04	44	EVQLVESGG GLVQPGRSL RLSCAASGFT FDSYGMHW VRQAPGKGL EWVSGISYN GGNTAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	188	QSALTQPAS VSGSPGQSIT ISCSGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVNE RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNNNFYVF GTGTKVTVL G
A23-3H05	46	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYNS GTIAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT	190	QSALTQPAS VSGSPGQSIT ISCSGSSSNV GGYNYVSW YQQHPGKAP KLMIYDVSN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL

		TVTVSS		G
A21-3A09	48	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMNW VRQAPGKGL EWVSGISYNS GTKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	192	QSALTQPAS VSGSPGQSIT ISCSGSSSDI GGYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A21-4B06	50	EVQLVESGG GLVQPGRSL RLSCAASGFT FDSYGMHW VRQAPGKGL EWVSGISYN GGSKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTTVTVSS	194	QSALTQPAS VSGSPGQSIT ISCSGSSSNI GSYNYVSW YQQHPGKAP KLMIYDVT RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A24-1B05	52	EVQLVESGG GLVQPGRSL RLSCAASGFT FDKYGMNW VRQAPGKGL EWVSGISYNS GNTAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	196	QSALTQPAS VSGSPGQSIT ISCAGSSSDI GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G

A23-3A08	54	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYNS GTTAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	198	QSALTQPAS VSGSPGQSIT ISCAGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A21-4C08	56	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMHW VRQAPGKGL EWVSGISYN AGNKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	200	QSALTQPAS VSGSPGQSIT ISCSGSSSNV GSYNYVSW YQQHPGKAP KLMIYDVNN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A23-4D09	58	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGVSYD AGNTAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	202	QSALTQPAS VSGSPGQSIT ISCSGSSSNI GSYNYVSW YQQHPGKAP KLMIYDVTD RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A23-3D03	60	EVQLVESGG	204	QSALTQPAS

		GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN AGSTAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQHPGKAP KLMIYDVTN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A21-1B03	62	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN AGNKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	206	QSALTQPAS VSGSPGQSIT ISCSGSSNI GSYNYVSW YQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A21-3D10	64	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMHW VRQAPGKGL EWVSGISYD AGTTAYADS VKGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	208	QSALTQPAS VSGSPGQSIT ISCGGTSSNI GGYNYVSW YQHPGKAP KLMIYDVTN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNTNFYVF GTGTKVTVL G
A21-3A10	66	EVQLVESGG GLVQPGRSL	210	QSALTQPAS VSGSPGQSIT

		RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYN AGNKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		ISCAGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A21-4H04	68	EVQLVESGG GLVQPGRSL RLSCAASGFT FDSYGMHW VRQAPGKGL EWVSGISYNS GNKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	212	QSALTQPAS VSGSPGQSIT ISCSGTSSDI GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNNNFYVF GTGTKVTVL G
A21-4F11	70	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN GGTKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	214	QSALTQPAS VSGSPGQSIT ISCGGTSSNI GGYNYVSW YQQHPGKAP KLMIYDVND RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A23-3G05	72	EVQLVESGG GLVQPGRSL RLSCAASGFT	216	QSALTQPAS VSGSPGQSIT ISCAGSSSNI

		FDTYGMHW VRQAPGKGL EWVSGISYNS GTIAYADSVR GRFTISRDN KNSLYLQMN SLRAEDTAL YYCAKGRSM DVWGQGTTV TVSS		GSYNYVSW YQQHPGKAP KLMIYDVSN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A23-3A10	74	EVQLVESGG GLVQPGRSL RLSCAASGFT FDKYGMHW VRQAPGKGL EWVSGISYN AGSKAYADS VKGRFTISR NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	218	QSALTQPAS VSGSPGQSIT ISCAGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVSD RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A25-1H04	76	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYNS GNTAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	220	QSALTQPAS VSGSPGQSIT ISCAGSSSDI GGYNYVSW YQQHPGKAP KLMIYDVSE RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A23-3B06	78	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW	222	QSALTQPAS VSGSPGQSIT ISCSGSSSDV GGYNYVSW

		VRQAPGKGL EWVSGISYNS GSKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS		YQQHPGKAP KLMIYDVSE RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A23-4A09	80	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMNW VRQAPGKGL EWVSGISYDS GNKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	224	QSALTQPAS VSGSPGQSIT ISCGGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A25-1D09	82	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYN GGTIAYADS VKGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTTVTVSS	226	QSALTQPAS VSGSPGQSIT ISCGGTSSDV GSYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A21-4E10	84	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL	228	QSALTQPAS VSGSPGQSIT ISCTGSSSNV GGYNYVSW YQQHPGKAP

		EWVSGVSYN AGNKAYADS VRGRFTISR NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		KLMIYDVSK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A23-3C04	86	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMHW VRQAPGKGL EWVSGISYDS GTTAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	230	QSALTQPAS VSGSPGQSIT ISCSGTSSDI GGYNYVSW YQQHPGKAP KLMIYDVTE PPSGVSNRFS GSKSGNTAS LTISGLQAED EADYYCASY SSNTFYVFG TGTKVTVLG
A23-3G06	88	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYNS GNIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	232	QSALTQPAS VSGSPGQSIT ISCAGTSSNI GGYNYVSW YQQHPGKAP KLMIYDVND RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A24-1E09	90	EVQLVESGG GLVQPGRSL RLSCAASGFT FDKYGMHW VRQAPGKGL EWVSGVSYN	234	QSALTQPAS VSGSPGQSIT ISCTGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVTN

		AGTTAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A23-3F03	92	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMHW VRQAPGKGL EWVSGISYNS GNIAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	236	QSALTQPAS VSGSPGQSIT ISCGGSSSNI GSYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A21-4F07	94	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN AGNKAYADS VKGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	238	QSALTQPAS VSGSPGQSIT ISCSGTSSNV GGYNYVSW YQQHPGKAP KLMIYDVSD RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A24-1A03	96	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN AGNTAYADS	240	QSALTQPAS VSGSPGQSIT ISCGGSSSNV GGYNYVSW YQQHPGKAP KLMIYDVSK RPSGVSNRF

		VKGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A24-1H11	98	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYNS GTTAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	242	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYEVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A21-3D09	100	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMNW VRQAPGKGL EWVSGISYNS GTKAYADSV KGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	244	QSALTQPAS VSGSPGQSIT ISCSGTSSNV GGYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A24-1D10	102	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMHW VRQAPGKGL EWVSGISYNS GNKAYADSV KGRFTISRDN	246	QSALTQPAS VSGSPGQSIT ISCSGSSSDI GGYNYVSW YQQHPGKAP KLMIYDVT RPSGVSNRF SGSKSGNTA

		AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TTVTVSS		SLTISGLQAE DEADYYCGS YSNNNFYVF GTGTKVTVL G
A21-4B04	104	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYD AGNIAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	248	QSALTQPAS VSGSPGQSIT ISCAGTSSNI GGYNYVSW YQQHPGKAP KLMIYDVSN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A23-4C12	106	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGVSYN SGNKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	250	QSALTQPAS VSGSPGQSIT ISCSGTSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSSNTFYVF GTGTKVTVL G
A21-4G06	108	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMNW VRQAPGKGL EWVSGISYN AGTKAYADS VRGRFTISRD NAKNSLYLQ	252	QSALTQPAS VSGSPGQSIT ISCAGSSSNV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE

		MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS		DEADYYCGS YSNSNFYVF GTGTKVTVL G
A23-3E04	110	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGVSWN SGSIAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA LYYCAKGRS MDVWGQGT TVTVSS	254	QSALTQPAS VSGSPGQSIT ISCTGSSSDV GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCSS YSSSTFYVF GTGTKVTVL G
A24-1C09	112	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMNW VRQAPGKGL EWVSGISYN GGNKAYADS VRGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	256	QSALTQPAS VSGSPGQSIT ISCTGTSSNV GSYNYVSW YQQHPGKAP KLMIYDVND RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
A24-1C04	114	EVQLVESGG GLVQPGRSL RLSCAASGFT FDGYGMHW VRQAPGKGL EWVSGISYNS GSTAYADSV RGRFTISRDN AKNSLYLQM NSLRAEDTA	258	QSALTQPAS VSGSPGQSIT ISCTGTSSNI GGYNYVSW YQQHPGKAP KLMIYDVTK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS

		LYYCAKGRS MDVWGQGT TVTVSS		YSNSNFYVF GTGTKVTVL G
A25-1H10	116	EVQLVESGG GLVQPGRSL RLStABLE 14ASGFTFDA YGMHWVRQ APGKGLEWV SGVSYNAGT TAYADSVRG RFTISRDNK NSLYLQMNS LRAEDTALY YCAKGRSMD VWGQGTTVT VSS	260	QSALTQPAS VSGSPGQSIT ISCGSSSDV GGYNYVSW YQQHPGKAP KLMIYEVSN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A21-4D08	118	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMHW VRQAPGKGL EWVSGVSYN SGNKAYADS VKGRFTISRD NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	262	QSALTQPAS VSGSPGQSIT ISCGGTSSDV GGYNYVSW YQQHPGKAP KLMIYDVND RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNNNFYVF GTGTKVTVL G
A24-1D08	120	EVQLVESGG GLVQPGRSL RLSCAASGFT FDNYGMHW VRQAPGKGL EWVSGISYNS GNTGYADSV RGRFTISRD AKNSLYLQM NSLRAEDTA	264	QSALTQPAS VSGSPGQSIT ISCAGSSSNV VSYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS

		LYYCAKGRS MDVWGQGT TTVTVSS		YDSNTFYVF GTGTKVTVL G
A24-1A08	122	EVQLVESGG GLVQPGRSL RLSCAASGFT FDAYGMHW VRQAPGKGL EWVSGISYD AGNTAYADS VRGRFTISR D NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	266	QSALTQPAS VSGSPGQSIT ISCTGSSSNI GGYNYVSW YQQHPGKAP KLMIYEVNN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCAS YSSNTFYVF GTGTKVTVL G
A21-4A07	124	EVQLVESGG GLVQPGRSL RLSCAASGFT FDTYGMHW VRQAPGKGL EWVSGVSYN SGSKAYADS VKGRFTISR D NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	268	QSALTQPAS VSGSPGQSIT ISCAGSSSNI GGYNYVSW YQQHPGKAP KLMIYDVND RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YSNSNFYVF GTGTKVTVL G
A24-1B09	126	EVQLVESGG GLVQPGRSL RLSCAASGFT FDRYGMHW VRQAPGKGL EWVSGVSYD GGTTAYADS VRGRFTISR D NAKNSLYLQ MNSLRAEDT ALYYCAKGR	270	QSALTQPAS VSGSPGQSIT ISCTGTSSNI GSYNYVSW YQQHPGKAP KLMIYDVNK RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF

		SMDVWGQG TTVTVSS		GTGTKVTVL G
A24-1E07	128	EVQLVESGG GLVQPGRSL RLSCAASGFT FDEYGMHW VRQAPGKGL EWVSGISYD AGSTAYADS VRGRFTISR D NAKNSLYLQ MNSLRAEDT ALYYCAKGR SMDVWGQG TTVTVSS	272	QSALTQPAS VSGSPGQSIT ISCAGSSSNV GGYNYVSW YQQHPGKAP KLMIYEVSN RPSGVSNRF SGSKSGNTA SLTISGLQAE DEADYYCGS YDSNTFYVF GTGTKVTVL G
H21-3A07	130	QVQLVESGG GVVQPGRSL RLSCAASGFT FSNYVMNW VRQAPGKGL EWVTVSYDS GNKYADSV KGRFTISRDN SKNTLYLQM NSLRAEDTA VYYCARGSR RDAFDVWGQ GTMVTVSSA	274	DIQMTQSPS TLSASVGDR VTITCRASQS ISNRLAWYQ QKPGKAPKL LIYKASNLES GVPSRFSGS GSGTEFTLTI SSLQPDDFA TYYCQQTNS FPLTFGGGT KVEIKRTV
H21-4D11	132	QVQLVESGG GVVQPGRSL RLSCAASGFT FSNYAMNW VRQAPGKGL EWVIISYDSS SKYYADSVK GRFTISRDN SKNTLYLQMN SLRAEDTAV YYCARGSGK	276	DIQMTQSPS TLSASVGDR VTITCQASQ GISNRLAWY QQKPGKAPK LLIYKASNL QSGVPSRFS GSGSGTEFT LTISSLQPDD FATYYCQQT NSFPLTFGG

		RDAFDVWGQ GTMVTVSSA		GTKVEIKRT V
H21-3C11	134	QVQLVESGG GVVQPGRSL RLSCAASGFT FSNYAMHW VRQAPGKGL EWVVVSVDG GNIYYADSV KGRFTISRDN SKNTLYLQM NSLRAEDTA VYYCARGSG RRDAFDVWG QGTMVTVSS A	278	DIQMTQSPS TLSASVGDR VTITCRASQS ISNRLAWYQ QKPGKAPKL LIYKASSLQS GVPSRFSGS GSGTEFTLTI SSLQPDDFA TYYCQQTNS FPLTFGGGT KVEIKRTV
H21-3A09	136	QVQLVESGG GVVQPGRSL RLSCAASGFT FSNYDIHWV RQAPGKGLE WVVVSVDGS NTYYADSVK GRFTISRDN KNTLYLQMN SLRAEDTAV YYCARGSGK RDAFDVWGQ GTMVTVSSA	280	DIQMTQSPS TLSASVGDR VTITCRASQS ISNRLAWYQ QKPGKAPKL LIYKASNLQ SGVPSRFSGS GSGTEFTLTI SSLQPDDFA TYYCQQTNS FPLTFGGGT KVEIKRTV
H21-4H04	138	QVQLVESGG GVVQPGRSL RLSCAASGFT FSSYAIHWVR QAPGKGLEW VVVSVDGGS KYYADSVKG RFTISRDN SKNTLYLQMNS LRAEDTAVY	282	DIQMTQSPS TLSASVGDR VTITCQASQS ISSRLAWYQ QKPGKAPKL LIYKASSLQS GVPSRFSGS GSGTEFTLTI SSLQPDDFA TYYCQQTNS

		YCARGSGRR DAFDVWGQ GTMVTVSSA		FPLTFGGGT KVEIKRTV
H23-3D08	140	QVQLVESGG GVVQPGRSL RLSCAASGFT FSDYDMHW VRQAPGKGL EWVVISYDG GSKYYADSV KGRFTISRDN SKNTLYLQM NSLRAEDTA VYYCARGSG QRDAFDVWG QGTMVTVSS A	284	DIQMTQSPS TLSASVGDR VTITCQASQ GISNRLAWY QQKPGKAPK LLIYKASNLE TGVPSRFSGS GSGTEFTLTI SSLQPDDFA TYYCQQTNS FPLTFGGGT KVEIKRTV
H21-4D09	142	QVQLVESGG GVVQPGRSL RLSCAASGFT FSNYINWV RQAPGKGLE WVSVSVDGG SIYYADSVKG RFTISRDN SK NTLYLQMNS LRAEDTAVY YCARGSGRR DAFDVWGQ GTMVTVSSA	286	DIQMTQSPS TLSASVGDR VTITCQASQ GIRNRLAWY QQKPGKAPK LLIYKASNLE QSGVPSRFS GSGSGTEFT LTISSLQPDD FATYYCQQT NSFPLTFGG GTKVEIKRT V
H24-1D11	144	QVQLVESGG GVVQPGRSL RLSCAASGFT FSSYAMHWV RQAPGKGLE WVAVISYDG SNKYYADSV KGRFTISRDN SKNTLYLQM	288	DIQMTQSPS TLSASVGDR VTITCRASQS ISSRLAWYQ QKPGKAPKL LIYKASSLET GVPSRFSGS GSGTEFTLTI SSLQPDDFA

		NSLRAEDTA VYYCARGSG GRDAFDVWG QGTMTVSS A		TYYCQQTNS FPLTFGGGT KVEIKRTV
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[481] Table 15

[Table 15]

Antibody name	heavy-chain variable regions		light-chain variable regions	
	SEQ ID NO:	Polynucleotide sequences	SEQ ID NO:	Polynucleotide sequences
A11-C07	17	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGACTCTGT GAGAGGCAG ATTCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAACTA	161	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGTG ATGATTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC

		CAGTTACCG TCTCCTCA		GTCTTGGGC
A11-G06	19	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAA TGTTGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA	163	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC AATAACAAC ACTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC

A12-C09	21	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAA CGATGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA	165	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A12-E05	23	GAAGTGCAG CTGGTCGAG	167	CAGTCTGCA CTTACTCAG

		AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA GAGGAAGAA TGATCGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA		CCAGCCAGT GCGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC AATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A12-E01	25	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA	169	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG

		CAACCTGCA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAC TTTTGGATGT GTGGGGCCA GGGAACTAC AGTTACCGT CTCCTCA		AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGTT CTTCTTACTC TAACAACAC TTTTTACGTT TTCGGAACC GGGACAAAG GTGACCGTC TTGGGC
A12-E04	27	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT	171	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC

		AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGACTCTGT GAGAGGCAG ATTCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAA TGATGGATG TGTGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC AATAACTCC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A12-F02	29	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA	173	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA

		GCGGGTTCA CCTTTGACG AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAT ATTGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA		TCAAGTAGC GATGTGGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A12-H04	31	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG	175	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACGGGA TCAAGTAGC GATGTGGGT

		AATATGGCA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATGGAATTC TGGTAGCAT TGCGTACGC TGA CTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAC TTTTGGATGT GTGGGGCCA GGGAACTAC AGTTACCGT CTCCTCA		GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAG GCTGAAGAC GAGGCTGAT TATTATTGT GGTGCTTAC TCTAACACC AATTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3H04	33	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA CCTATGGGA TGA ACTGGT	177	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA TCAAGTAGC GATGTTCGGT GGCTATAAT TATGTGTCC

		GAGACAGGC TCCAGGGAG GGTCTGGAG TGGGTGTCT GGCATTTC TATAATGGT GGTACCACA GCGTACGCT GACTCTGTG AGAGGCAGA TTCACATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGACACAGC CCTGTACTAT TTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGTG ATGATTTC GACGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4C03	35	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GAACGGGTG AGACAGGCT CCAGGAAGG	179	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCACCGGA TCAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA

		GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATTCTG GTACCATAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAC GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		GGCAAGGCC CCCAAACTG ATGATTTAC GACGTTAGC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCCTAC TCTAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1G10	37	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GCACTGGTG AGACAGGCT CCAGGGAAG GGTCTGGAG TGGGTGTCT	181	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACTG

		GGCATTTC TATAATTCTG GTACCAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAT GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		ATGATTTAC GACGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1F07	39	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGgAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCGTTTCAT ATAATTCTG	183	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATGTCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTACC

		GTACCACAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCAG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GACTACAGT TACCGTCTCC TCA		AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4B10	41	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGA ATATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATTCTG GTAACAAAG CGTACGCTG	185	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC

		ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAC GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4G04	43	gAAGTGCAG CTGTGAGAG GTGGGGGAG GCTTGGTAC AaCCtGgAAg AtCCCTTAGA CTCTCTTGCG CAGCAAGCG GGTTACCTT TGACAGCTA TGGGATGCA CTGGGTGAG ACAGGCTCA GGGAAGGGT CTGGAGTGG TGTCTGGCA TTTCATATAA TGGTGGTAA CACAGCGTA CGCTGACTC TGTGAGAGG CAGATTCAC	187	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACTG ATGATTTAC GACGTTAAC GAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC

		TATCTCCAG AGATAAGCC AAAAACAGC TTATACCTGC AGATGAATT CACTGAGAG CCGAGGACA CAGCCCTGT ACTATTGTG CTAGAGGAA GATATTCGG ATGTGTGGG GCCAGGAAC TACAGTTAC CGTCTCTTCA		AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACAAC AATTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3H05	45	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GAACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTTGG CATTTTCATAT AATTCTGGT ACCATAGCG TACGCTGAC TCTGTGAAA GGCAGATTC ACTATCTCC AGAGATAAC	189	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCGGCGGA TCAAGTAGC AATGTTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACCTG ATGATTTAC GACGTTAGC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA

		GCCAAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCGGG ACACAGCCC TGTA CTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-3A09	47	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA ACTATGGGA TGA ACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTACCAA GCGTACGCT GACTCTGTG AAAGGCAGA TTC ACTATCT CCAGAGATA ACGCCAAA ACAGCTTAT	191	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCAGCGGA TCAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC

		ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4B06	49	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAG CTATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGCTGG CATTTCATAT AATGGTGGT AGCAAAGCG TACGCTGAC TCTGTGAGA GGCAGATTC ACTATCTCC AGAGATAAC GCAAAAACA GCTTATACCT GCAGATGAA TTCACTGAG	193	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATATCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTACC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC

		AGCCAGGAC ACAGCCCTG TACTATTGTG CTAGAGGAA GATATTCGG ATGTGTGGG GCCAGGGAA CTACAGTTA CCGTCTCCTC A		GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1B05	51	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA AATATGGGA TGAAGTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTAACACA GCGTACGCT GACTCTGTG AGAGGCAGA TTCATATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG	195	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT

		CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCCGGATG TGTGGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3A08	53	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTTGG CATTTCATAT AATTCTGGT ACCACAGCG TACGCTGAC TCTGTGAAA GGCAGATTC ACTATCTCC AGAGATAAC GCCAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCGGG ACACAGCCC TGTA CTATTG TGCTAGAGG	197	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCGCCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC

		AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		AATTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4C08	55	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAC ATATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTTGG CATTTTCATAT AATGCCGGT AACAAAGCG TACGCTGAC TCTGTGAGA GGCAGATTC ACTATCTCC AGAGATAAC GCCAAAAAC AGCTTATAC CTGCAGATG AATTCAGT AGAGCCGGG ACACAGCCC TGTAATTG TGCTAGAGG AAGATATTC GGATGTGTG	199	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATGTCCGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAAC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTCTAC GTTTTTCGGA

		GGGCCAGGG AACTACAGT TACCGTCTCC TCA		ACCGGGACA AAGGTGACC GTCTTGGGC
A23-4D09	57	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG CCTATGGGA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCGTTTC ATATGATGC TGGTAACAC AGCGTACGC TGA CTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AATGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAACTA	201	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATATCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTACC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC

		CAGTTACCG TCTCCTCA		GTCTTGGGC
A23-3D03	59	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG CATATGGGA TGAAGTGGG TGAGACAGG CTCCAGGAA GGGTCTGGA GTGGGTGTC TGGCATTTC ATATAATGC TGGTAGCAC AGCGTACGC TGAATCTGT GAGAGGCAG ATCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GGGACACAG CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAATA CAGTTACCG TCTCCTCA	203	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA TCAAGTAGC GATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTAC GACGTTACC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC

A21-4B03	61	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GAACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCGG CATTTCATAT AATGCTGGT AACAAAGCG TACGCTGAC TCTGTGAGA GGCAGATTC ACTATCTCC AGAGATAAC GCCAAAAC AGCTTATAC CTGCAGATG AATTCAGTG AGAGCCGAG ACACAGCCC TGTACTATTT GCTAGAGGA AGATATTTCG GATGTGTGG GGCCAGGGA ACTACAGTT ACCGTCTCCT CA	205	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC AATATCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACCTG ATGATTTAC GACGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-3D10	63	GAAGTGCAG CTGGTCGAG	207	CAGTCTGCA CTTACTCAG

		AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA ACTATGGGA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATGATGC TGGTACCAC AGCGTACGC TGA CTCTGT GAAAGGCAG ATCACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA AAGGAAGAT ATTCGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA		CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA ACAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTACC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACACC AATTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-3A10	65	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC	209	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG

		AACCtGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTTGG CATTTCATAT AATGCTGGT AACAAAGCG TACGCTGAC TCTGTGAGA GGCAGATTC ACTATCTCC AGAGATAAC GCCAAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCGGG ACACAGCCC TGTA CTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4H04	67	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCtgaAG ATCCCTTAG	211	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC

		ACTCTCTTGC GCAGCAAGC GGGTTCACC TTTGACAGC TATGGGATG CACTGGGTG AGACAGGCT CCAGGGAAG GGTCTGGAG TGGGTGTCC GGCATTTCA TATAATTCTG GTAACAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCCT GAGAGCCGA GGACACAGC CCTGTACTAT TGTGCTAGA GGAAGATAT TCGGATGTG TGGGGCCAG GGAECTACA GTTACCGTCT CCTCA		ACCATTTC TGCAGCGGA ACAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAACTG ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTCTTAC TCTAACAAC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4F11	69	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA	213	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCGGCGGA

		GCGGGTTCA CCTTTGACG CATATGGGA TGA ACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATGG TGGTACCAA AGCGTACGC TGACTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGATACA GCCCTGTAC TATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA		ACAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTAAC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3G05	71	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA	215	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC AATATCGGT

		CATATGGGA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTACCATA GCGTACGCT GACTCTGTG AGAGGCAGA TTCACTATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCCGATG TGTGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3A10	73	GAAGTGCAG CTGGTCGAG AGTGGGGGA GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA ATATGGGAT GCACTGGTG	217	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC

		AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATAATGCTG GTAGCAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGA GACACAGCC CTGTACTATT GGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTAC GACGTTAGC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A25-1H04	75	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG CATATGGGA TGAAGTGGG TGAGACAGG CTCCAGGGA	219	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA

		AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTAACACA GCGTACGCT GACTCTGTG AGAGGCAGA TTCACATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC GAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3B06	77	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTTGG	221	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC GATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT

		CATTTCATAT AATTCTGGT AGCAAAGCG TACGCTGAC TCTGTGAAA GGCAGATTC ACTATCTCC AGAGATAAC GCCAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCGGG ACACAGCCC TGTA CTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		ATGATTTAC GACGTTAGC GAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-4A09	79	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA CTATGGGAT GAACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATGATTCTG	223	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCGGCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTACC

		GTAACAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A25-1D09	81	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTTACGC ATATGGGAT GCACTGGGT GAGACAGGC TCCAGGAAG GGTCTGGAG TGGGTGTCT GGCATTTC TATAATGGT GGTACCATA GCGTACGCT	225	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA ACAAGTAGC GATGTCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAAC AAGCGCCCC TCAGGGGTC

		GACTCTGTG AAAGGCAGA TTCACTATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG GGACACAGC CCTGTACTAT TGTGCTAGA GGAAGATAT TCGGATGTG TGGGGCCAG GGAACTACA GTTACCGTCT CCTCA		TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4E10	83	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GAACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCGTTTCAT ATAACGCTG GTAACAAAG CGTACGCTG ACTCTGTGA GAGGCAGAT	227	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA TCAAGTAGC AATGTGCGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC

		TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAC GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3C04	85	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGgAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAC ATATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATGATTCTG GTACCACAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA	229	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA ACAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACTG ATGATTTAC GACGTTACC GAGCCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA

		CGCAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCAGG ACACAGCCC TGTA CTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3G06	87	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGgAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GAACTGGTG AGACAGCTC CAGGGAAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATTCTG GTAACATAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA	231	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA ACAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTTAC GACGTTAAC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC

		CCTGCAGAT GAATTCCT GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1E09	89	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA ATATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCGTTTCAT ATAATGCTG GTACCACAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCAAAAAC AGCTTATAC CTGCAGATG AATTCCTG	233	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTACC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAG GCTGAAGAC

		AGAGCCAGG ACACAGCCC TGTACTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3F03	91	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA CATATGGGA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTAACATA GCGTACGCT GACTCTGTG AAAGGCAGA TTCATATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG	235	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA TCAAGTAGC AATATCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGTG ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT

		CCCTGTACT ATTGTGCTA GAGGAAGAT ATTTCGGATG TGTGGGGGCC AGGGAACTA CAGTTACCG TCTCCTCA		GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4F07	93	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GAACTGGGT GAGACAGGC TCCAGGAAG GGTCTGGAG TGGGTGTCT GGCATTTC TATAATGCT GGTAACAAA GCGTACGCT GACTCTGTG AAAGGCAGA TTCATATCT CCAGAGATA ACGCAAAA CAGCTTATA CCTGCAGAT GAATTCAT GAGAGCGAG GACACAGCC CTGTACTATT GTGCTAGAG	237	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCAGCGGA ACAAGTAGC AATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTAC GACGTTAGC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC

		GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		AATTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1A03	95	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG CATATGGGA TGAACGGGT GAGACAGGC TCCAGGAAG GGTCTGGAG TGGGTGTCT GGCATTTC TATAATGCT GGTAACACA GCGTACGCT GACTCTGTG AAAGGCAGA TTCATATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG GGACACAGC CCTGTACTAT TGTGCTAGA GGAAGATAT TCGGATGTG	239	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGGCGGA TCAAGTAGC AATGTGCGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAGC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTAC GTTTTCGGA

		TGGGGCCAG GGA ACTACA GTTACCGTCT CCTCA		ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1H11	97	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG CATATGGGA TGCACTGGG TGAGACAGG CTCCAGGGA AGGGTCTGG AGTGGGTGT CTGGCATTTC ATATAATTCT GGTACCACA GCGTACGCT GACTCTGTG AGAGGCAGA TTC ACTATCT CCAGAGATA ACGCCAAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG AGGACACAG CCCTGTACT ATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGAACTA	241	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCACCGGA TCAAGTAGC GATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG ATGATTAC GAAGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC

		CAGTTACCG TCTCCTCA		GTCTTGGGC
A21-3D09	99	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA CTATGGGAT GAACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATAATTCTG GTACCAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA	243	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA ACAAGTAGC AATGTCCGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAAC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC

A24-1D10	101	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA CTATGGGAT GCACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATTCTG GTAACAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAC GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA	245	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA TCAAGTAGC GATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACCTG ATGATTTAC GACGTTACC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACAAC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4B04	103	GAAGTGCAG CTGGTCAGA	247	CAGTCTGCA CTTACTCAG

		GTGGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATGATGCTG GTAACATAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA ACAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTAC GACGTTAGC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-4C12	105	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC	249	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG

		AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GAACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCGTTTCAT ATAATTCTG GTAACAAAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		AGTCCTGGA CAGTCGATC ACCATTTCC TGCAGCGGA ACAAGTAGC GATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTACC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4G06	107	GAAGTGCAG CTGGTCGAG AGTGGGGGA GCTTGGTAC AACCTGGAA GATCCCTTA	251	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC

		GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAC ATATGGGAT GAACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATGCTG GTACCAAAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCCT GAGAGCCGA GACACAGCC CTGTACTATT GGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		ACCATTTCC TGCGCCGGA TCAAGTAGC AATGTTCGGT GGCTATAAT TATGTGTCC TGGTACCAA CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTAACA AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A23-3E04	109	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTgAAG ATCCCTTAG ACTCTCTTGC GCAGCAAGC	253	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA

		GGGTTACCC TTTGACAAA TATGGGATG CACTGGGTG AGACAGGCT CCGGGAAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATAATGCTG GTACCACAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CCCAAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCGAGG ACACAGCCC TGTACTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		TCAAGTAGC GATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAACCTG ATGATTTAC GACGTTACC GATCGCCCC TCGGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1C09	111	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACG	255	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA ACAAGTAGC AATGTCGGT

		CATATGGGA TGAACGGGT GAGACAGGC TCCAGGAAG GGTCTGGAG TGGGTGTCT GGCATTTC TATAATGGT GGTAACAAA GCGTACGCT GACTCTGTG AGAGGCAGA TTCACATCT CCAGAGATA ACGCCAAA ACAGCTTAT ACCTGCAGA TGAATTCAC TGAGAGCCG GGACACAGC CCTGTACTAT TGTGCTAGA GGAAGATAT TCGGATGTG TGGGGCCAG GGAACCTACA GTTACCGTCT CCTCA		AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAAC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1C04	113	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGG ATATGGGAT GCACGGGTG	257	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA ACAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC

		AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCATTTCAT ATAATTCTG GTAGCACAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTAC GACGTTACC AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTTCGA ACCGGGACA AAGGTGACC GTCTTGGGC
A25-1H10	115	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTggAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC CTATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG	259	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCGGCGGA TCAAGTAGC GATGTGCGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA

		GTCTGGAGT GGGTGTCTG GCGTTTCAT ATAATGCTG GTACCACAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCAAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCAGG ACACAGCCC TGTACTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		GGCAAGGCC CCCAAACTG ATGATTTAC GAAGTTAGC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCCTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4D08	117	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAC ATATGGGAT GCACGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG	261	CAGGCGGAG GTGGGTCCG GCGGTGGCG GATCGCAGT CTGCACTTA CTCAGCCAG CCAGTGTGT CTGGGAGTC CTGGACAGT CGATCACCA TTTCCTGCG GCGGAACAA GTAGCGATG TCGGTGGCT ATAATTATG TGTCCTGGT

		GCGTTTCAT ATAATTCTG GTAACAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCCT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		ACCAGCAGC ACCCAGGCA AGGCCCCCA AACTGATGA TTTACGACG TTAACGATC GCCCCTCAG GGGTCTCCA ATCGCTTTT CTGGCAGTA AAAGCGGAA ACACAGCCT CCCTGACTA TCAGCGGCC TCCAAGCTG AAGACGAGG CTGATTATT ATTGTGGTT CTTACTCTA ACAACAATT TTTACGTTTT CGGAACCGG GACAAAGGT GACCGTCTT GGGC
A24-1D08	119	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAA CTATGGGAT GCACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT	263	CAGGCGGAG GTGGGTCCG GCGGTGGCG GATCGCAGT CTGCACTTA CTCAGCCAG CCAGTGTGT CTGGGAGTC CTGGACAGT CGATCACCA TTTCCTGCG CCGGATCAA GTAGCAATG TCGTGAGCT ATAATTATG

		GGGTGTCTG GCATTTTCAT ATAATTCTG GTAACACAG GGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCACT GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		TGTCTTGGT ACCAGCAGC ACCCAGGCA AGGCCCCCA AACTGATGA TTTACGACG TTAACAAGC GCCCCTCAG GGGTCTCCA ATCGCTTTT CTGGCAGTA AAAGCGGAA ACACAGCCT CCCTGACTA TCAGCGGCC TCCAAGCTG AAGACGAGG CTGATTATT ATTGTGGTT CTTACGATA GCAACACTT TTTACGTTTT CGGAACCGG GACAAAGGT GACCGTCTT GGGC
A24-1A08	121	GAAGTGCAG CTGGTCGAG AGTGGGGGA GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGC ATATGGGAT GCACTGGGT GAGACAGGC TCCAGGGAA	265	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTC TGCACCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA

		GGGTCTGGA GTGGGTGTC TGGCATTTC ATATGATGC TGGTAACAC AGCGTACGC TGA CTCTGT GAGAGGCAG ATTC ACTATC TCCAGAGAT AACGCCAAA AACAGCTTA TACCTGCAG ATGAATTCA CTGAGAGCC GAGGACACA GCCCTGTAC TATTGTGCTA GAGGAAGAT ATTCGGATG TGTGGGGCC AGGGA ACTA CAGTTACCG TCTCCTCA		GGCAAGGCC CCCAA ACTG ATGATTTAC GAAGTTAAC AATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GCTTCTTAC TCTAGCAAC ACTTTTTAC GTTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A21-4A07	123	GAAGTGCAG CTGGTCGAG AGTGGGGGA GGCTTGGTA CAACCTGGA AGATCCCTT AGACTCTCTT GCGCAGCAA GCGGGTTCA CCTTTGACA CCTATGGGA TGCACGGGT GAGACAGGC TCCAGGAAG GGTCTGGAG TGGGTGTCT	267	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC AATATCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAA ACTG

		GGCGTTTCA TATAATTCTG GTAGCAAAG CGTACGCTG ACTCTGTGA AAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAT GAGAGCCGG GACACAGCC CTGTACTATT GTGCTAGAG GAAGATATT CGGATGTGT GGGGCCAGG GAACTACAG TTACCGTCTC CTCA		ATGATTTAC GACGTTAAC GATCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC TCTAACTCC AATTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1B09	125	GAAGTGCAG CTGGTCGAG AGTGGGGAG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACAG ATATGGGAT GCATGGGTG AGACAGGCT CCAGGAAGG GTCTGGAGT GGGTGTCTG GCGTTTCAT ATGATGGTG	269	CAGTCTTCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCACCGGA ACAAGTAGC AATATCGGT AGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GACGTTAAC

		GTACCACAG CGTACGCTG ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCAAAAAC AGCTTATAC CTGCAGATG AATTCACTG AGAGCCAGG ACACAGCCC TGTACTATTG TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		AAGCGCCCC TCAGGGGTC TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
A24-1E07	127	GAAGTGCAG CTGGTCGAG AGTGGGGGG GCTTGGTAC AACCTGGAA GATCCCTTA GACTCTCTTG CGCAGCAAG CGGGTTCAC CTTTGACGA ATATGGGAT GCACTGGTG AGACAGGCT CCAGGGAGG GTCTGGAGT GGGTGTCTG GCATTTTCAT ATGATGCTG GTAGCACAG CGTACGCTG	271	CAGTCTGCA CTTACTCAG CCAGCCAGT GTGTCTGGG AGTCCTGGA CAGTCGATC ACCATTTCC TGCGCCGGA TCAAGTAGC AATGTCGGT GGCTATAAT TATGTGTCC TGGTACCAG CAGCACCCA GGCAAGGCC CCCAAAGT ATGATTTAC GAAGTTAGC AATCGCCCC TCAGGGGTC

		ACTCTGTGA GAGGCAGAT TCACTATCTC CAGAGATAA CGCCAAAAA CAGCTTATA CCTGCAGAT GAATTCAC GAGAGCCGA GACACAGCC CTGTACTATT TGCTAGAGG AAGATATTC GGATGTGTG GGGCCAGGG AACTACAGT TACCGTCTCC TCA		TCCAATCGC TTTTCTGGC AGTAAAAGC GGAAACACA GCCTCCCTG ACTATCAGC GGCCTCCAA GCTGAAGAC GAGGCTGAT TATTATTGT GGTTCTTAC GATAGCAAC ACTTTTTAC GTTTTCGGA ACCGGGACA AAGGTGACC GTCTTGGGC
H21-3A07	129	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCCGGT AAGTCTCTG AGACTCTCC TGCGCAGCC TCTGGCTTTA CATTCAGTA ACTACTACA TGAATTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCACTGTTTC TTACGATAG CGGCAACAA ATACTATGC AGATTCTGT GAAAGGGCG	273	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCGA GCTAGTCAG AGTATTAGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAACTTA GAAAGTGGG GTCCCATCA AGGTTTCAGC GGCAGTGGA

		ATTCACCATT TCCAGAGAC AACTCTAAG AACACTCTTT ATCTGCAGA TGAATAGCC TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTTG AAGACGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		TCTGGGACA GAATTCAC CTCACCATC AGCAGCCTG CAGCCTGAT GATTTTGCA ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H21-4D11	131	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGCGCAGCC TCTGGATTTA CATTCAGTA ACTACGCCA TGAATTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCATTATTTC TTACGATAG CAGCAGCAA ATACTATGC AGATTCTGT GAAAGGGCG ATTCACCATT	275	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCAA GCTAGTCAG GGTATTAGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAACTTA CAAAGTAGG GTCCCATCA AGGTTTCAGC GGCAGTGGA TCTGGGACA

		TCCAGAGAC AACTCTAAG AACACTCTTT ATCTGCAGA TGAATAGCC TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTGG GAAGCGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		GAATTCACT CTCACCATC AGCAGCCTG CAGCCTGAT GATTTTGCA ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H21-3C11	133	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGCGCAGCC TCTGGCTTTA CATTCAGTA ACTACGCCA TGCATTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCGTTGTTTC TTACGATGG CGGCAACAT ATACTATGC AGATTCTGT GAAAGGGCG ATTCACCATT TCCAGAGAC	277	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCGA GCTAGTCAG AGTATTAGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAGCTTA CAAAGTGGG GTCCCATCA AGGTTCAGC GGCAGTGGA TCTGGGACA GAATTCACT

		AACTCTAAG AACACTCTTT ATCTGCAGA TGAATAGCC TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTGG GCGGCGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		CTCACCATC AGCAGCCTG CAGCCTGAT GATTTTGCA ACTTACTAT TGTC AACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H21-3A09	135	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGCGCAGCC TCTGGCTTTA CATTCAGTA ACTACGACA TTCATTGGGT CAGACAGGC TCCAGGAAA AAGCTTGGA GTGGGTGGC CGTTGTTTCT TACGATGGC AGCAACACA TACTATGCA GATTCTGTG AAAGGGCGA TTCACCATT CCAGAGACA ACTCTAAGA	279	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCGA GCTAGTCAG AGTATTAGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAACTTA CAAAGTGGG GTCCCATCA AGGTTTCAGC GGCAGTGGA TCTGGGAAA GAATTCACT CTCACCATC

		ACACTCTTTA TCTGCAGAT GAATAGCCT GAGAGCTGA AGACACTGC CGTTTACTAT TGTGCGAGG GGGAGTGGG AAGCGGGAT GCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		AGCAGCCTG CAGCCTGAT GATTTTGCA ACTTACTAT TGTC AACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H21-4H04	137	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCCGTT TAAGTCTCT GAGACTCTC CTGCGCAGC CTCTGGCTTT ACACTTAGT AGCTACGCC ATTCATTGG GTCAGACAG GCTCCAGGA AAAGGCTTG GAGTGGGTG GCCGTTGTTT CTTACGATG GCGGCAGCA AATACTATG CAGATTCTG TGAAAGGGC GATTCACCA TTTCCAGAG ACAACTCTA AGAACA CTC	281	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCAA GCTAGTCAG AGTATTAGT AGCCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAGCTTA CAAAGTGGG GTCCCATCA AGGTTCAGC GGCGGTGGA TCTGGGACA GAATTC ACT CTCACCATC AGCAGCCTG

		TTTATCTGCA GATGAATAG CCTGAGAGC TGAAGACAC TGCCGTTTAC TATTGTGCG AGGGGGAGT GGGAGGCGG GATGCTTTTG ACGTGTGGG GCCAGGGCA CAATGGTCA CCGTATCAT CA		CAGCCTGAT GATTTTGCA ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H23-3D08	139	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGCGCAGAC TCTGGCTTTA CATTCAAGT ACTACGACA TGCATTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCGTTATTTT TTACGATGG CGGCAGCAA ATACTATGC AGATTCTGT GAAAGGGCG ATTCACCATT TCCAGAGAC AACTCTAAG AACACTCTTT	283	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCAA GCTAGTCAG GGTATTAGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAACTTA GAAACTGGG GTCCCATCA AGGTTCAGC GGCAGTGGA TCTGGGACA GAATTCATC CTCACCATC AGCAGCCTG

		ATCTGCAGA TGAATAGCC TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTGG GCAGCGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		CAGCCTGAT GATTTTGCA ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H21-4D09	141	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGCGCAGCC TCTGGCTTTA CATTCAGTA ACTACTACA TTAATTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCAGTGTTTC TTACGATGG CGGCAGCAT ATACTATGC AGATTCTGT GAAAGGGCG ATTCACCAT TCCAGAGAC AACTCTAAG AACACTCTTT ATCTGCAGA	285	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGTCAA GCTAGTCAG GGTATTCGT AACCGGTTG GCTTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAACTTA CAAAGTGGG GTCCCATCA AGGTTTCAGC GGCAGTGGA TCTGGGACA GAATTCACT CTCACCATC AGCAGCCTG CAGCCTGAT

		TGAATAGCC TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTGG GAGGCGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		GATTTTGCA ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
H24-1D11	143	CAAGTGCAG CTGGTGGAG TCTGGCGGA GGTGTGGTC CAACCTGGA AGGTCTCTG AGACTCTCC TGC GCAGCC TCTGGCTTTA CATTCAGTA GCTACGCCA TGCACTGGG TCAGACAGG CTCCAGGAA AAGGCTTGG AGTGGGTGG CCGTTATCTC TTACGATGG TAGCAATAA GTACTATGC AGATTCTGT GAAAGGGCG ATTCACCATT TCCAGAGAC AACTCTAAG AACACTCTTT ATCTGCAGA TGAATAGCC	287	GACATCCAG ATGACCCAG TCTCCTTCC ACCCTGTCT GCATCTGTA GGAGACAGA GTCACCATC ACTTGCCGG GCCAGTCAG AGTATTAGT AGCCGGTTG GCCTGGTAT CAGCAGAAA CCAGGGAAA GCCCCTAAG CTCCTGATC TATAAGGCA TCTAGCTTA GAAACTGGG GTCCCATCA AGGTTTCAGC GGCAGTGGA TCTGGGACA GAATTCACT CTCACCATC AGCAGCCTG CAGCCTGAT GATTTTGCA

		TGAGAGCTG AAGACACTG CCGTTTACTA TTGTGCGAG GGGGAGTGG GGGACGGGA TGCTTTTGAC GTGTGGGGC CAGGGCACA ATGGTCACC GTATCATCA		ACTTACTAT TGTCAACAG ACGAACAGT TTCCCTCTC ACTTTCGGC GGAGGGACC AAGGTGGAG ATCAAA
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[483] Table 16

[Table 16]

Clone name	Heavy-chain variable regions				Light-chain variable regions			
	SEQ ID NO:	CDR1	CDR2	CDR3	SEQ ID NO:	CDR1	CDR2	CDR3
A11-C07	18	EYGMH	GVSW NSGSI AYADS VRG	GRYSD V	162	TGSSS DVGG YNYVS	DVTKR PS	ASYSS NTFYV
A11-G06	20	EYGMH	GVSW NSGSI AYADS VRG	GRML DV	164	TGSSD VGGY NYVS	DVTKR PS	GSYNN NTFYV
A12-C09	22	EYGMH	GVSW NSGSI AYADS VRG	GRTM DV	166	TGSSD VGGY NTVS	DVTKR PS	GSYSS NTFYV
A12-E05	24	EYGMH	GVSW NSGSI AYADS VRG	GRML DV	168	TGSSS DVGG YNYVS	DVTKR PS	ASYSS NTFYV
A12-E01	26	EYGMH	GVSW NSGSI AYADS VRG	GRLLD V	170	TGSSS DVGG YNYVS	DVTKR PS	GSYSN NNFYV
A12-E04	28	EYGMH	GVSW NSGSI AYADS VRG	GRLFD V	172	TGSSS DVGG YNYVS	DVTKR PS	GSYSN SNFYV
A12-F02	30	EYGMH	GVSW NSGSI AYADS VRG	GRYLD V	174	TGSSS DVGG YNYVS	DVTKR PS	GSYDS NTFYV
A12-H04	32	EYGMH	GVSW NSGSI AYADS VRG	GRLLD V	176	TGSSS DVGG YNYVS	DVTKR PS	GAYSN TNFYV

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[485] Table 17

[Table 17]

clone name	heavy-chain variable regions				light-chain variable regions			
	SEQ ID NO:	CDR1	CDR2	CDR3	SEQ ID NO:	CDR1	CDR2	CDR3
A23-3H04	34	TYGMN	GISYNGGTAYADSVRG	GRYSDV	178	GGSSSDVGGYNYVS	DVNKRPS	GSYDSNTFYV
A24-1G10	38	AYGMH	GISYNSGTAYADSVKG	GRYSDV	182	GGSSSNIGGYNYVS	DVNKRPS	ASYSNSNFYV
A24-1F07	40	AYGMH	GVSYNSGTAYADSVRG	GRYSDV	184	SGSSSNVGSYNYVS	DVTKRPS	GSYSNSNFYV
A21-4B10	42	EYGMH	GISYNSGNKAYADSVRG	GRYSDV	186	SGSSSNIGGYNYVS	DVSKRPS	GSYDSNTFYV
A21-4G04	44	SYGMH	GISYNGGNTAYADSVRG	GRYSDV	188	SGSSSNIGGYNYVS	DVNERPS	GSYSNNFYV
A23-3H05	46	AYGMN	GISYNSGTIAYADSVKG	GRYSDV	190	GGSSSNVGGYNYVS	DVSNRPS	GSYSNSNFYV
A21-3A09	48	NYGMN	GISYNSGTAYADSVKG	GRYSDV	192	SGSSSDIGDYNYS	DVNKRPS	ASYSSNTFYV
A21-4B06	50	SYGMH	GIASYNNGSK	GRYSDV	194	SGSSSNIGSYNYVS	DVTDRPS	GSYSSNTFYV
A24-1B	52	KYGM	GISYN	GRYSD	196	AGSSS	DVSKR	GSYDS

05		N	SGNTA YADSV RG	V		DIGGY NTVS	PS	NTFYV
A23-3A 08	54	AYGM H	GISYN SGTTA YADSV KG	GRYSD V	198	AGSSS NIGGY NYVS	DVSKR PS	GSYSN SNFYV
A21-4C 08	56	TYGM H	GISYN AGNK AYADS VRG	GRYSD V	200	SGSSS NVGSY NYVS	DVNN RPS	GSYSS NTFYV
A23-4D 09	58	AYGM H	GVSYS AGNTA YADSV RG	GRYSD V	202	SGSSS NIGSY NYVS	DVTDR PS	GSYSS NTFYV
A23-3D 03	60	AYGM N	GISYN AGSTA YADSV RG	GRYSD V	204	TGSSS DVGG YNYVS	DVTNR PS	GSYDS NTFYV
A21-4B 03	62	AYGM N	GISYN AGNK AYADS VRG	GRYSD V	206	SGSSS NIGSY NYVS	DVNB RPS	ASYSS NTFYV
A21-3D 10	64	NYGM H	GISYD AGTTA YADSV KG	GRYSD V	208	GGTSS NIGGY NYVS	DVTNR PS	GSYSN TNFYV
A21-3A 10	66	AYGM H	GISYN AGNK AYADS VRG	GRYSD V	210	AGSSS NIGGY NYVS	DVSKR PS	GSYSN SNFYV
A21-4H 04	68	SYGM H	GISYN SGNKA YADSV KG	GRYSD V	212	SGTSS DIGGY NYVS	DVSKR PS	GSYSN NNFYV
A21-4F 11	70	AYGM N	GISYN GGTKA YADSV	GRYSD V	214	GGTSS NIGGY NYVS	DVND RPS	ASYSS NTFYV

			RG					
A23-3G 05	72	TYGM H	GISYN SGTIA YADSV RG	GRYSD V	216	AGSSS NIGSY NYVS	DVSNR PS	GSYDS NTFYV
A23-3A 10	74	KYGM H	GISYN AGSKA YADSV KG	GRYSD V	218	AGSSS NIGGY NYVS	DVSDR PS	GSYDS NTFYV
A25-1H 04	76	AYGM H	GISYN SGNTA YADSV RG	GRYSD V	220	AGSSS DIGGY NYVS	DVSER PS	GSYDS NTFYV
A23-3B 06	78	AYGM H	GISYN SGSKA YADSV KG	GRYSD V	222	SGSSS DVGG YNYVS	DVSER PS	GSYDS NTFYV
A23-4A 09	80	NYGM N	GIAYD SGNKA YADSV KG	GRYSD V	224	GGSSS NIGGY NYVS	DVTKR PS	ASYSS NTFYV
A25-1D 09	82	AYGM H	GISYN GGTIA YADSV KG	GRYSD V	226	GGTSS DVGSY NYVS	DVNK RPS	GSYSN SNFYV
A21-4E 10	84	AYGM H	GVSYN AGNK AYADS VRG	GRYSD V	228	TGSSS NVGG YNYVS	DVSKR PS	GSYSS NTFYV
A23-3C 04	86	AYGM N	GISYD SGTTA YADSV KG	GRYSD V	230	SGTSS DIGGY NYVS	DVTEP PS	ASYSS NTFYV
A23-3G 06	88	TYGM H	GISYN SGNIA YADSV RG	GRYSD V	232	AGTSS NIGGY NYVS	DVND RPS	GSYDS NTFYV
A24-1E	90	AYGM	GVSYN	GRYSD	234	TGSSS	DVTNR	GSYSN

09		N	AGTTA YADSV RG	V		NIGGY NYVS	PS	SNFYV
A23-3E 09	92	KYGM H	GISYN SGNIA YADSV KG	GRYSD V	236	GGSSS NIGSY NYVS	DVTKR PS	GSYDS NTFYV
A21-4F 07	94	TYGM H	GISYN AGNK AYADS VKG	GRYSD V	238	SGTSS NVGG YNYVS	DVSDR PS	GSYSN SNFYV
A24-1A 03	96	AYGM N	GISYN AGNTA YADSV KG	GRYSD V	240	GGSSS NVGG YNYVS	DVSKR PS	GSYSN SNFYV
A24-1H 11	98	AYGM H	GISYN SGTTA YADSV RG	GRYSD V	242	TGSSS DVGG YNYVS	EVNKR PS	ASYSS NTFYV
A21-3D 09	100	NYGM N	GISYN SGTKA YADSV KG	GRYSD V	244	SGTSS NVGG YNYVS	DVNK RPS	GSYSN SNFYV
A24-1D 10	102	NYGM H	GISYN SGNKA YADSV KG	GRYSD V	246	SGSSS DIGGY NYVS	DVTDR PS	GSYSN NNFYV
A21-4B 04	104	AYGM H	GISYD AGNIA YADSV RG	GRYSD V	248	AGTSS NIGGY NYVS	DVSNR PS	ASYSS NTFYV
A23-4C 12	106	AYGM N	GVSYN SGNKA YADSV RG	GRYSD V	250	SGTSS DVGG YNYVS	DVTKR PS	GSYSS NTFYV
A21-4G 06	108	TYGM N	GISYN AGTKA YADSV	GRYSD V	252	AGSSN VGGY NYVS	DVTKR PS	GSYSN SNFYV

			RG					
A23-3E 04	110	KYGM H	GISYN AGTTA YADSV KG	GRYSD V	254	TGSSS DVGG YNYVS	DVTDR PS	GSYSN SNFYV
A24-1C 09	112	AYFM N	GISYN GGNK AYADS VRG	GRYSD V	256	TFTSS NVGSY NYVS	DVND RPS	GSYDS NTFYV
A24-1C 04	114	GYGM H	GISYN SGSTA YADSV RG	GRYSD V	258	TGTSS NIGGY NYVS	DVTKR PS	GSYSN SNFYV
A25-1H 10	116	AYGM H	GVSYN AGTTA YADSV RG	GRYSD V	260	GGSSS DVGG YNYVS	EVSNR PS	GSYSN SNFYV
A21-4D 08	118	TYGM H	GVSYN SGNKA YADSV KG	GRYSD V	262	GGTSS DVGG YNYVS	DVND RPS	GSYSN NNFYV
A24-1D 08	120	NYGM H	GISYN SGNTG YADSV RG	GRYSD V	264	AGSSS NVVSY NYVS	DVNK RPS	GSYDS NTFYV
A24-1A 08	122	AYGM H	GISYD AGNTA YADSV RG	GRYSD V	266	TGSSS NIGGY NYVS	EVNNR PS	ASYSS NTFYV
A21-4A 07	124	TYGM H	GVSYN SGSKA YADSV KG	GRYSD V	268	AGSSS NIGGY NYVS	DVND RPS	GSYSN SNFYV
A24-1B 09	126	RYGM H	GVSYD GGTTA YADSV RG	GRYSD V	270	TGTSS NIGSY NYVS	DVNK RPS	GSYDS NTFYV
A24-1E	128	EYGM	GISYD	GRYSD	272	AGSSS	EVSNR	GSYDS

07		H	AGSTA YADSV RG	V		NVGG YNYVS	PS	NTFYV
H21-3A 07	130	NYYM N	TVSYD SGNKY YADSV KG	GS-RR DAFDV	274	RASQS ISNRL A	KASNL ES	QQTNS FPLT
H21-3C 11	132	NYAM N	IISYDS SSKYY ADSVK G	GSGKR DAFDV	276	QASQG ISNRL A	KASNL QS	QQTNS FPLT
H21-3C 11	134	NYAM H	VVSYD GGNIY YADSV KG	GSGRR DAFDV	278	RASQS ISNRL A	KASSL QS	QQTNS FPLT
H21-3A 09	136	NYDIH	VVSYD GSNTY YADSV KG	GSGKR DAFDV	280	RASQS ISNRL A	KASNL QS	QQTNS FPLT
H21-4H 04	138	SYAIH	VVSYD GGSKY YADSV KG	GSGRR DAFDV	282	QASQS ISSRLA	KASSL QS	QQTNS FPLT
H23-3D 08	140	SYSM H	VISYD GGSKY YADSV KG	GSGQR DAFDV	284	QASQG ISNRL A	KASNL ET	QQTNS FPLT
H21-4D 09	142	NYVIN	SVSYD GGSII YADSV KG	GSGRR DAFDV	286	QASQG IRNRL A	KASNL QS	QQTNS FPLT
H24-1D 11	144	SYAM H	VISYD GSNKY YADSV KG	GSGGR DAFDV	288	RASQS ISSRLA	KASSL ET	QQTNS FPLT

[486]

[487] # Table 1: Primer sequences used in construction of vector

[488] # Table 2: Amino acid sequences of heavy-chain and light-chain variable regions of

selected antibodies

[489] # Table 3: Polynucleotide sequences of heavy-chain and light-chain variable regions of selected antibodies

[490] # Table 4: CDR sequences of heavy-chain and light-chain variable regions of selected antibodies

[491] # Table 5: Results of SPR analysis by FcRn immobilization

[492]

[493] *# Table 6: Variable region sequences of 1Ag and 11Hg

[494] # Table 7: CDR sequences of 1Ag and 11Hg

[495] # Table 8: Results of ELISA and SPR analysis of 1Ag CDR-3 random mutations

[496] # Table 9: Results of affinity maturation by 11Hg CDR-3 random mutations

[497] # Table 10: Panning strategy of 1Ag sub-library

[498] # Table 11: Panning strategy of 11Hg sub-library

[499] # Table 12: Results of affinity maturation by 1Ag CDR-1 and CDR-2 mutations

[500] # Table 13: Results of affinity maturation by 11Hg CDR-1 and CDR-2 mutations

[501] # Table 14: Amino acid sequences of heavy-chain and light-chain variable regions of selected antibodies

[502] # Table 15: Polynucleotide sequences of heavy-chain and light-chain variable regions of selected antibodies

[503] # Table 16: CDR3 sequences of heavy-chain and light-chain variable regions of selected antibodies

[504] # Table 17: CDR sequences of heavy-chain and light-chain variable regions of selected antibodies

[505]

Sequence Listing Free Text

[506] Electric attachment.

Claims

- [Claim 1] A heavy-chain variable region of FcRn-specific antibody, which comprises CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 2 to 144, or in an amino acid sequence set forth in SEQ ID NO: 289 or 291, or a heavy-chain variable region having a sequence homology thereto of at least 90%.
- [Claim 2] The heavy-chain variable region of claim 1, wherein the heavy-chain variable region of FcRn-specific antibody has any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 2 to 144, an amino acid sequence set forth in SEQ ID NO: 289 or 291, or an amino acid sequence homology thereto at least 90%.
- [Claim 3] A light-chain variable region of FcRn-specific antibody, which comprises CDR1, CDR2 and CDR3 contained in any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 146 to 288, or in an amino acid sequence set forth in SEQ ID NO: 290 or 292, or a light-chain variable region having a sequence homology thereto of at least 90%.
- [Claim 4] The light-chain variable region of claim 3, wherein the light-chain variable region of FcRn-specific antibody has any one amino acid sequence selected from the group consisting of even numbers between SEQ ID NOS: 146 to 288, an amino acid sequence set forth in SEQ ID NO: 290 or 292, or an amino acid sequence homology thereto at least 90%.
- [Claim 5] A FcRn-specific antibody comprising any one selected from among the heavy-chain variable regions of claim 1 or 2 and any one selected from among the light-chain variable regions of claim 3 or 4, or a fragment thereof.
- [Claim 6] A FcRn-specific antibody comprising a heavy-chain variable region and a light-chain variable region selected from among the following heavy-chain and light-chain variable regions (1) to (74), and a fragment thereof:
- (1) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 2, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 146, or a light-chain variable region having a sequence homology thereto of at least 90%;

(2) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 4, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 148, or a light-chain variable region having a sequence homology thereto of at least 90%;

(3) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 6, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 150, or a light-chain variable region having a sequence homology thereto of at least 90%;

(4) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 8, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 152, or a light-chain variable region having a sequence homology thereto of at least 90%;

(5) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 10, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 154, or a light-chain variable region having a sequence homology thereto of at least 90%;

(6) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 12, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 156, or a light-chain variable region having a sequence homology thereto of at least 90%;

*(7) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 14, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO:

158, or a light-chain variable region having a sequence homology thereto of at least 90%;

(8) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 16, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 160, or a light-chain variable region having a sequence homology thereto of at least 90%, preferably at least 95%;

(9) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 18, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 162, or a light-chain variable region having a sequence homology thereto of at least 90%;

(10) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 20, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 164, or a light-chain variable region having a sequence homology thereto of at least 90%;

(11) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 22, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 166, or a light-chain variable region having a sequence homology thereto of at least 90%;

(12) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 24, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 168, or a light-chain variable region having a sequence homology thereto of at least 90%;

(13) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 26, or a heavy-chain variable region having a sequence homology thereto of at

least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 170, or a light-chain variable region having a sequence homology thereto of at least 90%;

(14) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 28, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 172, or a light-chain variable region having a sequence homology thereto of at least 90%;

(15) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 30, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 174, or a light-chain variable region having a sequence homology thereto of at least 90%;

(16) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 32, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 176, or a light-chain variable region having a sequence homology thereto of at least 90%;

(17) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 34, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 178, or a light-chain variable region having a sequence homology thereto of at least 90%;

(18) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 36, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 180, or a light-chain variable region having a sequence homology thereto of at least 90%;

(19) a heavy-chain variable region, which comprises CDR1, CDR2 and

CDR3 contained in an amino acid sequence of SEQ ID NO: 38, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 182, or a light-chain variable region having a sequence homology thereto of at least 90%;

(20) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 40, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 184, or a light-chain variable region having a sequence homology thereto of at least 90%;

(21) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 42, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 186, or a light-chain variable region having a sequence homology thereto of at least 90%;

(22) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 44, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 188, or a light-chain variable region having a sequence homology thereto of at least 90%;

(23) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 46, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 190, or a light-chain variable region having a sequence homology thereto of at least 90%;

(24) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 48, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 192, or a light-chain variable region having a sequence homology

thereto of at least 90%;

(25) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 50, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 194, or a light-chain variable region having a sequence homology thereto of at least 90%;

(26) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 52, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 196, or a light-chain variable region having a sequence homology thereto of at least 90%;

(27) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 54, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 198, or a light-chain variable region having a sequence homology thereto of at least 90%;

(28) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 56, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 200, or a light-chain variable region having a sequence homology thereto of at least 90%;

(29) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 58, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 202, or a light-chain variable region having a sequence homology thereto of at least 90%;

(30) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 60, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1,

CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 204, or a light-chain variable region having a sequence homology thereto of at least 90%;

(31) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 62, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 206, or a light-chain variable region having a sequence homology thereto of at least 90%;

(32) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 64, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 208, or a light-chain variable region having a sequence homology thereto of at least 90%;

(33) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 66, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 210, or a light-chain variable region having a sequence homology thereto of at least 90%;

(34) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 68, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 212, or a light-chain variable region having a sequence homology thereto of at least 90%;

(35) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 70, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 214, or a light-chain variable region having a sequence homology thereto of at least 90%;

(36) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 72, or a

heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 216, or a light-chain variable region having a sequence homology thereto of at least 90%;

(37) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 74, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 218, or a light-chain variable region having a sequence homology thereto of at least 90%;

(38) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 76, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 220, or a light-chain variable region having a sequence homology thereto of at least 90%;

(39) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 78, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 222, or a light-chain variable region having a sequence homology thereto of at least 90%;

(40) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 80, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 224, or a light-chain variable region having a sequence homology thereto of at least 90%;

(41) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 82, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 226, or a light-chain variable region having a sequence homology thereto of at least 90%;

(42) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 84, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 228, or a light-chain variable region having a sequence homology thereto of at least 90%;

(43) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 86, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 230, or a light-chain variable region having a sequence homology thereto of at least 90%;

(44) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 88, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 232, or a light-chain variable region having a sequence homology thereto of at least 90%;

(45) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 90, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 234, or a light-chain variable region having a sequence homology thereto of at least 90%;

(46) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 92, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 236, or a light-chain variable region having a sequence homology thereto of at least 90%;

(47) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 94, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO:

238, or a light-chain variable region having a sequence homology thereto of at least 90%;

(48) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 96, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 240, or a light-chain variable region having a sequence homology thereto of at least 90%;

(49) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 98, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 242, or a light-chain variable region having a sequence homology thereto of at least 90%;

(50) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 100, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 244, or a light-chain variable region having a sequence homology thereto of at least 90%;

(51) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 102, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 246, or a light-chain variable region having a sequence homology thereto of at least 90%;

(52) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 104, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 248, or a light-chain variable region having a sequence homology thereto of at least 90%;

(53) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 106, or a heavy-chain variable region having a sequence homology thereto of at

least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 250, or a light-chain variable region having a sequence homology thereto of at least 90%;

(54) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 108, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 252, or a light-chain variable region having a sequence homology thereto of at least 90%;

(55) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 110, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 254, or a light-chain variable region having a sequence homology thereto of at least 90%;

(56) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 112, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 256, or a light-chain variable region having a sequence homology thereto of at least 90%;

(57) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 114, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 258, or a light-chain variable region having a sequence homology thereto of at least 90%;

(58) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 116, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 260, or a light-chain variable region having a sequence homology thereto of at least 90%;

(59) a heavy-chain variable region, which comprises CDR1, CDR2 and

CDR3 contained in an amino acid sequence of SEQ ID NO: 118 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 262 or a light-chain variable region having a sequence homology thereto of at least 90%;

(60) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 120 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 264 or a light-chain variable region having a sequence homology thereto of at least 90%;

(61) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 122 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 266 or a light-chain variable region having a sequence homology thereto of at least 90%;

(62) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 124 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 268 or a light-chain variable region having a sequence homology thereto of at least 90%;

(63) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 126 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 270 or a light-chain variable region having a sequence homology thereto of at least 90%;

(64) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 128 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 272 or a light-chain variable region having a sequence homology

thereto of at least 90%;

(65) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 130 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 274 or a light-chain variable region having a sequence homology thereto of at least 90%;

(66) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 132 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 276 or a light-chain variable region having a sequence homology thereto of at least 90%;

(67) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 134 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 278 or a light-chain variable region having a sequence homology thereto of at least 90%;

(68) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 136 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 280 or a light-chain variable region having a sequence homology thereto of at least 90%;

(69) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 138 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 282 or a light-chain variable region having a sequence homology thereto of at least 90%;

(70) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 140 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1,

CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 284 or a light-chain variable region having a sequence homology thereto of at least 90%;

(71) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 142 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 286 or a light-chain variable region having a sequence homology thereto of at least 90%;

(72) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 144 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 288 or a light-chain variable region having a sequence homology thereto of at least 90%;

(73) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 289 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 290 or a light-chain variable region having a sequence homology thereto of at least 90%; and

(74) a heavy-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 291 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region, which comprises CDR1, CDR2 and CDR3 contained in an amino acid sequence of SEQ ID NO: 292 or a light-chain variable region having a sequence homology thereto of at least 90%.

[Claim 7]

A FcRn-specific antibody comprising a heavy-chain variable region and a light-chain variable region selected from among the following heavy-chain and light-chain variable regions (1) to (74), and a fragement thereof:

(1) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 2, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 146, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (2) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 4, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 148, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (3) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 6, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 150, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (4) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 8, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 152, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (5) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 10, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 154, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (6) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 12, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 156, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (7) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 14, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 158, or a light-chain variable region having a sequence homology thereto of at least 90%;
- *(8) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 16, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 160, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (9) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 18, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 162, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (10) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 20, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 164, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (11) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 22, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 166, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (12) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 24, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 168, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (13) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 26, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 170, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (14) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 28, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 172, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (15) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 30, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 174, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (16) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 32, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 176, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (17) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 34, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 178, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (18) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 36, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 180, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (19) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 38, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 182, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (20) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 40, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 184, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (21) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 42, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 186, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (22) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 44, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 188, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (23) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 46, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 190, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (24) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 48, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 192, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (25) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 50, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 194, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (26) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 52, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 196, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (27) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 54, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 198, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (28) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 56, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 200, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (29) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 58, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 202, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (30) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 60, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 204, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (31) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 62, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 206, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (32) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 64, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 208, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (33) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 66, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 210, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (34) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 68, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 212, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (35) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 70, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 214, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (36) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 72, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 216, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (37) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 74, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 218, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (38) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 76, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 220, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (39) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 78, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 222, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (40) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 80, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 224, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (41) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 82, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 226, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (42) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 84, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 228, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (43) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 86, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 230, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (44) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 88, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 232, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (45) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 90, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 234, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (46) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 92, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 236, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (47) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 94, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 238, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (48) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 96, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 240, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (49) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 98, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 242, or a light-chain variable region having a sequence homology thereto of at least 90%;

(50) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 100, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 244, or a light-chain variable region having a sequence homology thereto of at least 90%;

(51) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 102, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 246, or a light-chain variable region having a sequence homology thereto of at least 90%;

(52) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 104, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 248, or a light-chain variable region having a sequence homology thereto of at least 90%;

(53) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 106, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 250, or a light-chain variable region having a sequence homology thereto of at least 90%;

(54) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 108, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 252, or a light-chain variable region having a sequence homology thereto of at least 90%;

(55) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 110, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 254, or a light-chain variable region having a sequence homology thereto of at least 90%;

(56) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 112, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 256, or a light-chain variable region having a sequence homology thereto of at least 90%;

(57) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 114, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 258, or a light-chain variable region having a sequence homology thereto of at least 90%;

- (58) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 116, or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 260, or a light-chain variable region having a sequence homology thereto of at least 90%;
- (59) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 118 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 262 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (60) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 120 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 264 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (61) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 122 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 266 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (62) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 124 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 268 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (63) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 126 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 270 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (64) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 128 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 272 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (65) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 130 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 274 or a light-chain variable region having a sequence homology thereto of at least 90%;

- (66) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 132 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 276 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (67) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 134 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 278 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (68) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 136 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 280 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (69) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 138 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 282 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (70) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 140 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 284 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (71) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 142 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 286 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (72) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 144 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 288 or a light-chain variable region having a sequence homology thereto of at least 90%;
- (73) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 289 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 290 or a light-chain variable region having a sequence homology thereto of at least 90%;

- and
- (74) a heavy-chain variable region having an amino acid sequence of SEQ ID NO: 291 or a heavy-chain variable region having a sequence homology thereto of at least 90%, and a light-chain variable region having an amino acid sequence of SEQ ID NO: 292 or a light-chain variable region having a sequence homology thereto of at least 90%.
- [Claim 8] The FcRn-specific antibody and its fragement of any one of claims 5 to 7, wherein the antibody or its fragement is selected from among single-chain antibodies, diabodies, triabodies, tetrabodies, Fab fragments, F(ab#)2 fragments, Fd, scFv, domain antibodies, dual-specific antibodies, minibodies, scap, IgD antibodies, IgE antibodies, IgM antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies, derivatives in antibody constant regions, and synthetic antibodies based on protein scaffolds, which have the ability to bind to FcRn.
- [Claim 9] A pharmaceutical composition for treating autoimmune diseases, the composition comprising the antibody or the antibody fragment of any one of claims 5 to 8, and at least one pharmaceutically acceptable carrier.
- [Claim 10] The pharmaceutical composition of claim 9 wherein the autoimmune diseases are selected from among immune neutropenia, Guillain-Barre syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome, pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, lupus, and idiopathic thrombocytopenic purpura (ITP).
- [Claim 11] A polynucleotide that encodes the heavy-chain variable region or the light-chain variable region of the FcRn-specific antibody of any one of claims 1 to 4.
- [Claim 12] The polynucleotide of claim 11, wherein the polynucleotide sequence has either any one sequence selected from the group consisting of uneven numbers between SEQ ID NOS: 1 to 287, or a sequence having a sequence homology thereto of at least 90%
- [Claim 13] A polynucleotide that encodes the heavy-chain variable region or the light-chain variable region of the FcRn-specific antibody or the antibody fragment of any one of claims 5 to 8.
- [Claim 14] The polynucleotide of claim 13, wherein the polynucleotide sequence is selected from the following polynucleotide sequences:

- (1) a sequence of SEQ ID NO: 1 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 145 or a sequence having a sequence homology thereto of at least 90%;
- (2) a sequence of SEQ ID NO: 3 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 147 or a sequence having a sequence homology thereto of at least 90%;
- (3) a sequence of SEQ ID NO: 5 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 149 or a sequence having a sequence homology thereto of at least 90%;
- (4) a sequence of SEQ ID NO: 7 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 151 or a sequence having a sequence homology thereto of at least 90%;
- (5) a sequence of SEQ ID NO: 9 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 153 or a sequence having a sequence homology thereto of at least 90%;
- (6) a sequence of SEQ ID NO: 11 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 155 or a sequence having a sequence homology thereto of at least 90%;
- (7) a sequence of SEQ ID NO: 13 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 157 or a sequence having a sequence homology thereto of at least 90%;
- (8) a sequence of SEQ ID NO: 15 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 159 or a sequence having a sequence homology thereto of at least 90%;
- (9) a sequence of SEQ ID NO: 17 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 161 or a sequence having a sequence homology thereto of at least 90%;
- (10) a sequence of SEQ ID NO: 19 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 163 or a sequence having a sequence homology thereto of at least 90%;
- (11) a sequence of SEQ ID NO: 21 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 165 or a sequence having a sequence homology thereto of at least 90%;
- (12) a sequence of SEQ ID NO: 23 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 167 or a sequence having a sequence homology thereto of at least 90%;
- (13) a sequence of SEQ ID NO: 25 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 169 or a sequence having a sequence homology thereto of at least 90%;
- (14) a sequence of SEQ ID NO: 27 or a sequence having a sequence

homology thereto of at least 90%, and a sequence of SEQ ID NO: 171 or a sequence having a sequence homology thereto of at least 90%;

(15) a sequence of SEQ ID NO: 29 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 173 or a sequence having a sequence homology thereto of at least 90%;

(16) a sequence of SEQ ID NO: 31 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 175 or a sequence having a sequence homology thereto of at least 90%;

(17) a sequence of SEQ ID NO: 33 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 177 or a sequence having a sequence homology thereto of at least 90%;

(18) a sequence of SEQ ID NO: 35 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 179 or a sequence having a sequence homology thereto of at least 90%;

(19) a sequence of SEQ ID NO: 37 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 181 or a sequence having a sequence homology thereto of at least 90%;

(20) a sequence of SEQ ID NO: 39 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 183 or a sequence having a sequence homology thereto of at least 90%;

(21) a sequence of SEQ ID NO: 41 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 185 or a sequence having a sequence homology thereto of at least 90%;

(22) a sequence of SEQ ID NO: 43 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 187 or a sequence having a sequence homology thereto of at least 90%;

(23) a sequence of SEQ ID NO: 45 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 189 or a sequence having a sequence homology thereto of at least 90%;

(24) a sequence of SEQ ID NO: 47 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 191 or a sequence having a sequence homology thereto of at least 90%;

(25) a sequence of SEQ ID NO: 49 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 193 or a sequence having a sequence homology thereto of at least 90%;

(26) a sequence of SEQ ID NO: 51 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 195 or a sequence having a sequence homology thereto of at least 90%;

(27) a sequence of SEQ ID NO: 53 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 197

or a sequence having a sequence homology thereto of at least 90%;

(28) a sequence of SEQ ID NO: 55 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 199 or a sequence having a sequence homology thereto of at least 90%;

(29) a sequence of SEQ ID NO: 57 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 201 or a sequence having a sequence homology thereto of at least 90%;

(30) a sequence of SEQ ID NO: 59 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 203 or a sequence having a sequence homology thereto of at least 90%;

(31) a sequence of SEQ ID NO: 61 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 205 or a sequence having a sequence homology thereto of at least 90%;

(32) a sequence of SEQ ID NO: 63 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 207 or a sequence having a sequence homology thereto of at least 90%;

(33) a sequence of SEQ ID NO: 65 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 209 or a sequence having a sequence homology thereto of at least 90%;

(34) a sequence of SEQ ID NO: 67 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 211 or a sequence having a sequence homology thereto of at least 90%;

(35) a sequence of SEQ ID NO: 69 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 213 or a sequence having a sequence homology thereto of at least 90%;

(36) a sequence of SEQ ID NO: 71 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 215 or a sequence having a sequence homology thereto of at least 90%;

(37) a sequence of SEQ ID NO: 73 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 217 or a sequence having a sequence homology thereto of at least 90%;

(38) a sequence of SEQ ID NO: 75 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 219 or a sequence having a sequence homology thereto of at least 90%;

(39) a sequence of SEQ ID NO: 77 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 221 or a sequence having a sequence homology thereto of at least 90%;

(40) a sequence of SEQ ID NO: 79 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 223 or a sequence having a sequence homology thereto of at least 90%;

- (41) a sequence of SEQ ID NO: 81 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 225 or a sequence having a sequence homology thereto of at least 90%;
- (42) a sequence of SEQ ID NO: 83 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 227 or a sequence having a sequence homology thereto of at least 90%;
- (43) a sequence of SEQ ID NO: 85 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 229 or a sequence having a sequence homology thereto of at least 90%;
- (44) a sequence of SEQ ID NO: 87 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 231 or a sequence having a sequence homology thereto of at least 90%;
- (45) a sequence of SEQ ID NO: 89 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 233 or a sequence having a sequence homology thereto of at least 90%;
- (46) a sequence of SEQ ID NO: 91 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 235 or a sequence having a sequence homology thereto of at least 90%;
- (47) a sequence of SEQ ID NO: 93 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 237 or a sequence having a sequence homology thereto of at least 90%;
- (48) a sequence of SEQ ID NO: 95 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 239 or a sequence having a sequence homology thereto of at least 90%;
- (49) a sequence of SEQ ID NO: 97 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 241 or a sequence having a sequence homology thereto of at least 90%;
- (50) a sequence of SEQ ID NO: 99 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 243 or a sequence having a sequence homology thereto of at least 90%;
- (51) a sequence of SEQ ID NO: 101 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 245 or a sequence having a sequence homology thereto of at least 90%;
- (52) a sequence of SEQ ID NO: 103 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 247 or a sequence having a sequence homology thereto of at least 90%;
- (53) a sequence of SEQ ID NO: 105 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 249 or a sequence having a sequence homology thereto of at least 90%;
- (54) a sequence of SEQ ID NO: 107 or a sequence having a sequence

homology thereto of at least 90%, and a sequence of SEQ ID NO: 251 or a sequence having a sequence homology thereto of at least 90%;

(55) a sequence of SEQ ID NO: 109 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 253 or a sequence having a sequence homology thereto of at least 90%;

(56) a sequence of SEQ ID NO: 111 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 255 or a sequence having a sequence homology thereto of at least 90%;

(57) a sequence of SEQ ID NO: 113 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 257 or a sequence having a sequence homology thereto of at least 90%;

(58) a sequence of SEQ ID NO: 115 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 259 or a sequence having a sequence homology thereto of at least 90%;

(59) a sequence of SEQ ID NO: 117 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 261 or a sequence having a sequence homology thereto of at least 90%;

(60) a sequence of SEQ ID NO: 119 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 263 or a sequence having a sequence homology thereto of at least 90%;

(61) a sequence of SEQ ID NO: 121 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 265 or a sequence having a sequence homology thereto of at least 90%;

(62) a sequence of SEQ ID NO: 123 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 267 or a sequence having a sequence homology thereto of at least 90%;

(63) a sequence of SEQ ID NO: 125 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 269 or a sequence having a sequence homology thereto of at least 90%;

(64) a sequence of SEQ ID NO: 127 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 271 or a sequence having a sequence homology thereto of at least 90%;

(65) a sequence of SEQ ID NO: 129 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 273 or a sequence having a sequence homology thereto of at least 90%;

(66) a sequence of SEQ ID NO: 131 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 275 or a sequence having a sequence homology thereto of at least 90%;

(67) a sequence of SEQ ID NO: 133 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 277

or a sequence having a sequence homology thereto of at least 90%;

(68) a sequence of SEQ ID NO: 135 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 279 or a sequence having a sequence homology thereto of at least 90%;

(69) a sequence of SEQ ID NO: 137 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 281 or a sequence having a sequence homology thereto of at least 90%;

(70) a sequence of SEQ ID NO: 139 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 283 or a sequence having a sequence homology thereto of at least 90%;

(71) a sequence of SEQ ID NO: 141 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 285 or a sequence having a sequence homology thereto of at least 90%; and

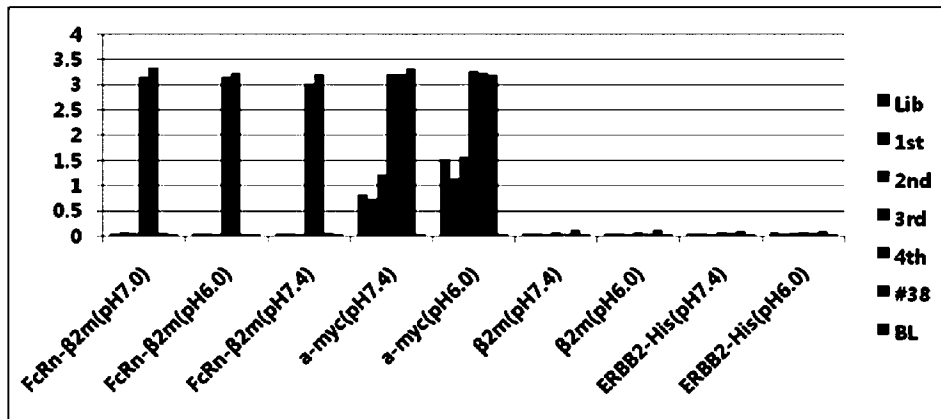
(72) a sequence of SEQ ID NO: 143 or a sequence having a sequence homology thereto of at least 90%, and a sequence of SEQ ID NO: 287 or a sequence having a sequence homology thereto of at least 90%.

- [Claim 15] A recombinant expression vector comprising the polynucleotide sequence of any one of claims 11 to 14.
- [Claim 16] A host cell transformed with the recombinant expression vector of claim 15.
- [Claim 17] The host cell of claim 16, wherein the host cell is selected from animal cells, plant cells, yeast cells, *E. coli*, and insect cells.
- [Claim 18] The host cell of claim 16, wherein the transformed host cell is selected from monkey kidney cells (COS7), NSO cells, SP2/0, Chinese hamster ovary (CHO) cells, W138, baby hamster kidney (BHK) cells, MDCK, myeloma cells, HuT 78 cells and HEK293 cells, *E. coli*, *Bacillus subtilis*, *Streptomyces* sp., *Pseudomonas* sp., *Proteus mirabilis* or *Staphylococcus* sp., *Aspergillus* sp., *Pichia pastoris*, *Saccharomyces cerevisiae*, *Schizosaccharomyces* sp., and *Neurospora crassa*.
- [Claim 19] A method for producing an FcRn-specific antibody, a fragment thereof or a variable region, the method comprising culturing the recombinant expression vector or the host cell of any one of claims 15 to 18.
- [Claim 20] A composition for diagnosis of autoimmune diseases, the composition comprising the antibody or the fragment thereof of any one of claims 5 to 8.
- [Claim 21] The composition of claim 20, wherein the autoimmune diseases are selected from among immune neutropenia, Guillain-Barre syndrome, epilepsy, autoimmune encephalitis, Isaac's syndrome, nevus syndrome, pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, mucous

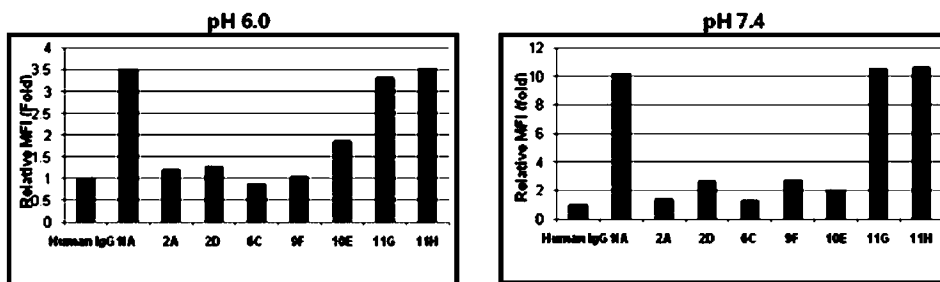
membrane pemphigoid, antiphospholipid syndrome, autoimmune anemia, autoimmune Grave's disease, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, lupus, and idiopathic thrombocytopenic purpura (ITP).

- [Claim 22] A composition for detecting the presence of FcRn comprising the antibody or the fragment thereof of any one of claims 5 to 8.
- [Claim 23] A method for detecting the presence of FcRn comprising the antibody or the fragment thereof of any one of claims 5 to 8.
- [Claim 24] The method of claim 23, wherein the detection of the presence of FcRn is performed in vitro and in vivo.
- [Claim 25] The method of claim 23, wherein the antibody or the fragment thereof is labeled with a detectable substance.
- [Claim 26] The method of claim 25, wherein the labeling is performed with any one material selected from enzymes, prosthetic groups, fluorescent materials, luminescent materials, and radioactive materials.
- [Claim 27] The method of claim 23, wherein the detection of the presence of FcRn is performed using at least one method selected from the group consisting of enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), tissue immunohistochemistry, and competition immunoassay.

[Fig. 1]



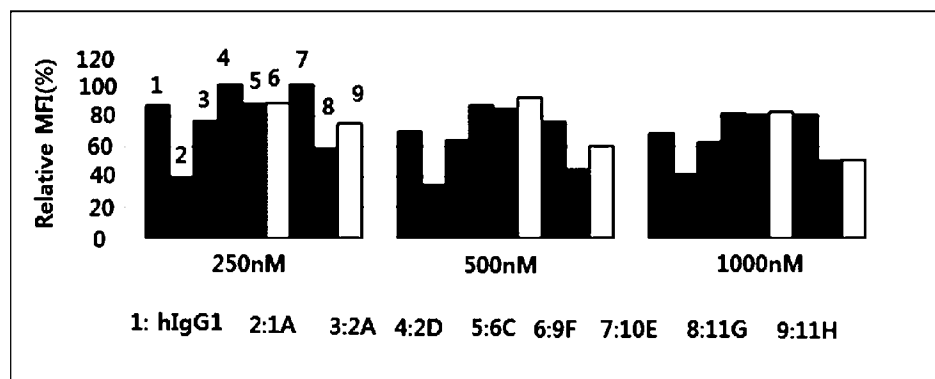
[Fig. 2]



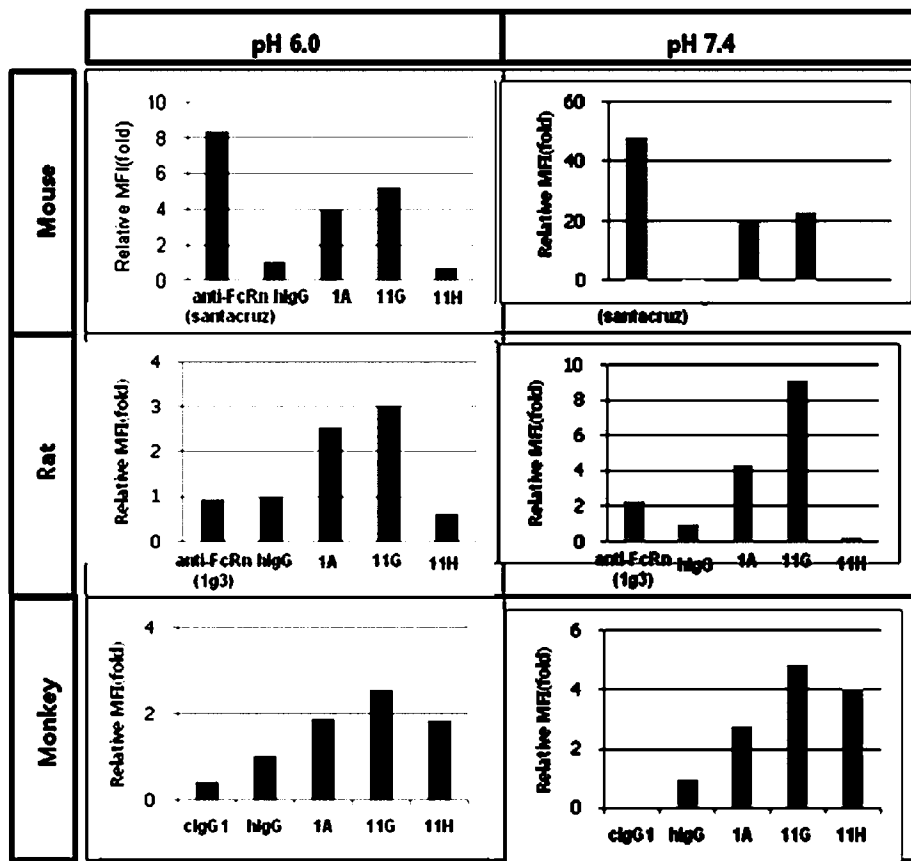
pH	Sample	Relative MFI (Fold)							
		Human IgG ₁	1A	2A	2D	6C	9F	10E	11G
6.0		1.0	3.5	1.2	0.9	0.9	1.1	1.9	3.3
7.4		1.0	10.2	1.4	1.3	1.3	2.7	2.0	10.6

[Fig. 3]

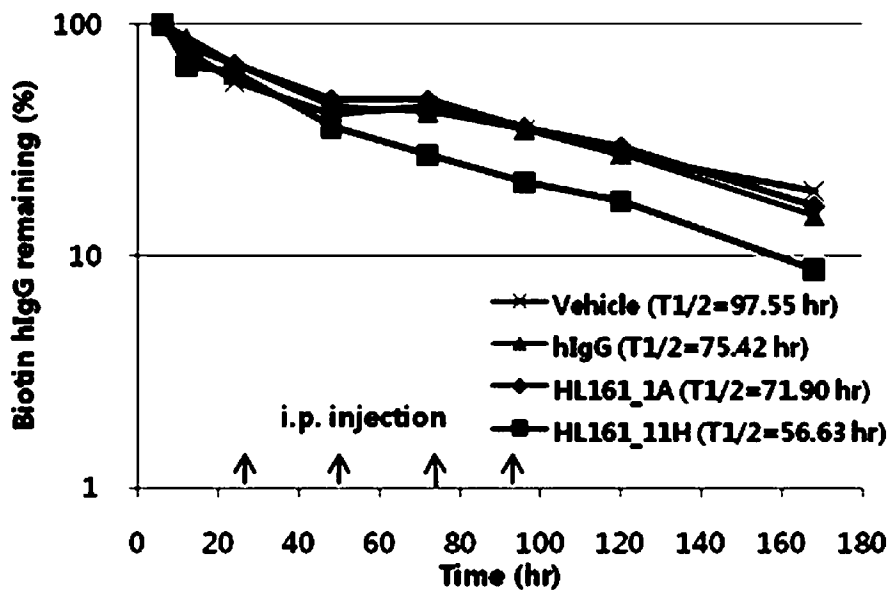
HL161 Hit Ab	250nM	500nM	1000nM
hIgG1	87.4%	69.9%	69.1%
1A	40.0%	34.4%	41.5%
2A	77.1%	64.1%	63.3%
2D	101.2%	87.4%	82.4%
6C	88.2%	84.7%	81.1%
9F	88.6%	92.5%	83.2%
10E	101.4%	76.8%	81.0%
11G	58.4%	44.7%	50.8%
11H	75.4%	60.4%	51.8%



[Fig. 4]



[Fig. 5]



[Fig. 6]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/005495**A. CLASSIFICATION OF SUBJECT MATTER****C07K 16/28(2006.01)i, C12N 15/13(2006.01)i, A61K 39/395(2006.01)i, A61P 37/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K 16/28; A61K 39/395; C07K 16/42; C12N 15/13; A61P 37/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: FcRn-specific antibody, pH independent, β 2-microglobulin**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007-0092507 A1 (BALTHASAR et al.) 26 April 2007 See abstract and claims 1-6.	1-7, 11-12
A	CHRISTIANSON et al., 'Monoclonal antibodies directed against human FcRn and their applications' MAbs, Vol.4, Issue 2, pp.208-216 (2012) See abstract and figure 1.	1-7, 11-12
A	SCHWAB et al., 'Intravenous immunoglobulin therapy: how does IgG modulate the immune system?' Nature Reviews Immunology, Vol.13, No.3, pp.176-189 (15 February 2013) See abstract and pages 177 and 181.	1-7, 11-12
A	RATH et al., 'The immunologic functions of the neonatal Fc receptor for IgG' Journal of Clinical Immunology, Vol.33, Supplement 1, pp.S9-S17 (05 September 2012) See abstract and page S10.	1-7, 11-12



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 October 2014 (14.10.2014)

Date of mailing of the international search report

14 October 2014 (14.10.2014)

Name and mailing address of the ISA/KR

International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701,
Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

KIM, Seung Beom

Telephone No. +82-42-481-3371



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/005495

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of :

a. a sequence listing filed or furnished

☐

on paper

☒

in electronic form

b. time of filing or furnishing

☒

contained in the international application as filed

☐

filed together with the international application in electronic form

☐

furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10,14,16-18,21,24-27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 10,14,16-18,21 and 24-27 are unclear since they refer to the multiple dependent claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 8-9,13,15,19-20,22-23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Inventions 1~8 (claims 1-27, partially) relate to each of FcRn-specific antibodies corresponding to HL161-1A~HL161-1IH in Table 2.
2. Inventions 9-72 (claims 1-27, partially) relate to each of FcRn-specific antibodies corresponding to A11-C07~H24-1D11 in Table 14.
3. Inventions 73-74 (claims 1-27, partially) relate to each of FcRn-specific antibodies corresponding to 1Ag~1IHg in Table 6.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-27, partially, relating to HL161-1A

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2014/005495

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PRAETOR et al., 'beta2-microglobulin is important for cell surface expression and pH-dependent IgG binding of human FcRn' Journal of Cell Science, Vol.115, No.11, pp.2389-2397 (2002) See abstract.	1-7, 11-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2014/005495Patent document
cited in search reportPublication
datePatent family
member(s)Publication
date

US 2007-0092507 A1

26/04/2007

CA 2637929 A1

02/08/2007

EP 1986690 A2

05/11/2008

JP 2009-524664 A

02/07/2009

US 2005-0079169 A1

14/04/2005

US 7662928 B2

16/02/2010

WO 2007-087289 A2

02/08/2007

WO 2007-087289 A3

09/10/2008