

DESCRIPTION

ANTI-PD-L1 ANTIBODY

TECHNICAL FIELD

The present invention relates to an anti-PD-L1 antibody. More specifically, the present invention relates to an anti-PD-L1 antibody comprising a variable region containing complementarity-determining regions (CDR) of a rat anti-bovine PD-L1 antibody and a constant region of an antibody of an animal other than rat.

BACKGROUND ART

Programmed cell death 1 (PD-1), an immunoinhibitory receptor, and its ligand programmed cell death ligand 1 (PD-L1) are molecules identified by Prof. Tasuku Honjo et al., Kyoto University, as factors which inhibit excessive immune response and are deeply involved in immunotolerance (Non-Patent Document No. 1: Ishida Y, Agata Y, Shibahara K, Honjo T The EMBO Journal. 1992 Nov; 11(11):3887-3895). Recently, it has been elucidated that these molecules are also involved in immunosuppression in tumors. In the field of human medical care, an antibody drug that inhibits the effect of PD-1 has been developed and put into practical use (OpdivoTM, Ono Pharmaceutical Co., Ltd.)

To date, the present inventors have been developing an immunotherapy for animal refractory diseases targeting PD-1 or PD-L1, and have revealed that this novel immunotherapy is applicable to multiple-diseases and multiple-animals. (Non-Patent Document No. 2: Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology. 2014 Aug;142(4):551-61; Non-Patent Document No. 3: Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S, Ohashi K. PLoS One. 2014 Jun 10; 9(6):e98415; Non-Patent Document No. 4: Mingala CN, Konnai S, Ikebuchi R, Ohashi K. Comp. Immunol. Microbiol. Infect. Dis. 2011 Jan; 34(1):55-63.)

However, the antibodies which the present inventors have prepared to date are rat antibodies, and therefore it is impossible to administer those antibodies repeatedly to animals other than rat.

PRIOR ART LITERATURE

Non-Patent Documents

Non-Patent Document No. 1: Ishida Y, Agata Y, Shibahara K, Honjo T The EMBO Journal. 1992 Nov; 11(11):3887-3895.

Non-Patent Document No. 2: Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology. 2014 Aug; 142(4):551-61.

Non-Patent Document No. 3: Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S, Ohashi K. PLoS One. 2014 Jun 10; 9(6):e98415.

Non-Patent Document No. 4: Mingala CN, Konnai S, Ikebuchi R, Ohashi K. Comp. Immunol. Microbiol. Infect. Dis. 2011 Jan; 34(1):55-63.

DISCLOSURE OF THE INVENTION

PROBLEM FOR SOLUTION BY THE INVENTION

It is an object of the present invention to provide an anti-PD-L1 antibody capable of repeated administration even to animals other than rat.

MEANS TO SOLVE THE PROBLEM

The present inventors have determined the variable regions of a rat anti-bovine PD-L1 monoclonal antibody (4G12) capable of inhibiting the binding of canine PD-1 to PD-L1, and then combined genes encoding the resultant variable regions with genes encoding the constant regions of a canine immunoglobulin (IgG-D equivalent to human IgG4) to thereby obtain a chimeric antibody gene, which was introduced into Chinese hamster ovary cells (CHO cells). By culturing/proliferating the resultant CHO cells, the present inventors have succeeded in preparing a rat-canine chimeric anti-PD-L1 antibody. Further, the present inventors have determined the CDRs of the variable region of the rat anti-bovine PD-L1 monoclonal antibody 4G12.

Furthermore, the present inventors have determined the variable regions of the rat anti-bovine PD-L1 monoclonal antibody 4G12 capable of inhibiting the binding of bovine PD-1 to PD-L1, and then combined genes encoding the resultant variable regions with genes encoding the constant regions of a bovine immunoglobulin (bovine IgG1, with mutations having been introduced into the putative binding sites of Fcγ receptors in CH2 domain in order to inhibit ADCC activity; see Fig. 19 for amino acid numbers and mutations: 250 E→P, 251 L→V, 252 P→A, 253 G→deletion, 347 A→S, 348 P→S; Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology 2014 Aug; 142(4):551-561) to thereby obtain a chimeric antibody gene. This gene was introduced into Chinese hamster ovary cells (CHO cells). By culturing/proliferating the resultant cells, the present inventors

have succeeded in preparing a rat-bovine chimeric anti-PD-L1 antibody. The present invention has been achieved based on these findings.

A summary of the present invention is as described below.

- (1) An anti-PD-L1 antibody comprising (a) a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat; and (b) a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.
- (2) The antibody of (1) above, wherein the light chain variable region and the heavy chain variable region are derived from rat.
- (3) The antibody of (2) above, wherein the light chain variable region is the light chain variable region of a rat anti-bovine PD-L1 antibody and the heavy chain variable region is the heavy chain variable region of a rat anti-bovine PD-L1 antibody.
- (4) The antibody of (3) above, wherein the light chain variable region has the amino acid sequence as shown in SEQ ID NO. 1 and the heavy chain variable region has the amino acid sequence as shown in SEQ ID NO: 2.
- (5) The antibody of any one of (1) to (4) above, wherein the light chain constant region of an antibody of an animal other than rat has the amino acid sequence of the constant region of lambda chain or kappa chain.
- (6) The antibody of any one of (1) to (5) above, wherein the heavy chain constant region of an antibody of an animal other than rat has the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4.
- (7) The antibody of any one of (1) to (5) above, wherein the animal other than rat is bovine and the heavy chain constant region of the bovine antibody has mutations introduced therinto that reduce ADCC activity and/or CDC activity.
- (8) The antibody of (6) above, wherein the animal other than rat is canine; the light chain constant region of the canine antibody has the amino acid sequence of the constant region of lambda chain; and the heavy chain constant region of the canine antibody has the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4.

- (9) The antibody of (7) above, wherein the light chain constant region of the bovine antibody has the amino acid sequence of the constant region of lambda chain and the heavy chain constant region of the bovine antibody has mutations introduced therein that reduce ADCC activity and/or CDC activity.
- (10) The antibody of (8) above, wherein the light chain constant region of the canine antibody has the amino acid sequence as shown in SEQ ID NO: 3 and the heavy chain constant region of the canine antibody has the amino acid sequence as shown in SEQ ID NO: 4.
- (11) The antibody of (9) above, wherein the light chain constant region of the bovine antibody has the amino acid sequence as shown in SEQ ID NO: 100 and the heavy chain constant region of the bovine antibody has the amino acid sequence as shown in SEQ ID NO: 102.
- (12) The antibody of any one of (1) to (11) above which has a four-chain structure comprising two light chains and two heavy chains.
- (13) A pharmaceutical composition comprising the antibody of any one of (1) to (12) above as an active ingredient.
- (14) The composition of (13) above for prevention and/or treatment of cancers and/or inflammations.
- (15) The composition of (14) above, wherein the cancers and/or inflammations are selected from the group consisting of neoplastic diseases, leukemia, Johne's disease, anaplasmosis, bacterial mastitis, mycotic mastitis, mycoplasma infections (such as mycoplasma mastitis, mycoplasma pneumonia or the like), tuberculosis, *Theileria orientalis* infection, cryptosporidiosis, coccidiosis, trypanosomiasis and leishmaniasis.
- (16) An artificial genetic DNA comprising (a') a DNA encoding a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat and (b') a DNA encoding a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.
- (17) A vector comprising the artificial genetic DNA of (16) above.

- (18) A host cell transformed with the vector of (17) above.
- (19) A method of preparing an antibody, comprising culturing the host cell of (18) above and collecting an anti-PD-L1 antibody from the resultant culture.
- (20) A DNA encoding a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat.
- (21) A DNA encoding a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.

The present specification encompasses the contents disclosed in the specifications and/or drawings of Japanese Patent Applications No. 2016-159088, No. 2016-159089, No. 2017-110723 and No. 2017-61454 based on which the present patent application claims priority.

EFFECT OF THE INVENTION

According to the present invention, a novel anti-PD-L1 antibody has been obtained. This antibody is applicable even to those animals other than rat.

BRIEF DESCRIPTION OF THE DRAWINGS

[Fig. 1] Inhibition of the binding of recombinant canine PD-L1 to recombinant canine PD-1. The binding of canine PD-L1-Ig to canine PD-1-Ig was detected on ELISA plates. The optical density (O.D.) without addition of antibody was taken as 100%. O.D. at each antibody concentration was shown as relative value. Among rat anti-bovine PD-L1 monoclonal antibodies 4G12 (Rat IgG2a (κ)), 5A2 (Rat IgG1 (κ)) and 6G7 (Rat IgM (κ)) which showed cross-reaction with canine PD-L1, clones 4G12 and 6G7 exhibited a high binding inhibition capacity.

[Fig. 2] Schematic drawings of pDC6 vector and a rat-canine chimeric anti-PD-L1 antibody.

[Fig. 3] Expression and purification of rat-canine chimeric anti-PD-L1 antibodies c4G12 and c6G7. SDS-PAGE was performed under non-reducing conditions, followed by

visualization of bands by CBB staining. a: purification with protein A alone. b: a + gel filtration chromatography.

[Fig. 4] PD-1/PD-L1 binding inhibition activities of rat-canine chimeric anti-PD-L1 antibodies c4G12 and c6G7.

[Fig. 5] Establishment of cell clones capable of high expression of rat-canine chimeric anti-PD-L1 antibody c4G12.

[Fig. 6] SDS-PAGE images of rat-canine chimeric anti-PD-L1 antibody c4G12. Rat anti-bovine PD-L1 antibody 4G12 and rat-canine chimeric anti-PD-L1 antibody c4G12 were electrophoresed under reducing conditions and non-reducing conditions, followed by visualization of bands by CBB staining. Under reducing conditions, a band of antibody's heavy chain was detected at around 50 kDa and a band of antibody's light chain at around 25 kDa. No bands other than the bands of interest were detected.

[Fig. 7] Inhibitory activities of rat anti-bovine PD-L1 antibody 4G12 and rat-canine chimeric anti-PD-L1 antibody c4G12 against canine PD-1/PD-L1 binding and CD80/PD-L1 binding. Rat anti-bovine PD-L1 monoclonal antibody 4G12 and rat-canine chimeric anti-PD-L1 antibody c4G12 reduced the amounts of binding of PD-L1-Ig to canine PD-1-Ig and CD80-Ig. No change due to chimerization of the antibody was observed in binding inhibition activity

[Fig. 8] Canine immune cell activation effect by rat-canine chimeric anti-PD-L1 antibody c4G12. Canine PBMCs were cultured under stimulation for 3 days, followed by determination of IL-2 and IFN- γ concentrations in the supernatant by ELISA. Further, nucleic acid analogue EdU was added to the culture medium at day 2 of the culture under stimulation, followed by determination of the EdU uptake by flow cytometry. Rat-canine chimeric anti-PD-L1 antibody c4G12 increased the production of IL-2 and IFN- γ from canine PBMCs and enhanced proliferation of CD4⁺ and CD8⁺ lymphocytes.

[Fig. 9] Expression of PD-L1 in oral melanoma (A) and undifferentiated sarcoma (B)

[Fig. 10] CT images and appearances of tumor in a test of treatment by administering rat-canine chimeric anti-PD-L1 antibody c4G12 to a dog with oral melanoma. (a,d) Before the start of the treatment, (b,e) at week 10 of the treatment, and (c,f) at week 34 of the treatment. A remarkable anti-tumor effect was recognized upon five administrations of the antibody (at week 10 from the start of the treatment). At week 34, a further reduction of tumor was confirmed.

[Fig. 11] Time-dependent changes in the longest diameter of the tumor in the dog

with oral melanoma shown in Fig. 10. Reduction by 30% or more compared to the baseline longest diameter was regarded as partial response (PR).

[Fig. 12] CT images in a test of treatment by administering rat-canine chimeric anti-PD-L1 antibody c4G12 to a dog with undifferentiated sarcoma. (a,c) Before the start of the treatment, (b,d) at week 3 of the treatment. A remarkable reduction of tumor was recognized upon two administrations of the antibody.

[Fig. 13] CT images in a test of treatment by administering rat-canine chimeric anti-PD-L1 antibody c4G12 to dogs with oral melanoma (pulmonary metastatic cases). (a,d,g) Before the start of the treatment, (b,e,h) at week 6 of the treatment, and (c,f,i) at week 18 of the treatment. A plurality of pulmonary metastatic lesions disappeared upon nine administrations of the antibody.

[Fig. 14] Time-dependent changes in the proportion survival of dogs with oral melanoma after the occurrence of pulmonary metastasis. In the antibody administration group, the survival duration may have been prolonged compared to the control group.

[Fig. 15] CDR1, CDR2 and CDR3 regions in the light chain variable region and the heavy chain variable region of rat anti-bovine PD-L1 antibody 4G12 are illustrated.

[Fig. 16] Cross-reactivity of rat anti-bovine PD-L1 antibody 4G12. It was confirmed that rat anti-bovine PD-L1 antibody 4G12 binds to ovine PD-L1 and porcine PD-L1.

[Fig. 17] Reactivity of rat anti-bovine PD-L1 antibody 4G12 with water buffalo leukocytes. Rat anti-bovine PD-L1 antibody 4G12 strongly bound to blood macrophages (CD14⁺ CD11b⁺ cells) of water buffalo, whereas rat anti-bovine PD-L1 antibody 4G12 bound weakly to lymphocytes (CD14⁻CD11b⁻ cells) of water buffalo. It is believed that this difference in binding reflects the expression levels of PD-L1 in macrophages and lymphocytes.

[Fig. 18] Inhibition test on rat anti-bovine PD-L1 antibody 4G12 against ovine or porcine PD-1/PD-L1 binding. It was demonstrated that rat anti-bovine PD-L1 antibody 4G12 is capable of inhibiting ovine and porcine PD-1/PD-L1 binding in a concentration dependent manner.

[Fig. 19] The amino acid sequence of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12. CDR1, CDR2 and CDR3 regions in the light chain variable region and the heavy chain variable region of rat anti-bovine PD-L1 antibody 4G12 are shown. Further, amino acids introduced as mutations to bovine IgG1 (CH2 domain) are also shown (amino acid numbers and mutations: 250 E→P, 251 L→V, 252 P→A, 253 G →deletion, 347 A→S,

348 P→S).

[Fig. 20] Schematic drawings of pDC6 vector and rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12.

[Fig. 21] Confirmation of the purity of purified rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12.

[Fig. 22] Binding specificity of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12.

[Fig. 23] Inhibitory activity of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 against bovine PD-1/PD-L1 binding (the test results of inhibition against binding of bovine PD-L1 expressing cells and soluble bovine PD-1).

[Fig. 24] Inhibitory activity of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 against bovine PD-1/PD-L1 binding (the test results of inhibition against binding of bovine PD-1 expressing cells and soluble bovine PD-L1).

[Fig. 25] Activation effect of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 on bovine lymphocyte response (in terms of cell proliferation).

[Fig. 26] Activation effect of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 on bovine lymphocyte response to BLV antigen (in terms of IFN- γ production).

[Fig. 27] The proliferation response of T cells against BLV antigen in a calf experimentally infected with BLV through administration of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12.

[Fig. 28] Changes in BLV provirus loads in the calf experimentally infected with BLV through administration of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12.

BEST MODES FOR CARRYING OUT THE INVENTION

Hereinbelow, the present invention will be described in detail.

The present invention provides an anti-PD-L1 antibody comprising (a) a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and a light chain constant region of an antibody of an animal other than rat; and (b) a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and a heavy chain constant region of an antibody of an animal other than rat.

CDR1, CDR2 and CDR3 in the light chain variable region (VL) of rat anti-bovine PD-L1 antibody 4G12 are a region consisting of the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), a region consisting of the amino acid sequence of WAT and a region consisting of the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38), respectively (see Fig. 15).

Further, CDR1, CDR2 and CDR3 in the heavy chain variable region (VH) of rat anti-bovine PD-L1 antibody 4G12 are a region consisting of the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), a region consisting of the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and a region consisting of the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41), respectively (see Fig.15).

In the amino acid sequences of QSLLYSENQKDY (SEQ ID NO: 37), WAT and GQYLVYPFT (SEQ ID NO: 38), as well as the amino acid sequences of GYTFTSNF (SEQ ID NO: 39), IYPEYGNT (SEQ ID NO: 40) and ASEEAVISLVY (SEQ ID NO: 41), one, two, three, four or five amino acids may be deleted, substituted or added.

As used herein, the term “antibody” is a concept encompassing not only full-length antibodies but also antibodies of smaller molecular sizes such as Fab, F(ab)₂, ScFv, Diabody, V_H, V_L, Sc(Fv)₂, Bispecific sc(Fv)₂, Minibody, scFv-Fc monomer and scFv-Fc dimer.

In the anti-PD-L1 antibody of the present invention, VL and VH thereof may be derived from rat. For example, VL thereof may be the VL of a rat anti-bovine PD-L1 antibody, and VH thereof may be the VH of the rat anti-bovine PD-L1 antibody.

The amino acid sequence of the VL and the amino acid sequence of the VH of the rat anti-bovine PD-L1 antibody are shown in SEQ ID NOS: 1 and 2, respectively. The amino acid sequences as shown in SEQ ID NOS: 1 and 2 may have deletion(s), substitution(s) or addition(s) of one or several (e.g., up to five, about 10 at the most) amino acids. Even when such mutations have been introduced, the resulting amino acid sequences are capable of having the function as VL or VH of the PD-L1 antibody.

The VL and VH of an antibody of an animal other than rat may be derived from an animal which produces a PD-L1 that cross-reacts with rat anti-bovine PD-L1 antibody 4G12.

There are two types of immunoglobulin light chain, which are called Kappa chain (κ) and Lambda chain (λ). In the anti-PD-L1 antibody of the present invention, the light chain constant region (CL) of an antibody of an animal other than rat may have the amino acid sequence of the constant region of either Kappa chain or Lambda chain. However, the relative abundance of Lambda chain is higher in ovine, feline, canine, equine and bovine, and that of Kappa chain is higher in mouse, rat, human and porcine. Since a chain with a higher

relative abundance is considered to be preferable, an ovine, feline, canine, equine or bovine antibody preferably has the amino acid sequence of the constant region of Lambda chain whereas a mouse, rat, human or porcine antibody preferably has the amino acid sequence of the constant region of Kappa chain.

The heavy chain constant region (CH) of an antibody of an animal other than rat may have the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4. Immunoglobulin heavy chain is classified into γ chain, μ chain, α chain, δ chain and ϵ chain depending on the difference in constant region. According to the type of heavy chain present, five classes (isotypes) of immunoglobulin are formed; they are IgG, IgM, IgA, IgD and IgE.

Immunoglobulin G (IgG) accounts for 70-75% of human immunoglobulins and is the most abundantly found monomeric antibody in plasma. IgG has a four-chain structure consisting of two light chains and two heavy chains. Human IgG1, IgG2 and IgG4 have molecular weights of about 146,000, whereas human IgG3 has a long hinge region that connects Fab region and Fc region and has a larger molecular weight of 170,000. Human IgG1 accounts for about 65%, human IgG2 about 25%, human IgG3 about 7%, and human IgG4 about 3% of human IgG. They are uniformly distributed inside and outside of blood vessels. Having a strong affinity for Fc receptors and complement factors on effector cell surfaces, human IgG1 induces antibody-dependent cell cytotoxicity (ADCC) and also activates complements to induce complement-dependent cell cytotoxicity (CDC). Human IgG2 and IgG4 are low at ADCC and CDC activities because their affinity for Fc receptors and complement factors is low.

Immunoglobulin M (IgM), which accounts for about 10% of human immunoglobulins, is a pentameric antibody consisting of five basic four-chain structures joined together. It has a molecular weight of 970,000. Usually occurring only in blood, IgM is produced against infectious microorganisms and takes charge of early stage immunity.

Immunoglobulin A (IgA) accounts for 10-15% of human immunoglobulins. It has a molecular weight of 160,000. Secreted IgA is a dimeric antibody consisting of two IgA molecules joined together. IgA1 is found in serum, nasal discharge, saliva and breast milk. In intestinal juice, IgA2 is found abundantly.

Immunoglobulin D (IgD) is a monomeric antibody accounting for no more than 1% of human immunoglobulins. IgD is found on B cell surfaces and involved in induction of antibody production.

Immunoglobulin E (IgE) is a monomeric antibody that occurs in an extremely small

amount, accounting for only 0.001% or less of human immunoglobulins. Immunoglobulin E is considered to be involved in immune response to parasites but in advanced countries where parasites are rare, IgE is largely involved in bronchial asthma and allergy among other things.

With respect to canine, sequences of IgG-A (equivalent to human IgG2), IgG-B (equivalent to human IgG1), IgG-C (equivalent to human IgG3) and IgG-D (equivalent to human IgG4) have been identified as the heavy chain of IgG. In the antibody of the present invention, an IgG's heavy chain constant region with neither ADCC activity nor CDC activity is preferable (IgG4 in human). In the case where the constant region of an immunoglobulin equivalent to human IgG4 has not been identified, one may use a constant region that has lost both ADCC activity and CDC activity as a result of introducing mutations into the relevant region of an immunoglobulin equivalent to human IgG4.

With respect to bovine, sequences of IgG1, IgG2 and IgG3 have been identified as the heavy chain of IgG. In the antibody of the present invention, an IgG's heavy chain constant region with neither ADCC activity nor CDC activity is preferable (IgG4 in human). Although the constant region of wild-type human IgG1 has ADCC activity and CDC activity, it is known that these activities can be reduced by introducing amino acid substitutions or deletions into specific sites. In bovine, the constant region of an immunoglobulin equivalent to human IgG4 has not been identified, so mutations may be added at the relevant region of an immunoglobulin equivalent to human IgG1 and the resultant constant region then used. As one example, the amino acid sequence of the CH of a bovine antibody (IgG1 chain, GenBank: X62916) having mutations introduced into CH2 domain and a nucleotide sequence for such amino acid sequence (after codon optimization) are shown in SEQ ID NOS: 102 and 102, respectively.

When an animal other than rat is canine, an anti-PD-L1 antibody is more preferable in which (i) the CL of a canine antibody has the amino acid sequence of the constant region of Lambda chain and (ii) the CH of the canine antibody has the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4.

When an animal other than rat is bovine, an anti-PD-L1 antibody is more preferable in which (i) the CL of a bovine antibody has the amino acid sequence of the constant region of Lambda chain and (ii) the CH of the bovine antibody has mutations introduced therein that reduce ADCC activity and/or CDC activity.

The anti-PD-L1 antibody of the present invention encompasses rat-canine chimeric antibodies, caninized antibodies, complete canine-type antibodies, rat-bovine chimeric antibodies, bovinized antibodies and complete bovine-type antibodies. However, animals are

not limited to canine and bovine and may be exemplified by human, porcine, simian, mouse, feline, equine, goat, sheep, water buffalo, rabbit, hamster, guinea pig and the like.

For example, the anti-PD-L1 antibody of the present invention may be an anti-PD-L1 antibody in which the CL of a canine antibody has the amino acid sequence as shown in SEQ ID NO: 3 and the CH of the canine antibody has the amino acid sequence as shown in SEQ ID NO: 4.

As a further example, the anti-PD-L1 antibody of the present invention may be an anti-PD-L1 antibody in which the CL of a bovine antibody has the amino acid sequence as shown in SEQ ID NO: 100 and the CH of the bovine antibody has the amino acid sequence as shown in SEQ ID NO: 102.

The amino acid sequences as shown in SEQ ID NOS: 3 and 4 as well as SEQ ID NOS: 100 and 102 may have deletion(s), substitution(s) or addition(s) of one or several (e.g., up to five, about 10 at the most) amino acids. Even when such mutations have been introduced, the resulting amino acid sequences are capable of having the function as CL or CH of the PD-L1 antibody.

The anti-PD-L1 antibody of the present invention may have a four-chain structure comprising two light chains and two heavy chains.

The anti-PD-L1 antibody of the present invention may be prepared as described below. Briefly, an artificial gene is synthesized which comprises (i) the identified variable region sequences of a rat anti-bovine PD-L1 antibody and (ii) the constant region sequences of an antibody of an animal other than rat (e.g., canine or bovine) (preferably, human IgG4 antibody; antibody equivalent to human IgG4 antibody; or an immunoglobulin equivalent to human IgG1, in which mutations have been introduced into the relevant region to reduce ADCC activity and/or CDC activity). The resultant gene is inserted into a vector (e.g., plasmid), which is then introduced into a host cell (e.g., mammal cell such as CHO cell). The host cell is cultured, and the antibody of interest is collected from the resultant culture.

The amino acid sequence and the nucleotide sequence of the VL of the rat anti-bovine PD-L1 antibody identified by the present inventors are shown in SEQ ID NOS: 1 and 5, respectively. Further, the nucleotide sequence after codon optimization is shown in SEQ ID NO: 15.

The amino acid sequence and the nucleotide sequence of the VH of the rat anti-bovine PD-L1 antibody identified by the present inventors are shown in SEQ ID NOS: 2 and 6, respectively. Further, the nucleotide sequence after codon optimization is shown in SEQ ID NO: 16.

The amino acid sequence and the nucleotide sequence of the CL (Lambda chain, GenBank: E02824.1) of a canine antibody are shown in SEQ ID NOS: 3 and 7, respectively. Further, the nucleotide sequence after codon optimization is shown in SEQ ID NO: 17.

The amino acid sequence and the nucleotide sequence of the CL (Lambda chain, GenBank: X62917) of a bovine antibody are shown in SEQ ID NOS: 100 and 101, respectively. Further, the nucleotide sequence after codon optimization is shown in SEQ ID NO: 104.

The amino acid sequence and the nucleotide sequence of the CH (IgG-D chain, GenBank: AF354267.1) of the canine antibody are shown in SEQ ID NOS: 4 and 8, respectively. Further, the nucleotide sequence after codon optimization is shown in SEQ ID NO: 18.

The amino acid sequence and the nucleotide sequence (after codon optimization) of the CH (IgG1 chain, modified from GenBank: X62916) of the bovine antibody are shown in SEQ ID NOS: 102 and 103, respectively.

Further, SEQ ID NO: 9 shows the amino acid sequence of a chimeric light chain consisting of the VL of the rat anti-bovine PD-L1 antibody and the CL (Lambda chain, GenBank: E02824.1) of the canine antibody. The nucleotide sequence (after codon optimization) of the chimeric light chain consisting of the VL of the rat anti-bovine PD-L1 antibody and the CL (Lambda chain, GenBank: E02824.1) of the canine antibody is shown in SEQ ID NO: 19.

Further, SEQ ID NO: 105 shows the amino acid sequence of a chimeric light chain consisting of the VL of the rat anti-bovine PD-L1 antibody and the CL (Lambda chain, GenBank: X62917) of the bovine antibody. The nucleotide sequence (after codon optimization) of the chimeric light chain consisting of the VL of the rat anti-bovine PD-L1 antibody and the CL (Lambda chain, GenBank: X62917) of the bovine antibody is shown in SEQ ID NO: 107.

SEQ ID NO: 10 shows the amino acid sequence of a chimeric heavy chain consisting of the VH of the rat anti-bovine PD-L1 antibody and the CH (IgG-D chain, GenBank: AF354267.1) of the canine antibody. The nucleotide sequence (after codon optimization) of the chimeric heavy chain consisting of the VH of the rat anti-bovine PD-L1 antibody and the CH (IgG-D chain, GenBank: AF354267.1) of the canine antibody is shown in SEQ ID NO: 20.

SEQ ID NO: 106 shows the amino acid sequence of a chimeric heavy chain consisting of the VH of the rat anti-bovine PD-L1 antibody and the CH (IgG1 chain, modified from

GenBank: X62916) of the bovine antibody. The nucleotide sequence (after codon optimization) of the chimeric heavy chain consisting of the VH of the rat anti-bovine PD-L1 antibody and the CH (IgG1 chain, modified from GenBank: X62916) of the bovine antibody is shown in SEQ ID NO: 108.

Amino acid sequences and nucleotide sequences of CLs and CHs for various animals other than the above may be obtained from known databases for use in the present invention.

Amino acid sequences and nucleotide sequences of CLs and CHs for canine, ovine, porcine, water buffalo, human and bovine are summarized in the table below.

Table.

(Table)

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Canine (Scientific Name: <i>Canis lupus familiaris</i>)	Canine Ig heavy chain constant region (CH1~CH3)	IgG-D GCCTCCACCACGGCCCGCTCGGTTTTCCCACTGGCC CCAGCTGCGGGTCCACTTCCGGCTCCACGGTGGCC CTGGCCTGCCTGGTGTCAAGCTACTTCCCGAGCCT GTAAGTGTCTCTGGAATTCGGGTCCTTGACGAGC GGTGTGCACACCTTCCCGTCCGTCCTGCAGTCCTCA GGGCTCTACTCCCTCAGCAGCACGGTGACAGTGCC TCCAGCAGGTGGCCACGGAGACCTTCACCTGCAAC GTGGTCCACCCGGCCAGCAACACTAAAGTAGACAAG CCAGTGCCCAAGAGTCCACCTGCAAGTGTATATCC CCATGCCAGTCCCTGAATCACTGGGAGGGCCTTCG GTCTTCATCTTTCCCGGAACCCAGGACATCCTC AGGATTACCCGAACCCGAGATCACTGTGTGGTG TTAGATCTGGGCGTGAGGACCTGAGGTGCAGATC AGCTGGTTCGTGGATGGTAAGGAGTGCACACAGCC AAGAGCGAGCCTCGTGAGCAGCAGTTCAACAGCAAC TACCGTGTGGTACGGTCTCTCCCATTTGAGCACGAG GACTGGCTCACCAGAAAGGAGTTCAGGTGAGAGTC AACCAATAGGCCTCCCGTCCCGCATCGAGAGGACT ATCTCCAAAGCCAGAGGGCAAGCCATCAGCCAGT GTGTATGTCTGCCACCATCCCAAGGAGTTGTCA TCCAGTGACACGGTCACCTGACCTGCCTGATCAA GACTTCTTCCACCTGAGATTGATGTGGAGTGGCAG AGCAATGGACAGCGGAGCCCGAGAGCAAGTACCAC ACGACTGGCCCCAGCTGGACGAGGACGGTCTCTAC TTCTGTACAGCAAGCTCTCTGTGGACAGAGCCGC TGGAGCAGGGAGACACCTTCAATGTGGGTGATG CATGAAGCTCTACAGAACCACTACACAGATCTATCCC TCTCCATTCTCCGGTAAATGA (SEQ ID NO: 8)	ASTTAPSVFPLAPSCGSTSGSTVALAC LVSGYFPEPVTVSWNSGLTSGVHTFP SVLQSSGLYLSSTVTPSSRWPSSETF TONVHPASNTKVDKVPKESTCKCIS POPVPESLGGPSVFPPKPKDILRTRT PEITCVVLDLGREDEPVGISWFDGKEV HTAKTQPREQQFNSTYRVVSVLPIEHQ DWLTGKEFKORVNHGLPSPERTISKA RGQAHQPSVYVLPSPKELSSSDIVTL TCLIKDFPPEIDVEWQSNQGPPEPSKY HTTAPQLDEGYSFLYSKLSVDKSRWQ QGDFTFCVMHEALQNHYTDLSLSHS PGK* (SEQ ID NO: 4)	AF354267	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=dog&group=IGHC	Tang L. et al., Vet. Immunol. Immunopathol. 80 (3-4), 259-270 (2001). PMID: 11457479
	Canine Ig light chain constant region	Ig lambda (CL) CAGCCCAAGGCCTCCCCCTCGGTACACTCTTCCCG CCCTCCTCTGAGGAGCTCGGCGCCAAACAGGCCACC CTGGTGTGCCTCATCAGCGACTTCTACCCAGCGGC GTGACGGTGGCCTGGAAGGCAAGCGGCAGCCCGT CACCACGGCGTGGAGACCAAGCCCTCAAGCA GAGCAACAACAGTACGCGGCCAGCAGCTACCTGAG CCTGACGCTGACAAGTGGAAATCTCAGACGAGCTT CAGCTGCCTGTGACGACAGAGGGAGCACCGTGG AGAAGAAGGTGGCCCCCGCAGAGTGTCTTAG (SEQ ID NO: 7)	QPKASPSVTLFFPSPSEELGANKATLVC LISDFYPSGVTVAWKASGSPVTQGVET TKPSKQSNNKYAASSYLSLTPDKWKSH SFSQGLVTHEGSTVEKKVAPAECS* (SEQ ID NO: 3)	E02824	Not registered	None

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Ovine (Scientific Name: Ovis aries)	Ovine heavy chain constant region (CH1~CH3)	IgG1 GCCTCAACAACACCCCGAAAGTCTACCCCTGACT TCTTGCTGGGGGACAGTCCAGCTCCATCGTGACC CTGGGCTGCTGGTCTCCAGCTATATGCCCGAGCCG GTGACCGTGACCTGGAAGTCTGGTGCCCTGACGAGC GGCGTGCACACCTTCCCGGCCATCTGCAGTCTCCG GGGCTCTACTCTCTCAGCAGCGTGGTGACCGTGCCG GGCAGACCTCAGGAGCCGAGACCTTCAATCTGCAAC GTAGCCCAACCGGCCGACGACCAAGGTGGACAAG CGTGTGAGCCCGGATGCCCGACCCATGCAAAAGAT TGCCGATGCCACCCCTGAGCTCCCGCGAGGACCC GTCTGTCTTCACTTCCACCGAAACCCAGGACAC CCTTACAATCTCTGGAACGCCGAGGTACAGTGTGT GGTGGTGAGCTGGGCCAGGATGACCCGAGGTGC AGTTCTCTCGTGGTGGTGGACAACGTGGAGGTGGCA CGGCCAGGACAAAGCGAGAGAGGAGGAGTTCACCA GACCTTCCCGCTGGTGGGCGCTGCCCATCCAGC ACCAAGACTGGAAGTGGAGGAAAGGAGTTCAGATGCA AGGTCCACAACGAAGCCTCCCGGCCCATCGTGA GGACCATCTCCAGGACCAAGGCGAGGCCGCGGAG CCGCGAGGTGACGTCTGCCCGACCCAGGAAGAG CTCAGCAAAAGCAGCTCAGCGTCACCTGCCTGGTGC ACCGGCTTCTACCCAGACTACATCGCCGTGGAGTGG CAGAAATGGCAGCGCTGAGTGGGAGCAGCAATC GGCAGCAGCACATCCAGCTGGACCGCGACGCTCC TACTCTGTACAGCAGGCTCAGGTTGGAAGAAG AGCTGGCAAGAGGAGACACTACGCTGTGTGGTG ATGACAGGCTCTGCACAACCACTACACACAGAAG TGGATCTTAAGCCTCCGGGTAATGA (SEQ ID NO: 43)	ASTTPPKVYPLTSCGDTSSSIVTLGC LVSSYMPPEVTVTWNSGALTSGVHTF PAILOSSLYSLSSVTVPASTSGAQT FICNVHPASSTKVDKRVPGCPDPCK HCRCPPPELPGPSVFIFPPKPKDILT SGTPEVTQVVDVGGDDPEVGFWSFV DNVEVTRARTKPREEQFNSTFRVVSAL PIQHDDWITGKEFKCKVHNEALPPIV RTISRTKGQAREPOVYVLAAPPQELSK STLSVTCLVTGFYPDYIAVEWQKNGGP ESEDKYGTTSQLDADGSYFLYSRLRV DKNSWQEGDTYACVVMHEALHNHYTQ KSISKPPGK* (SEQ ID NO: 42)	X69797	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetables&species=sheep&group=IGHC	Dufour V. et al., J. Immunol., 156, 2163-2170 (1996). PMID: 8690905
		IgG2 GCCTCCACACAGCCCCGAAAGTCTACCCCTGACT TCTTGCTGGGGGACAGTCCAGCTCCATCGTGACC GTGACCGTGGGCTGCTGGTCTCCAGCTATATGCCCG GAGCGGTGACCGTGACCTGGAAGTCTGGTGCCCTG ACGAGCGGGGTGCACACCTTCCCGGCCATCTGCAG TCTTCCGGGCTCTACCTCTCAGCAGCGTGGTGACCC GTGCGCGCCAGCACCTCAGGAGCCGAGACCTTCACT TGCAACGTAGCCCCACCGCCGAGCAGGCCCAAGGTG GACAAAGCTGTTGGGATCTCCAGTACTCTCAAG TGTTCTAAGCCCGCTTGGGTGAGCCGACCGTGTGTC TTCACTTCTCCCGCCGAAACCCAGGACAGCCCTCATG ATCAGGAAACCGCCGAGGTGACGTGTGTGGTGGTG GACGTGGGCGAGGTTGACCCGAGGTGCAATCTCC TGGTTCGTGGACAACGTGGAGGTGGCGCAGGCCGAG ACAAAGCGGAGAGGAGGAGTTCAACAGCACCTTCC CGCGTGGTGAAGCCCGCTCCCGATCCAGCAAGCAGCAG TGGACTGGAGGAAAGGAGTTCAAGTGCAGGCTCCAC AGCAAAAGCCCTCCCGGCCCATCTGAGGACCATC TCCAGGCCCAAGGCGGAGGCCGCGGAGCCGCGAGGT GTACGTCTGGCCCAACCCAGGAAGAGCTCAGCAA AAGCAGCGTCAGCGTCACCTGCCTGGTCAACCGGCTT CTACCCAGACTACATCGCCGTGGAGTGGAGAGAGCC GGGGAGCCCTGAGTGGAGGACAGTACGGCAGCAGC CACATCCAGCTGGAGCCGAGCGTCTACTTCTCT GTACAGCAGGCTCAGGTTGGACAGAGCAGCTGGCA AAGAGGAGACACCTACCGCTGTGTGGTGATGCACGA GGCTCTGCACAACCACTACACACAGAAGTCGATCTC TAAGCCTCCGGGTAATGA (SEQ ID NO: 45)	ASTTAPKVYPLTSCGDTSSSSIVTL GCLVSSYMPPEVTVTWNSGALTSGVHT TFPAILOSSLYSLSSVTVPASTSGA QTICNVHPASSAKVDKRVGISSDYS KCKSPPCVSRPSVFIFPPKPKDSLMITG IPEVTCVVVDVGGGDPFVQSWFVUN VEVTRARTKPREEQFNSTFRVVSALPI QHDHWTGGKEFKCKVHSGKLPPIVIR ISRAKGAREPOVYVLAAPPQELSKST LSVTCLVTGFYPDYIAVEWQKNGGP EDKYGTTSQLDADGSYFLYSRLRVDK SSWQEGDTYACVVMHEALHNHYTQKS ISKPPGK* (SEQ ID NO: 44)	X70983		Clarkson C.A. et al., Mol. Immunol., 30, 1195-1204 (1993). PMID: 8413324
	Ovine light chain constant region	Ig kappa (CK) CCATCCGTCTTCTCTTCAAACCATCTGAGGAACAG CTGAGGACCGGAAGTGTCTCTGTCTGTGCTTGGTG AATGATTCTACCCCAAGATATCAATGTCAAGGTGA AAGTGGATGGGTTACCCAGAACGCACTTCCAGA ACAGCTTCACAGACCGAGGACGCAAGAAAGACCT ACAGCCTCAGCAGCACCTGACACTGTCCAGCTCAG AGTACCAGGCCATAACGCTATGCGTGTGAGGTCA GCCACAAGAGCCTGCCACCGCCCTCGTCAAGAGCT TGAATAAGAAATGAATGTTAG (SEQ ID NO: 47)	PSVFLFKPSEEQLRTGTVSVVCLVND FYPKDNVKKVVDGVTQNSNFQNSFTDQ DSKSTYSLSSTLTLSSSEYQSHNAYA CEVSHKSLPTALVKSFNKEC* (SEQ ID NO: 46)	X54110	Not registered	Jenne C.N. et al., Dev. Comp. Immunol., 30 (1-2), 165-174 (2006). PMID: 16083958
		Ig lambda (CL) GGTCAGGCCAAGTCCGACCCCTGGGTCAACCTGTCT CCGCTTCCACGGAGGAGCTCAGTACCAACAAGGCC ACCGTGGTGTGTCTCATCAACGACTTCTACCCGGGT AGCGTGAACGTGGTCTGGAAGGAGATGGCAGCACC ATCAATCAGAACGTGAAGACCCAGGCGCTCCAA CAGAGCAACAGCAAGTACGCGGCCAGCGACTACCTG ACCGTGAAGGCGGAGGTGGAAGTCTAAGAGCAGT TACACCTGGAGGTTCAGGCACGAGGGAGCACCGTG ACGAAGACAGTGAAGCCCTCAGAGTGTCTTAG (SEQ ID NO: 49)	GUPKSAPSVTLFPPSTEELSTNKATV VLINDFYPGSVNVVWKADGSTINQNV TTQASKGNSKYAASSYLTLTGSEWKS KSSYTCVTHEGSTVTKTKVPSECS* (SEQ ID NO: 48)	AY734681		

	Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	MGIT Database	Reference	
	Porcine (Scientific Name: <i>Sus scrofa</i>)	IgG1 ⁺	GCCCCAAGACGGCCCCATCGGTCTACCCCTCTGGCCCCCTGGCGAGGGACACGCTCTG GCCCTAACGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGACCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGATGGAAGAGCAACGGACGCGGAGCGAGAGGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAGCTCGCGGTGGACA AGGCAAGATGGGACCATGGAGACAATTTGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 51)	APKTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKARWHDGTEFCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 50)	U03781	http://www.imst.org/LMGITreporter/index.php?section=LocusGenes&reporter=genetab&species=PIg&group=IGHC	Butler J.E. et al., Immunogenetics 61(3): 209-230 (2009). PMID: 19048248	
			IgG1 ⁺	GCCCCAAGACGGCCCCATCGGTCTACCCCTCTGGCCCCCTGGCGAGGGACACGCTCTG GCCCTAACGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGATCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGATGGAAGAGCAACGGACGCGGAGCGAGAGGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAACTTCGCGGTGGACA AGGCAAGATGGGACCATGGAGACAATTTGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 53)	APKTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKARWHDGTEFCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 52)	U03778		Koschovics T. et al., Immunol. 153(8): 3565-3573 (1994). PMID: 7350379
			IgG2 ⁺	GCCCCAAGACGGCCCCATCGGTCTACCCCTCTGGCCCCCTGGCGAGGGACACGCTCTG GCCCTAACGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGATCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGAGTGGCAAGAAAGGACGCGGAGCGGAGGAGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAACTTCGCGGTGGACA AGGCAAGATGGGACCATGGAGACAATTTGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 55)	APKTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKASWQGGGIFQCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 54)	U03779		
			IgG2 ⁺	GCCCCAAGACGGCCCCATCGGTCTACCCCTCTGGCCCCCTGGCGAGGGACACGCTCTG GCCCTAACGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGATCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGAGTGGCAAGAAAGGACGCGGAGCGGAGGAGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAACTTCGCGGTGGACA AGGCAAGTGGGAGGTGGAGGCTATTCGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 57)	APKTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKASWQGGGIFQCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 56)	U03780		
		IgG3	GCCTATCAACACAGCTCCATCGGTCTACCCCTCTGGCCCCCTGTGGAGGGACGCTGTCTGA TCTAATCAAGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGATCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGAGTGGCAAGAAAGGACGCGGAGCGGAGGAGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAACTTCGCGGTGGACA AGGCAAGTGGGAGGTGGAGGCTATTCGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 59)	AYNTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKASWQGGGIFQCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 58)	EU372658			
			IgG4 ⁺	ACCTTCCCATCCGCTCGAGCGGTCAAGGCGTCTACTCCCTCAGCAGCATGGTGACCGT GCCCGCCAGCAGCGCTTCCAGCAAGAGCTACACCTGCAATGTCAACACCCCGGCCGACCA CAGCAAGCTGGACAGGCTGTTGGAGCAAAAGCAGCAACACCATGTCCCATATGCCCA GCCCTGTGAAGGGCCCGGCCCTCGGCGCTTCTCATCTTCCCTCCAAACCCAGGACACCCCT CATGATCTCCCGGACCCCAAGGTCAAGTGGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT CGAGAGTCCAGTTCCTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT CCAAAGGAGGAGGAGTTCAGGAGCAGCTTACGAGTGGTGGTGGTGGTGGTGGTGGTGGTGGT CCAGAGCTGGGTGAACGGGAGGAGTTCAGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT CCGACCATCAAGAGATCATCTCCAAAGGCCAAAGGCCAGACCCGGGAGCCGAGGTGTAC ACCGTGGCCGCCACCCAGGAGGAGTGTCCAGGAGCAAGTCAACGCTTAACCTGGCTGGT CACTGGCTGTACCGACCTGACATGATGTGAGTGGAGGAGCAGGACCAAGAGGAGCGCGAGC CAGAGGGCAATTACCGGACACCCCGGCCGAGCAGGAGTGGAGCGGAGCTTACTTCTGT TACAGCAAGCTGGCGGTGGACAAGGCCAGCTGACGAGCTGGAGACACATTCAGTGTGG GGTGTGTCAGAGGCTCTGCACAAACCTACACCCGAAGTCCATCTCCAAGACTCAGGTAATATGA (SEQ ID NO: 61)	TFPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKASWQGGGIFQCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 60)	U03782		
			IgG4 ⁺	GCCCCAAGACGGCCCCATCGGTCTACCCCTCTGGCCCCCTGGCGAGGGACGCTGTCTG GCCCTAACGTGGCCTTGGGCTGGCTGGCCTCAAGCTACTTCCCCGAGCCAGTGACCGTG ACCTTGGAACTCGGGGCCCTGACCAAGTGGCGTGCATACCTTCCCATCCGCTCTGCAGCC GTACAGGCTCTACTCCCTCAGCAGCATGGTGACCGTGGCGGCCGAGCAGCGCTGTCCAGCA AGAGCTTACACCTGCAATGTGAACACCGCGGCCGACACACCAAGGTGGACAAGCGTGTT GGACAACAGACAAACACCATGTCCCATATGCCACGGCTGTGAATCAACACGGGCGCTC GGTGTTCATCTTCCCTGATGCAAGGACACCGCTGATCTGTCGAGGACCGCGGAGG TCAAGTGGGTGGTGGTGAGCTGCAGCAAGGACGACGCCGAGGTCCAGTTCTCCTGGTAC GTGAGCGCGGTAGAGGTGCACACGGCCGAGCAGAGGCCAAAGGAGGAGGAGCTTCAACAG CACCTACCGCTGTGGTACGGCTCTGCCCATCCAGCACCAGGAGTGGTGAAGGGGAAGG AGTTCAAGTGCAGAGGTGAACAGCTAGACCTCCGAGCCGACATCAGCAGGATCATCTCC AAGGCTATAGGCGCAGAGCGGGGAGCGCGAGGTGTACACCCCTGCCCCACCGCGCGAGG AGCGTGTCCAGGAGCAAAAGTCAACCTAACCTGCCTGGTCAATTGGCTTCTACCCACCTGAC ATCCATGTGTGAGTGGCAAGAAAGGACGCGGAGCGGAGGAGGCAATTACCGGACGAC CCCGCCCGACGAGAGCTGGAGCGGAGCTTCTCTGTACAGCAAACTTCGCGGTGGACA AGGCAAGTGGGAGGTGGAGGCTATTCGAGTGTGGCGGTGATGCACGAGGCTCTGCAC AACCACATACCCAGAAGTCCATCTCCAAGACTCAGGGTAATATGA (SEQ ID NO: 63)	APKTAPSVYPLAPCGRDVSFNPVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYSLSMVTVPASSLS KSYTCNVNHPATTTKDKRVGHTKTP PCPIQPCAGEGPGSFIFPPKPKDITLMI SRTPEVTCVYVDVSKHEAEVQFSWYV DGEVHTAETRPKEEONSTYRVSV LPIQHODWLNGKEFKCKVNNVDLPAPI TRISKAKGOTREPQVYTLPPPAEELS RSKVITCLVGFYPFDIWEVWNSGQ PEPEGNVTRTPPGQVDGTYFLYSKL AVDKASWQGGGIFQCAVMHEALHNHY TOKSISKTPGK* (SEQ ID NO: 62)	EU372654		

(Continued)

		<p>IgG5⁺</p> <p>GC0CCCAAGACGGCCCATCGGCTACCCCTGTGGCCCCCTGCAGAGGGACACGCTGTG GCCCTAAGCTGGCCTTGGGCTGCCCTGGTCTCAAGCTACTTCCCGAGCCAGTGACCGTG ACCTTGAAGCTCGGGGGCCCTGACCACTGGCGTGCACACCTTCCCATCCGCTCGTGAGCG GTGAGGGCTTACTGCTGAGCAGCATGGTGACCGTCCGGCCCAAGCTTGTCCAGCA AGCGCTATACGTGCAATGTCAACACCCAGCCAGCCAAACCAAGGTGACCTGTGTGT GGAAGCAGCTGTGCCATATGCCAGGCTGTGAAGTGGCCGGGCCCTCGGTTTCATCTT CCCTCCAAACCCCAAGGACATCCTCATGATCTCCCGAGCCCGGAGGTGACGTGGGTGG TGGTGAGCTGCACAGCAAGCAGCCGAGTCCATTTCTCTGGTACGTGAGCGCGAA GAGGTGCACACCGCCGAGACGAGCCAAAGGAGGACGTTCAACAGCACCTACCGCTG GGTCAAGCTCTGCCCATCCAGCAGGAGGACTGGCTGAAGGGGAAGGAGTTGAGTGCA AGGTCAACCAAGAGCCTCCGAGGCCCATCAGCAGGACCATCTCCAGGCCAAAGGG GTGGTACGAGCGCCGAGGTGTACACCCCTGCCCGCCGCGGAGGAGCTGTCCAAAGA GCATAGTCACGCTAACCTGCCTGGTCAAAAGCATCTTCCCGNCTTTCATCCATGTTAGT GGAAATCAACGAAACCAAGCCAGAGCAGCATATCGACACCCCGCCCTCAGGAG GACGAGGACAGGACCTACTTCTGTACAGCAAGCTCCGGTGGACAGGCAAGATGGGA CCATGGAGAAACATTTGAGTGTGGGTGATCCAGGAGGTGTGCACAAACCATACACCC AGAAGTCCATCTCCAGACTCAGGTAAATGA (SEQ ID NO: 65)</p>	<p>APKTAPSVYPLAPCSRDTSGPNVALG GLVSSYFPEPVTVTWNSGALTSVHT FPSVLQPSGLYLSSTMVTPAHSLS KRYTONVNHPTATKVDLCVGRPCP CPGCEVAGPSVFIFPPKPKDILMSRTP EVTCTVVDVSKHEAEVQFSWYVDGEE VHTAETRPKEQFNSTYRVVSVLPQH EDWLKKEFECKVNNDLPAPIRRI KAKGVRSPEVYTLPPAEELSKSVIT LTCLVKSIFPFIHVEWKNKPEPEN YRTITPQDEEDRTYFLYSLKAVDKAR WDHGETTECAVMHEALHNHYTKSIS KTQK* (SEQ ID NO: 64)</p>	EU372657	
		<p>IgG5⁺</p> <p>GCCTACAAACACAGCTGCATCGGCTACCCCTGTGGCCCCCTGTGGCAGGAGCGTGTG TCTAATAGCTGGCCTTGGGCTGCCCTGGTCTCAAGCTACTTCCCGAGCCAGTGACCGTG CCTGGAAGTGGGGGCCAGACAGCTGGGCTGCACACCTTCCCATCCGCTCGTGAGCGCG TACAGGCTTACTTCCCTCAGCAGCAGCGTGACCGTGGCGGCCACAGCTTGTCCAGCAA GTGGTTCAAGTGTGCAATGTCAACACCCGCGCAGCAGCAGCATGGTGTGTGTGTG GAAAAGAGCCAAAGCTCGATGTCCCATATGCCAGGCTGTGAAGTGGCCGGGCCCTCG GTCTTTCATCTTCCCTCCAAACCCCAAGGACATCCTCATGATCTCCCGAGCCCGGAGGT CAGCTGGCTGGTGGTGGAGCTGCAGCAAGGAGCAGCGGAGGTGACGTTCTCTGGTACG TGACCGCGCAGAGGTGCACAGCGCGCAGCAGCAGCATGGTGTGTGTGTGTGTGTGTG ACCTTACCGGCTGGTGCAGCTCTGCCCATCCAGCAGGAGGACTGGCTGAAGGGGAAGGA GTTCCAGTGCAGAGTCAACACAGGAGCCTCCAGGCCCATCAGCAGGACCATCTCCA AGGCCAAAGGGTGTGTACGAGCCCGGAGGTGTACACCGCTGCCCGCCCGCCGAGGA GCTGTCCAGAGGATAGTCAAGCTTAACTGGCTGGTAAAGCTTCTTCCCGCTTTCAT CCATGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT CCTTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT TTCAAGTGGCAGGTGAGGAGCTCACTGTGGGTGATGCACGAGGCTGTGCACAAACCA CTACACCC (SEQ ID NO: 67)</p>	<p>AYNTAPSVYPLAPCGRDSDHNNVALG GLVSSYFPEPVTVTWNSGALTSVHT FPSVLQPSGLYLSSTMVTPAHSLSK CFTCNVNHPTATKVDLCVGRPCP CPGCEVAGPSVFIFPPKPKDILMS RTPVTCVVDVSKHEAEVQFSWYVD GEEVHTAETRPKEQFNSTYRVVSVL PIHEDWLKKEFECKVNNDLPAPIRRI RTSKAGGVRSPEVYTLPPAEELSK SVITLTCLVKSIFPFIHVEWKNKPE PENAYRTITPQDEEDGTFLYKFSVE KFRWHSQGHICAVMHEALHNHYT (SEQ ID NO: 66)</p>	EU372656	
		<p>IgG6⁺</p> <p>GC0CCCAAGACGGCCCATCGGCTACCCCTGTGGCCCCCTGC6GAGGGACACGCTGTG GCCCTAAGCTGGCCTTGGGCTGCCCTCAAGCTACTTCCCGAGCCAGTGACCGTG ACCTTGAAGCTCGGGGCCCTGACCACTGGCGTGCATACCTTCCCATCCGCTCGTGAGCG GTGAGGGCTTACTTCCCTCAGCAGCATGGTGACCGTGGCGGCCAGGAGCTGTCCAGCA GAGGCTACAGCTGCATGTGCAACACCCGCGCAGCAGCAGCATGGTGTGTGTGTGTGT GAGCAGCATGTGCCATATGCCAGGCTGTGAAGGGCCGGGCCCTCGGTTTCATCTT CCCTCCAAACCCCAAGGACATCCTCATGATCTCCCGAGCAGCCAGGTGACGTGGGTGG TGGTAGATGTGAGCCAGGAAACCGGAGGTGACGTTCTCTGGTATGTGAGCGGTGTA GAGGTGCACAGCGCCGAGCAGGCGCAAGGAGGCGGAGTTCAACAGCACCTACCGTG GGTCAAGCTCTGCCCATCCAGCAGGAGGACTGGCTGAAGGGGAAGGAGTTGAGTGCA AGGTCAACCAAGAGCCTCCAGCCCGCCATCAGCAAGGATCATCTCCAGGCCAAAGGG CCGAGCGCGGAGCGCGAGGTGTACACCGCTGTCCCATCCGCGGAGGAGCTGTCCAGGA GCAAGGTGAGCATTAACCTGCTGTGATGTGCGGAGCCGCGAGGTGACATCGATGTGCG TGGAGAGCAGCAGGACGCGGAGCGAGGAGGCAATTACCGCACCACCCCGCCGAGC AGGAGCTGCAGCGGAGCTACTTCTGTACAGCAAGCTCCGGTGGACAGGCGAGCTGG CAGCGTGGAGCCCATTCAGTGTGGGTGATGCACGAGGCTGTGCACAAACCATACAGC CT (SEQ ID NO: 69)</p>	<p>APKTAPSVYPLAPCGRDTSQPNVALG GLASSYFPEPVTWNSGALTSVHT FPSVLQPSGLYLSSTMVTPASSLS KSYTONVNHPTATKVDLCVGRPCP CPAGECPSPVFIFPPKPKDILMSRTP PQVTCVVDVSDENFEVQFSWYVDG VEVHTAETRPKEQFNSTYRVVSVLPI QHEDWLKKEFECKVNNDLPAPIRRI SKAGVRSPEVYTLPPAEELSKSVIT SITCLVTFYPPIDVWKNNGOPEPE GNVRTITPQDQDVTGTYFLYSLKAVDK ASWGRQDFGCAVMHEALHNHYT (SEQ ID NO: 68)</p>	EU372655	
		<p>IgG6⁺</p> <p>GC0CCCAAGACGGCCCATCGGCTACCCCTGTGGCCCCCTGC6GAGGGACACGCTGTG GCCCTAAGCTGGCCTTGGGCTGCCCTCAAGCTACTTCCCGAGCCAGTGACCGTG ACCTTGAAGCTCGGGGCCCTGACCACTGGCGTGCATACCTTCCCATCCGCTCGTGAGCG GTGAGGGCTTACTTCCCTCAGCAGCATGGTGACCGTGGCGGCCAGGAGCTGTCCAGCA GAGGCTACAGCTGCATGTGCAACACCCGCGCAGCAGCAGCATGGTGTGTGTGTGTGT GAGCAGCATGTGCCATATGCCAGGCTGTGAAGGGCCGGGCCCTCGGTTTCATCTT CCCTCCAAACCCCAAGGACATCCTCATGATCTCCCGAGCAGCCAGGTGACGTGGGTGG TGGTAGATGTGAGCCAGGAAACCGGAGGTGACGTTCTCTGGTATGTGAGCGGTGTA GAGGTGCACAGCGCCGAGCAGGCGCAAGGAGGCGGAGTTCAACAGCACCTACCGTG GGTCAAGCTCTGCCCATCCAGCAGGAGGACTGGCTGAAGGGGAAGGAGTTGAGTGCA AGGTCAACCAAGAGCCTCCAGCCCGCCATCAGCAAGGATCATCTCCAGGCCAAAGGG CCGAGCGCGGAGCGCGAGGTGTACACCGCTGTCCCATCCGCGGAGGAGCTGTCCAGGA GCAAGGTGAGCATTAACCTGCTGTGATGTGCGGAGCCGCGAGGTGACATCGATGTGCG TGGAGAGCAGCAGGACGCGGAGCGAGGAGGCAATTACCGCACCACCCCGCCGAGC AGGAGCTGCAGCGGAGCTACTTCTGTACAGCAAGCTCCGGTGGACAGGCGAGCTGG CAGCGTGGAGCCCATTCAGTGTGGGTGATGCACGAGGCTGTGCACAAACCATACAGC CT (SEQ ID NO: 69)</p>	<p>APKTAPSVYPLAPCGRDTSQPNVALG GLASSYFPEPVTWNSGALTSVHT FPSVLQPSGLYLSSTMVTPASSLS KSYTONVNHPTATKVDLCVGRPCP CPAGECPSPVFIFPPKPKDILMSRTP PQVTCVVDVSDENFEVQFSWYVDG VEVHTAETRPKEQFNSTYRVVSVLPI QHEDWLKKEFECKVNNDLPAPIRRI SKAGVRSPEVYTLPPAEELSKSVIT SITCLVTFYPPIDVWKNNGOPEPE GNVRTITPQDQDVTGTYFLYSLKAVDK ASWGRQDFGCAVMHEALHNHYT (SEQ ID NO: 68)</p>	EU372653	
Porcine Ig light chain constant region	<p>Ig kappa (CK) variant 1</p> <p>Ig kappa (CK) variant 2</p> <p>Ig lambda (CL) variant 1</p> <p>Ig lambda (CK) variant 2</p>	<p>APKTAPSVYPLAPCGRDTSQPNVALG GLASSYFPEPVTWNSGALTSVHT FPSVLQPSGLYLSSTMVTPASSLS KRYTONVNHPTATKVDLCVGRPCP CPGCEVAGPSVFIFPPKPKDILMSRTP EVTCTVVDVSDENFEVQFSWYVDGEE VHTAETRPKEQFNSTYRVVSVLPQH EDWLKKEFECKVNNDLPAPIRRI KAKGVRSPEVYTLPPAEELSKSVIT LTCLVKSIFPFIHVEWKNKPEPEN YRTITPQDEEDRTYFLYSLKAVDKAR WDHGETTECAVMHEALHNHYTKSIS KTQK* (SEQ ID NO: 70)</p>	<p>FP312898</p> <p>CU694848</p> <p>CU467669</p> <p>CU467599</p>	<p>http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=Porcine</p> <p>http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=Porcine</p> <p>http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=Porcine</p> <p>http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=Porcine</p>	<p>Schwartz J.C. et al. Immunogenetics, 64, 303-311 (2012). PMID: 22109540</p>

Species	Ig Domain		Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Water buffalo (Scientific Name: Bubalus bubalis)	Water buffalo Ig heavy chain constant region (CH1*CH3)	IgG1?	GAGCGGGGTGCACACCTTCCCGGCGGTCTCTAGTCC TCCGGGCTCTACTGCTGAGCAGACGGTGAACCGCC CCCGCAGCGCAGCAAAACCAAGGACACCTCACAAT CGTAGCCACCCCGCCAGCAGCACAAGGTGGACAAG GCTGTTGTTCCCCCATGCAGACCGAAACCGCTGATTG CTGCCACCCCTGAGCTCCCGGAGGACCGCTCTGTC TTCACTTCCCGCAGCAAAACCAAGGACACCTCACAAT CTCTGGAACCTCTGAGGTGACGTGTGTGGTGGAC GTGGGCCAGGATGACCCGAGGTGAAGTTCTCTGGT TCGTGACAGATGTGGAGGTAACACAGCCAGGACGAA GCCAAGAGAGGAGCGATTCAACAGCACCTACCGGTG GTACGGCCCTGCCCATCCAGCACAACGACTGGACTG GAGGAAGAGGATTCAAGTGCAAGGTCTACAATGAAGGC CTCCAGCCCGCATCGTGAGGACCATCTCCAGGACCA AAGGGCAGGCCCGGAGCCGCGAGGTGACGCTCTGGC CCCAACCCAGGACGAGCTCAGCAAAAGCAGGTGACG ATCAGTTGCTGATGGTCACTGGCTCTACCCAGACTACAT CGCGCTAGAGTGCAGAAAGATGGGGAGCCCTGAGTCA GAGGACAATATGGCAGCGCCCGCCCGCTGGACA GGGATGGCTCTACTTCTGTACAGCAGGCTCAGGGT GAACAAGAAGCTGGCAAGAAGGAGGCGCTACAGC TGTGTAGTGATGATGAGGC (SEQ ID NO: 73)	SGVHTFFPAVLQSSGLYLSSTVTPAS ATKSQTFITONVAHPASSTKVDKAVP PRPKPCDDCPPELPQGSVFIFPPK PKDITLISGTPEVTVCVVDVGHDDPEV KFSWFVDVDEVNTARTKPREEQFNSTY RVVSALPIQHNDWTGGKEFKVKVNEG LPAPIVRTISRTKGQAREPQVYVLAPP QDELSKSTVSITCMVTGFYPDYIAVEW QKDGQPESEDKYGTTPPQLDSGGSYF LYSRLRVNKNWSQEGGAYTCVVMHE (SEQ ID NO: 72)	NW_005690903	Not registered	None
		IgG2?	GCCTCCATCACAGCCCGAAAGTCTACCGTCTGACTTC TTCCCGGGGGAAGCTCCAGTCCAGTCTGAGCGCTG GGCTGCCTGGTCTCCAGCTACATGCCGAGCCGGTGA CCGTGACCTGGAACCTGGGTGCCCTGAAGAGCGCGGT GCACACCTTCCCGCGCGTCTTCACTGCTCTGGGCTC TACTCTCTCAGCAGCAGCGTGACCGCGCCCGCAGCG CCACAAAAGCCAGACCTTCACTGCAACGTAGCCAC CCCGCCAGCAGCAGCAAGGTGGACAAGGCTGTTGGT TCTCCAGTGAAGTGCAGAAAGTTCAGCGCTGTGTG AGGGGACCATCTGTTCTCATCTTCCCGCAAAACCAA AGACACCTGATGATCACAGGAATCCCGAGGTGCAT GTGTGGTGGTGGACGTGGCGCGGATAACCCGAGGT GCAGTTCTCTGGTTCGTGGGTGATGTGAGGTGCAC ACGGGCGAGTGAAGCCGAGAGGAGGACGTTCAACA GCACCTACCGGTGGTCAAGCAGCTGCCCATCCAGCA CAATGACTGGACTGGAGGAAGGAGTTCAAGTGAAG GTCAACACAAAGGCTCCAGCCCGCATCGTGAGGA CCATCTCCAGACCAAGGCGCAGCGCCGAGACCCCA GGTGTACGTCTGGCCCGCCCGCAGGAAGAGCTCAGC AAAGCACGGTCAGCTCACTTGCATGGTCACTGGCTT CTACCCAGCTACATCGCGCTGAGTGGCATAGAGACC GGCAGGCTGAGTCGGAGGACAAGTACCGCAGCAGCCC GCCCGAGCTGGACAGCGATGGCTCCTACTTCTGTAC AGCAGGCTCAAGGTGAACAAGAAGAGCTGGCAAGAAG GAGGCGCTCAGCGTGTGTAGTGATGATGAGGC (SEQ ID NO: 75)	ASITAPKVYPLTSRGETSSSTVTLGC LVSSYMPEPVTVTVNSGALKSGVHTF PAVLQSSGLYLSSTVTPASATKSQT FTCNVAHPASSTKVDITAVGFSDDCK FPKPCVVRGPFVIFPPKPKDITLMITGNP EVTVCVVDVGRDNPVQFSWFVGDVE VHTGRSKPREEQFNSTYRVVSTLPIQH NDWTGGKEFKVKVNNKGLPAPIVRTIS RTKGQAREPQVYVLAPPQELSKSTVS VTCMVTGFYPDYIAVEWHDRQAESED KYRTTPPQLDSGGSYFLYSLRVNKNWS WQEGGAYTCVVMHE (SEQ ID NO: 74)	NW_005766143		
		IgG3?	GCCTCCACCACAGCCCGAAAGTCTACCGTCTGGCAT CCAGCTGCGGGGACAGCTCCAGCTCCACCGTGACCTG GGGCTGCCTGGTCTCCAGCTACATGCCGAGCCGGTG ACCGTGACCTGGAACCTGGGTGCCCTGAAGAAGCGCG TGACACCTTCCCGCGCGTCCGGAGTCTCCGGGCT CTACTCTCTCAGACCATGGTGACATGCCACACGCA CCGAGGAACCCAGACCTTCACTGCAACGTAGCCCA CCCGCCAGCAGCACCAAGGTGGACACGGCTGTCACT GCAAGGCATCCGGTCCCGAAGACACCAAGAGACCTA TCATCTCTGTAACCCCGCAACCCAGGAGCCAGAGAT GAAAAGACACCCCTGCCAGTGTCCCAATGCCAGAAC TCTGGAGGACTGTCTGTCTCATCTTCCCGCAAAAC CCAGGACACCGCTCACAATCTCTGGAACGCCCGAGGT CAGCTGTGTGGTGGTGAAGTGGCCAGGATGACCC CAAGTGAGATTTGTCGTGCTGTGATGAGTGGAGG TGACACACAGCCAGGATGAAGCCAGAGAGGAGCAGTT CAACAGCACTACCGGTGGTCAAGCGCCTGCCATC CAGCACCAGGACTGGCTGCCGGAAAAGGAGTTCAAGT GCAAGGTCAACAACAAGGCTCCCGGCCCGCATGCT GAGGACCATCTCCAGGACCAAGGGCAGGCCCGGAG CCACAGGTGATGTCTGGCCCGCACCCGGGGAAGAGG TCAGCAAAAGACCGTCAAGCTCACTGCGTAAATCAC GGCTTCTACCCAGAGAGGTGACGTGGAGTGGCAGA GAAATGGGCGAGCTGAGTCAGAGGACAAGTACACAC GACCCACCCCGAGCTGACGCTGACGGCTCCTACTTC CTGTACAGCAGGCTCAGGCTGAACAGGAGCAGCTGG AGGAAGGAGACCATACAGCTGTGCAAGTGTGATGAA GCTTTACGGAATCACTACAAAGAGAAGCCCATCTCGAG GTCTCGGGTAAATGA (SEQ ID NO: 77)	ASTTAPKVYPLASSCGDTSSTVTLGC LVSSYMPEPVTVTVNSGALKNGVHTF PAVRQSSGLYLSMVTMTPTSTAGTG TFTCNVAHPASSTKVDITAVTARHPVP KTPETPIHPVRFPTGEPRDEKTPCGCP KOPELGLSVFIFPPKPKDITLISGTP EVTVCVVDVGDDPEVQFSWFVDDVE VHTARMKPREEQFNSTYRVVSALPIQH QDWLREKEFKVKVNNKGLPAPIVRTIS TKGQAREPQVYVLAPPRELSKSTLSL TCLITGFYPEDVDEWQRNGQPESEDK YHTTPPQLDADGSYFLYSLRVNRRSSW QEGDHYTCAVMHEALRNHYKEKPSRS PGK* (SEQ ID NO: 76)	NW_005784206		
	Water buffalo Ig light chain constant region (CL)	Ig lambda?	CAGCCCAAGTCGACCCCTGAGTCAACCTGTTCCAC CCTCCAGCGGAGGCTCAGCGCCAAAGGCCACCT GTTGTGCTCATCAGCACTTCTACCGGTGAGATGA CGGTGCCAGGAGGCGAGCGGACACCATCACCCG GAACGTGGAGACCAACCGGCTCCAAACAGAGCAAC AGCAAGTACCGCGCCAGAGCTACCTGAGCCTGACGG GCAGCGAGTGGAAATCGAAAGGCAATTACAGCTGCGA GGTCAAGCAGGAGGAGCAGCTGACAAGACAGGTG AAGCCCTCAGAGTGTCTTAG (SEQ ID NO: 79)	QPKSAPSVTLFPPSTEELSANKATLVC LISDFYPGSMYVARKADGSTITRNVETT RASKGNSKSYAASSYLSLTGSEWKS SYSCVTHEGSTVTKTVKPSSECS* (SEQ ID NO: 78)	NW_005690786	Not registered	None

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Human (Scientific Name: Homo sapiens)	Human Ig heavy chain constant region (CH1~CH3)	IgG4 variant 1 GAGTCCAAATATGGTCCCCCATGCCATCATGCCA GCACCTGAGTTCTCTGGGGGACCATCAGTCTTCTCTG TTCCCCCAAAACCCAAAGGACACTCTCATGATCTCG CGGACCCCTGAGGTACGTCAGTCGGTGGTGGACGTG AGCCAGGAAGAGCCCGAGGTCCAGTTCAACTGGTAC GTGGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGCGGGAGGAGCAGTTCACACGACGTAACCGTGTAC GTACGCGTCTCACCCTCTCGACCAAGGACTGGCTG AACGGCAAGGAGTACAAGTGCACAGGTCTCCAACAAA GGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAA GCCAAAGGGCAGCCCGAGAGGCCACAGGTGTACACC CTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAG GTACAGCTGACCTTGCGTGGTCAAAGAGCTTCTACCCG AGCCACATCCCGTGGAGTGGAGGACAATGGCAAGACAAG CCGCGGGAGGAGCAGTTCACACGACGTAACCGTGTG GTACAGCTCTCACCCTCGTGCACAGGACTGGCTG AACGGCAAGGAGTACAAGTGCACAGGTCTCCAACAAA GGCCTCCCGTCTCCATCGAGAAAACCATCTCCAACAAA GGCCTCCCGTCTCCATCGAGAAAACCATCTCCAACAAA GCCAAAGGGCAGCCCGAGGAGCAGTTCACCGTGTAC GACTCCGACGGTCTCTTCTCTCTACAGCAGGCTA ACCGTGGACAAGGAGCAGGTGGCAGGAGGGGAATGTC TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC CACTACACACAGAAGAGGCTCTCCCTGTCTCTGGGT AAATGA (SEQ ID NO: 14)	ESKYGPPCPSCPAEFLGGPSVFLFPP KPKDGLMSRTPEVT VQFNWYVDGVEVHNKTKPREEQFNS TYRVVSVLTVLHDLWLNKKEYCKKVS NKGLPSSIEKTISKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIA VWESNGLQPNYNYKIIHPVLDSGGSFL YSRLTVDKSRWQEGNVFSCSMVHEAL HNHYTQKLSLSLQK* (SEQ ID NO: 12)	K01316	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=human&group=IGHC	Ellison J. et al., DNA, 1, 11-18 (1981). PMID: 6299662
	IgG4 variant 2 GAGTCCAAATATGGTCCCCGTGCCATCATGCCA GCACCTGAGTTCTCTGGGGGACCATCAGTCTTCTCTG TTCCCCCAAAACCCAAAGGACACTCTCATGATCTCG CGGACCCCTGAGGTACGTCAGTCGGTGGTGGACGTG AGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGCGGGAGGAGCAGTTCACACGACGTAACCGTGTG GTACAGCTCTCACCCTCGTGCACAGGACTGGCTG AACGGCAAGGAGTACAAGTGCACAGGTCTCCAACAAA GGCCTCCCGTCTCCATCGAGAAAACCATCTCCAACAAA GCCAAAGGGCAGCCCGAGGAGCAGTTCACCGTGTAC GACTCCGACGGTCTCTTCTCTCTACAGCAGGCTA ACCGTGGACAAGGAGGAGTGGCAGGAGGGGAATGTC TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC CACTACACAGAGAAGAGGCTCTCCCTGTCTCTGGGT AAATGA (SEQ ID NO: 81)	ESKYGPPCPSCPAEFLGGPSVFLFPP KPKDGLMSRTPEVT VQFNWYVDGVEVHNKTKPREEQFNS TYRVVSVLTVHDLWLNKKEYCKKVS NKGLPSSIEKTISKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIA VWESNGLQPNYNYKITPPVLDSGGSFL YSRLTVDKSRWQEGNVFSCSMVHEAL HNHYTQKLSLSLQK* (SEQ ID NO: 80)	AJ001563		Brusco A. et al., Eur. J. Immunogenet., 25, 349-355 (1998). PMID: 9805657	
	IgG4 variant 3 GCACCTGAGTTCTCTGGGGGACCATCAGTCTTCTCTG TTCCCCCAAAACCAAGGACACTCTCATGATCTCG CGGACCCCTGAGGTACGTCAGTCGGTGGTGGACGTG AGCCAGGAAGAGCCCGAGGTCCAGTTCAACTGGTAC GTGGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGCGGGAGGAGCAGTTCACACGACGTAACCGTGTG GTACGCGTCTCACCCTCTCGACCAAGGACTGGCTG AACGGCAAGGAGTACAAGTGCACAGGTCTCCAACAAA GGCCTCCCGTCTCCATCGAGAAAACCATCTCCAACAAA GCCAAAGGGCAGCCCGAGAGGCCACAGGTGTACACC CTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAG GTACAGCTGACCTTGCGTGGTCAAAGAGCTTCTACCCG AGCCACATCCCGTGGAGTGGAGGACAATGGCAAGACAAG CCGCGGAGAACACTACAAGCAGCAGCTCCCGTGTG GACTCCGACGGTCTCTTCTCTCTACAGCAAGCTC ACCGTGGACAAGCAGCAGTGGCAGGAGGGGAAGCTG TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC CACTACACGACAGAAGAGGCTCTCCCTGTCTCTGGGT AAATGA (SEQ ID NO: 83)	APEFLGGPSVFLFPPKPKDGLMSRTPE VTCVVVDVSQEDPEVQFNWYVDGVEV HNKTKPREEQFNSTYRVVSVLTVLHQ DNLNKGKEYCKVSNKGLPSSIEKTIS KAGQPREPQVYTLPPSQEFMTKNQVSI TCLVKGFYPSDIAVEWESNGLQPNYNY KITPPVLDSGGSFFLYSKLTVDKSRWQ EGNVFSCSMVHEALHNHYTQKLSLSLQ K* (SEQ ID NO: 82)	AJ001564			
Human Ig light chain constant region	Ig kappa (CK)	ACTGTGGCTGCACCATCTGTCTTCACTTCCCGCCA TCTGATGAGCAGTTGAAATCTGTATCCAGAGAGGCGC AAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACCTCCAGGAGAGTGTACAGAGAGGAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACGCTGACG CTGAGCAAAAGCAGACTACGAGAAGACAAAGTCTAC GCCTGGGAAGTCAACCATCAGGGCTGAGCTCGCCC GTCAAGAAAGAGCTTCAACAGGGGAGAGTGTATG (SEQ ID NO: 13)	TVAAPSVFIFPPSDEQLKSGTASVCL LNNFYPREAKVQWKVDNALQSGNSQ E SVTEQDSKDSYSLSSLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11)	X96754	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=human&group=IGKC	None

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Bovine (Scientific Name: Bos taurus)	Ig heavy chain constant region (CH1 ⁺ CH3)	IgG1 variant 1 GCCTCCACACAGCCGCGGAAAGTGTACCCCTGTGAGTCTTGCTGGCGGAGACCTGACAGCTGCACCGTGCCTGGCTGCTGCTCCAGCTACATGCCCGGCGGTGACCGCTGCACTGGAACCTCGGTCGCCCTGAAGAGCGGCGTGCACACCTTCGCCGGCTGTCCCTGACCTCCGGGGCTGTACTCTCTCAGCAGCATGGTGACCGCTCGCGCGCAGAGCTCAGGACAGACCTTCAGCTGGAACGATAGCCAGCGCGGAGCAGCAGCAAGTGGACAGAGCTGTGATGCTCCACATGCAAGCAGCAACCCCTGTGACTGTGCCACCCCGCTGAGTCCCGGAGAGCCGCTGCTTCTTATCTGCCACCGGAACCCAGGACACCCCTCACAATCTCGGGAACGCCGAGGTCACTGTGTTGGTGGAGCTGGGCGACATGACCCCGAGGTGAAGTTCTCTGTTCTCTGACAGAGTGGAGSTAATAACACGACGACAGCAAGCCGACAGAGGAGAGCTTCAACAGCAACCTACCCGGTGTGTCA GCGCCCTGCGCATCCAGCAGCAGGACTGGACTGGAGGAAGAGGTTCAAGTGGAAAGTGCACAACGAAAGCGTCCGGGCGCGCA TCGTGAGGACCATCTCCAGGACCAAGAGCGCCGCGCGGAGGCGCAGCTGTATGTCTGGCCCGCCAGGACAGAGGTGACGA AAGACACGCTGACCGTCACTGCATGGTCAACGACTTCTACCC AGACTACATCGCGCTGGAGTGGCAGGAAGAACGGGACGCTGCA GTCCGAGGACAAATACCGCAGCAGCGCCCGCCAGCTGGACGCG CAGAGCTGCTTACTTCTGTACAGCAGAGCTCAAGGTGGACAGG AACACCTGGCAGGAGGACAGCTACAGCTGTGTGGTGATG CACGAGGCCCTGCACAATCACTACAGCGAAGTCCACCTCTA AGTCTGGGGTAAATGA (SEQ ID NO: 92)	ASTTAPKVIYPLSSCCGDKSSSTVTLGLVSSYMPEVTVWNSGALKSGVHTFPALVQSSGLYSLSMVTVPGSTG GTTCTCNVHAPASSTKVKDAVPTKCPSPDCDCCPPE LPFGSPVFPPKPKDOLLTISGPEVTCVVVDVGHDDPE VKFSWFVDDVEVNTATKPRPEQFNSTYRVVLSALRQH QDWTKGKFKCKVHNEGLPAPVIRTSIRTKGPAREPQV YVLAAPPQELSKSVLSLTCMVTSPFYDIAVEWQRNG PESEKYGITPPQLDADSSYFLSKLRVDRNSWQEGDT YTCVMEALHNHYTKSTSKSAGK+ (SEQ ID NO: 84)	X62916	http://www.imgt.org/IMGTre perture/index.php?function=ousGenes&report=&selec=able&species=bovine&group3 GHG	Symons D.B. et al., J. Immunogenetics, 14, 273-283 (1987). PMID: 3141517 Symons D.B. et al., Mol. Immunol., 26, 841-850 (1989). PMID: 2513487 Kacsokovics I. and Butler J.E., Mol. Immunol., 33, 189-195 (1996). PMID: 8649440 Raburani H. et al., Immunogenetics, 46, 326-331 (1997). PMID: 9218535 Saint S.S. et al., Scand. J. Immunol., 65, 32-8 (2007). PMID: 17212764
	IgG1 variant 2	GCCTCCACACAGCCGCGGAAAGTGTACCCCTGTGAGTCTTGCTGGCGGAGCAAGTCCAGCTGCACCGTGCCTGGCTGCTGCTCCAGCTACATGCCCGGCGGTGACCGTCACTGGAACCTCGGTCGCCCTGAAGAGCGGCGTGCACACCTTCGCCGGCTGCTTCACTCTCCGGGCTGTACTCTCTCAGCAGCATGGTGACCGTCCCGCGCAGCAGCTCAGGACAGACCTTCACCTGGAACGTGAC CCACCGCGCGCAGCAGCAGCAAGGTGGACAAGGCTGTGATCC CACATGGAACCAATCAACCTGTGACTGTGCCACCGCCCTGAG CTCCCGGAGBAGCCCTGTGCTGTGATGTGCCACGGAAGCCCA AGGACACCTCGCAATCTCGGGAACGCCGAGGTCACTGTGTTGGTGGTGGAGCTGGGCGACATGACCCCGAGGTGAAGTTCTCTGCTGGTGGAGCGCTGGAGGTAACACGACCCAGCAGCA AGCCGAGAGGAGGAGCAGTTCAACAGCAACCTACCGCGTGTGTCA GCGGCTTGGCATTCACGACACAGGACTGGACTGGAGGAAGAAG AGTTCAAGTGGAAAGTGCACAACGAAAGCGTCCGGGCGCGCA TCGTGAGGACCATCTCCAGGACCAAGAGCGCGCGCGGAGCGC GCGAGCTGTATGTCTCGGCCCGCCAGGACAGAGGTCTGACGA AAGCAGCGTGCAGCTCACTGATGGTCAACAGCTTCTATCCCA AGACTACATCGCGCTGGAGTGGCAGGAAGAACGGGACGCTGCA GTCCGAGGACAAATACCGCAGCAGCCCGCCAGCTGGACGCG CAGCAGCTCCTACTTCTGTACAGCAGAGCTCAGGTTGGACAGG AACACCTGGCAGGAGGAGACACCTACAGCTGTGTGGTGATG CACGAGGCCCTGCACAATCACTACAGCGAAGTCCACCTCTA AGTCTGGGGTAAATGA (SEQ ID NO: 93)	ASTTAPKVIYPLSSCCGDKSSSTVTLGLVSSYMPEVTVWNSGALKSGVHTFPALVQSSGLYSLSMVTVPGSTG GTTCTCNVHAPASSTKVKDAVPTKCPSPDCDCCPPE LPFGSPVFPPKPKDOLLTISGPEVTCVVVDVGHDDPE VKFSWFVDDVEVNTATKPRPEQFNSTYRVVLSALRQH QDWTKGKFKCKVHNEGLPAPVIRTSIRTKGPAREPQV YVLAAPPQELSKSVLSLTCMVTSPFYDIAVEWQRNG PESEKYGITPPQLDADSSYFLSKLRVDRNSWQEGDT YTCVMEALHNHYTKSTSKSAGK+ (SEQ ID NO: 85)	X176101 (M29278)		
	IgG1 variant 3	GCCTCCACACAGCCGCGGAAAGTGTACCCCTGTGAGTCTTGCTGGCGGAGCAAGTCCAGCTGCACCGTGCCTGGCTGCTGCTCCAGCTACATGCCCGGCGGTGACCGTCACTGGAACCTCGGTCGCCCTGAAGAGCGGCGTGCACACCTTCGCCGGCTGCTTCACTCTCCGGGCTGTACTCTCTCAGCAGCATGGTGACCGT CGCGCGCAGAGCTCAGGACAGAGCTTCACCTGCAACGCTGACGCT AGCCCAACCCCGCGCAGCAGCAGAGTGGACAAGGCTGTTGA TCCAGATGCAAAACCAACCTGTGACTGTGCCACCGCTGAGTCT CCGCTGGAGACCCCTGTGCTTCTATCTGCCACCGGAACCCCA AGGACACCTCGAATCTCGGGAACCGCTGAGCGAGTCACTGTG TGGTGGTGGAGCTGGAGGTAACACGACCCAGCAGCA AGCCGAGAGGAGGAGCAGTTCAACAGCAACCTACCGCGTGTGTCA GCGGCTTGGCATTCACGACACAGGACTGGACTGGAGGAAGAAG AGTTCAAGTGGAAAGTGCACAACGAAAGCGTCCGAGCCDCCAT CCGTGAGGACCATCTCCAGGACCAAGAGCGCGCGCGGAGCGC GCGAGGTGTATGTCTCGGCCCGCCAGGAGAGGACTCAGCAA AAGCAGCGTGCAGCTCACTGCATGGTCAACAGCTTCTACCCA GACTACATCGCGCTGGAGTGGCAGAGAATATGGGACGCTGAG TCAGAGGAAGATACCGCAGCAGCCCTCCCAAGCTGGACGCGC GACGCTGTGATGTCTGTCACAGAGGCTGAGGTGTGACAGG AACACCTGGCAGGAGGAGACACCTACAGCTGTGTGGTGATG CACGAGGCCCTGCACAATCACTACAGCGAAGTCCACCTCTA AGTCTGGGGTAAATGA (SEQ ID NO: 94)	ASTTAPKVIYPLSSCCGDKSSSTVTLGLVSSYMPEVTVWNSGALKSGVHTFPALVQSSGLYSLSMVTVPGSTG GTTCTCNVHAPASSTKVKDAVDRCKTDCDCCPPE LPFGSPVFPPKPKDOLLTISGPEVTCVVVDVGHDDPE VKFSWFVDDVEVNTATKPRPEQFNSTYRVVLSALRQH QDWTKGKFKCKVHNEGLPAPVIRTSIRTKGPAREPQV YVLAAPPQELSKSVLSLTCMVTSPFYDIAVEWQRNG PESEKYGITPPQLDADSSYFLSKLRVDRNSWQEGDT YTCVMEALHNHYTKSTSKSAGK+ (SEQ ID NO: 86)	S82409		
	IgG2 variant 1	GCCTCCACACAGCCGCGGAAAGTGTACCCCTGTGGCATCCAGCTGGCGGAGACCTGACAGCTGCACCGTGCCTGGCTGCTGCTCCAGCTACATGCCCGGCGGTGACCGTCACTGGAACCTCGGTCGCCCTGAAGAGCGGCGTGCACACCTTCGCCGGCTGTCCCTGACCTCCGGGGCTGTACTCTCTCAGCAGCATGGTGACCGT CGCGCGCAGAGCTCAGGACAGACCTTCAGCTGGAACGATAGCCCAACCCCGCGCAGCAGAGTGGACAAGGCTGTTGA TCCAGATGCAAAACCAACCTGTGACTGTGCCACCGCTGAGTCT CCGCTGGAGACCCCTGTGCTTCTATCTGCCACCGGAACCCCA AGGACACCTCGAATCTCGGGAACCGCTGAGCGTGGTGTGA GCTGGGCGACGATTAACCCGAGGTGACGTTCTCTGTGTTGAT GATGACGCTGGAGCTGGCAGAGGCGAGGTGGACGCAAGGA GAGACAGTTCAACGACGACGTACCCGCTGGTCAAGCGCTGCC CATCCAGCAGCAGGACTGGACTGGAGGAAGAAGGTCAAGTG CAAAGTCAACACAAGGCGCTCTCGGCCCGCATGTTGAGGATC ATCTCCAGAGCAAAAGGCGCGCGCGCGAGCGGAGCTGTAT GTCTCGAGCCACCCAGGAGAGAGCTGAGCAAGACGCTCT AGGCTCAACCTGCATGGTCAACCGGCTTCTACCCAAAGATGTAG CCGTGGAGTGGCAGAGAACCGCGCAGCTGAGTCGGAGGACA AGTACCGGACACCGCCCGCCAGCTGGACACGACCGGCTCCT ACTTCTGTACAGCAGCTCAGGTTGGACAGACAGCTGGCA GAGAGAGCCCTACACAGTGTGTGGTGATGACGAGGCCCT GCACAATCACTCAGAACTCCACTTAAAGTCTTCGGGCT AAATGA (SEQ ID NO: 95)	ASTTAPKVIYPLSSCGDTSSTVTLGLVSSYMPEVTVWNSGALKSGVHTFPALVQSSGLYSLSMVTVPASSG GTTCTCNVHAPASSTKVKDAVQSDSKHNDPCVRE PSVFIFPPKPKDLMITGFNFTCVVVDVHNDPEVFS WFVDDVEHTARSKPREQFNSTYRVVLSALRQH QDWTKGKFKCKVHNEGLPAPVIRTSIRTKGPAREPQV DLP PKEELSKSVLSLTCMVTSPFYDIAVEWQRNG KYRTTPPQLDTRSYFLSKLRVDRNSWQEGDTCV MEALHNHYMKSTSKSAGK+ (SEQ ID NO: 87)	S82407		

(Continued)

[illegible]

The amino acid sequences as shown in SEQ ID NOS: 4, 3, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 12, 80, 82, 84-91, 100, 102 and 11 may have deletion(s), substitution(s) or addition(s) of one or several (e.g., up to five, about 10 at the most) amino acids. Even when such mutations have been introduced, the resulting amino acid sequences are capable of having the function as the constant region of Ig heavy chain or light chain.

Although the constant region of wild-type human IgG1 has ADCC activity and CDC activity, it is known that these activities can be reduced by introducing amino acid substitutions and deletions into specific sites. In the case of animals other than human where the constant region of an immunoglobulin equivalent to human IgG4 has not been identified, mutations may be introduced into the relevant region of an immunoglobulin equivalent to human IgG1 so that the resultant constant region with reduced ADCC activity and CDC activity can be used.

The present invention provides an artificial genetic DNA comprising (a') a DNA encoding a light chain comprising a light chain variable region (VL) containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region (CL) of an antibody of an animal other than rat and (b') a DNA encoding a heavy chain comprising a heavy chain variable region (VH) containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region (CH) of an antibody of an animal other than rat. The present invention also provides a DNA encoding a light chain comprising a VL containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the CL of an antibody of an animal other than rat (i.e., the DNA of (a') above). Further, the present invention also provides a DNA encoding a heavy chain comprising a VH containing CDR1 having GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the CH of an antibody of an animal other than rat (i.e., the DNA of (b') above).

For (a) a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino

acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat; and (b) a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat, reference should be had to the foregoing description. The DNA of (a') is a DNA (gene) encoding the light chain of (a); and the DNA of (b') is a DNA (gene) encoding the heavy chain of (b). An artificial genetic DNA comprising the DNA of (a') and the DNA of (b') may be synthesized on commercial synthesizer. Restriction enzyme recognition sites, KOZAK sequences, poly-A addition signal sequences, promoter sequences, intron sequences or the like may be added to the artificial genetic DNA.

The present invention also provides a vector comprising the above-mentioned artificial genetic DNA.

As the vector, Escherichia coli-derived plasmids (e.g., pBR322, pBR325, pUC12 or pUC13); Bacillus subtilis-derived plasmids (e.g., pUB110, pTP5 or pC194), yeast-derived plasmids (e.g., pSH19 or pSH15); bacteriophages such as λ phage; animal viruses such as retrovirus or vaccinia virus; or insect pathogen viruses such as baculovirus may be used. In the Examples described later, pDC6 (Japanese Patent No. 5704753, US Patent 9096878, EU Patent 2385115, Hong Kong (China) patent HK1163739 and Australia Patent 2009331326) was used.

The vector may also comprise promoters, enhancers, splicing signals, poly-A addition signals, intron sequences, selection markers, SV40 replication origins, and so forth.

The present invention also provides a host cell transformed by the above vector. It is possible to prepare the anti-PD-L1 antibody of the invention by culturing the host cell and collecting the antibody of interest from the resultant culture. Therefore, the present invention also provides a method of preparing an antibody, comprising culturing the above-described host cell and collecting the anti-PD-L1 antibody of the invention from the culture. In the method of the present invention for preparing an antibody, a vector incorporating an artificial genetic DNA comprising a DNA encoding the light chain and a DNA encoding the heavy chain may be transfected into a host cell. Alternatively, a vector incorporating a DNA encoding the light chain and a vector incorporating a DNA encoding the heavy chain may be co-transfected into a host cell.

Examples of the host cell include, but are not limited to, bacterial cells (such as

Escherichia bacteria, Bacillus bacteria or Bacillus subtilis), fungal cells (such as yeast or Aspergillus), insect cells (such as S2 cells or Sf cells), animal cells (such as CHO cells, COS cells, HeLa cells, C127 cells, 3T3 cells, BHK cells or HEK 293 cells) and plant cells. Among these, CHO-DG44 cell (CHO-DG44(dfhr⁻)) which is a dihydrofolate reductase deficient cell is preferable.

Introduction of a recombinant vector into a host cell may be performed by the methods disclosed in Molecular Cloning 2nd Edition, J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989 (e.g., the calcium phosphate method, the DEAE-dextran method, transfection, microinjection, lipofection, electroporation, transduction, scrape loading, the shotgun method, etc.) or by infection.

The resultant transformant may be cultured in a medium, followed by collection of the anti-PD-L1 antibody of the present invention from the culture. When the antibody is secreted into the medium, the medium may be recovered, followed by isolation and purification of the antibody from the medium. When the antibody is produced within the transformed cells, the cells may be lysed, followed by isolation and purification of the antibody from the cell lysate.

Examples of the medium include, but are not limited to, OptiCHO medium, Dynamis medium, CD CHO medium, ActiCHO medium, FortiCHO medium, Ex-Cell CD CHO medium, BalanCD CHO medium, ProCHO 5 medium and Cellvento CHO-100 medium.

The pH of the medium varies depending on the cell to be cultured. Generally, a pH range from 6.8 to 7.6 is used; mostly, a pH range from 7.0 to 7.4 is appropriate.

When the cell to be cultured is CHO cells, culture may be performed by methods known to those skilled in the art. For example, it is usually possible to perform culturing in a gas-phase atmosphere having a CO₂ concentration of 0-40%, preferably 2-10%, at 30-39°C, preferably around 37°C.

The appropriate period of culture is usually from one day to three months, preferably from one day to three weeks.

Isolation and purification of the antibody may be performed by known methods. Known isolation/purification methods which may be used in the present invention include, but are not limited to, methods using difference in solubility (such as salting-out or solvent precipitation); methods using difference in molecular weight (such as dialysis, ultrafiltration, gel filtration or SDS-polyacrylamide gel electrophoresis); methods using difference in electric charge (such as ion exchange chromatography); methods using specific affinity (such as affinity chromatography); methods using difference in hydrophobicity (such as reversed phase high performance liquid chromatography); and methods using difference in isoelectric

point (such as isoelectric focusing).

The anti-PD-L1 antibody of the present invention may be used as an antibody drug for animals or human. Therefore, the present invention provides a pharmaceutical composition comprising the above-described anti-PD-L1 antibody as an active ingredient.

The pharmaceutical composition of the present invention may be used for prevention and/or treatment of cancers and/or infections. Examples of cancers and/or infections include, but are not limited to, neoplastic diseases (e.g., malignant melanoma, lung cancer, gastric cancer, renal cancer, breast cancer, bladder cancer, esophageal cancer, ovarian cancer and the like), leukemia, Johne's disease, anaplasmosis, bacterial mastitis, mycotic mastitis, mycoplasma infections (such as mycoplasma mastitis, mycoplasma pneumonia or the like), tuberculosis, *Theileria orientalis* infection, cryptosporidiosis, coccidiosis, trypanosomiasis and leishmaniasis.

The anti-PD-L1 antibody of the present invention may be dissolved in buffers such as PBS, physiological saline or sterile water, optionally filter-sterilized with a filter or the like, and then administered to animal subjects (including human) by injection. To the solution of this antibody, additives (such as coloring agents, emulsifiers, suspending agents, surfactants, solubilizers, stabilizers, preservatives, antioxidants, buffers, isotonicizing agents, pH adjusters and the like) may be added. As routes of administration, intravenous, intramuscular, intraperitoneal, subcutaneous or intradermal administration and the like may be selected. Transnasal or oral administration may also be used.

The dose and the number of times and frequency of administration of the anti-PD-L1 antibody of the present invention may vary depending on the symptoms, age and body weight of the animal subject, the method of administration, the dosage form and so on. For example, 0.1-100 mg/kg body weight, preferably 1-10 mg/kg body weight, per adult animal may usually be administered at least once, at such a frequency that enables confirmation of the desired effect.

While the pharmaceutical composition of the present invention may be used alone, it may be used in combination with surgical operations, radiation therapies, other immunotherapies such as cancer vaccine, or molecular target drugs. Synergistic effect can be expected from such combinations.

EXAMPLES

Hereinbelow, the present invention will be described in more detail with reference to the following Examples. However, the present invention is not limited to these Examples.

[Example 1] Rat-Canine Chimeric Anti-PD-L1 Antibody

1. Introduction

Programmed cell death 1 (PD-1), an immunoinhibitory receptor, and its ligand programmed cell death ligand 1 (PD-L1) are molecules identified by Prof. Tasuku Honjo et al., Kyoto University, as factors which inhibit excessive immune response and are deeply involved in immunotolerance. Recently, it has been elucidated that these molecules are also involved in immunosuppression in tumors. In the subject Example, for the purpose of establishing a novel therapy for canine neoplastic diseases, a chimeric antibody gene was prepared in which a variable region gene of a rat anti-bovine PD-L1 monoclonal antibody (4G12) capable of inhibiting the binding of canine PD-1 to PD-L1 was linked to a constant region gene of a canine immunoglobulin (IgG4). The resultant chimeric antibody gene was introduced into Chinese hamster ovary cells (CHO cells), which were cultured to produce a rat-canine chimeric anti-PD-L1 antibody c4G12. The effect of this chimeric antibody was confirmed *in vitro* and *in vivo*.

2. Materials and Methods

2.1 Bovine PD-L1 Monoclonal Antibody Producing Cells

The nucleotide sequence of bovine PD-L1 was identified (Ikebuchi R, Konnai S, Shirai T, Sunden Y, Murata S, Onuma M, Ohashi K. Vet Res. 2011 Sep 26;42:103). Based on the sequence information, a recombinant bovine PD-L1 was prepared. Rat was immunized with this recombinant protein to prepare a rat anti-bovine PD-L1 antibody (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology. 2014 Aug;142(4):551-61; Clone 4G12 which would later serve as the variable region of the canine chimeric antibody of interest is described in this article.)

2.2 Identification of Full-Length Canine PD-1 and PD-L1 Genes

To determine the full lengths of canine PD-1 and PD-L1 cDNAs, PCR primers were first designed based on the putative nucleotide sequences of canine PD-1 and PD-L1 already registered at The National Center for Biotechnology Information (NCBI) (GenBank accession number; XM_543338 and XM_541302). Briefly, primers to amplify the inner sequence of the open reading frame (ORF) of each gene were designed (cPD-1 inner F and R, cPD-L1 inner F and R), and PCR was performed. For the amplified products, nucleotide sequences were determined with a capillary sequencer according to conventional methods. Further, to determine the nucleotide sequences of full-length PD-1 and PD-L1 cDNA, primers (cPD-1 5' GSP and 3' GSP; cPD-L1 5' GSP and 3' GSP) were designed based on the canine PD-1 and PD-L1 cDNA sequences determined above. 5'-RACE and 3'-RACE were

then performed using the 5'-RACE system for rapid amplification of cDNA ends and 3'-RACE system for rapid amplification of cDNA ends (Invitrogen), respectively. The resultant gene fragments of interest were sequenced as described (Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S, Ohashi K. PLoS One. 2014 Jun 10;9(6):e98415).

Primer (cPD-1 inner F): AGGATGGCTCCTAGACTCCC (SEQ ID NO: 21)

Primer (cPD-1 inner R): AGACGATGGTGGCATACTCG (SEQ ID NO: 22)

Primer (cPD-L1 inner F): ATGAGAATGTTTAGTGTCTT (SEQ ID NO: 23)

Primer (cPD-L1 inner R): TTATGTCTCTTCAAATTGTATATC (SEQ ID NO: 24)

Primer (cPD-1 5'GSP): GTTGATCTGTGTGTTG (SEQ ID NO: 25)

Primer (cPD-1 3'GSP): CGGGACTTCCACATGAGCAT (SEQ ID NO: 26)

Primer (cPD-L1 5'GSP): TTTTAGACAGAAAGTGA (SEQ ID NO: 27)

Primer (cPD-L1 3'GSP): GACCAGCTCTTCTTGGGGAA (SEQ ID NO: 28)

2.3 Construction of Canine PD-1 and PD-L1 Expressing COS-7 Cells

For preparing canine PD-1-EGFP and PD-L1-EGFP expression plasmids, PCR was performed using a synthesized beagle PBMC-derived cDNA as a template and primers designed by adding *Xho*I and *Bam*HI recognition sites (PD-1) and *Bgl*II and *Eco*RI recognition sites (PD-L1) on the 5' side (cPD-1-EGFP F and R; cPD-L1-EGFP F and R). The resultant PCR products were digested with *Xho*I (Takara) and *Bam*HI (Takara) (PD-1) and with *Bgl*II (New England Biolabs) and *Eco*RI (Takara) (PD-L1), and then purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics), followed by cloning into pEGFP-N2 vector (Clontech) treated with restriction enzymes in the same manner. The resultant expression plasmids of interest were extracted with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmids are designated as pEGFP-N2-cPD-1 and pEGFP-N2-cPD-L1.

Primer (cPD-1-EGFP F): CCGCTCGAGATGGGGAGCCGGCGGGGGCC (SEQ ID NO: 29)

Primer (cPD-1-EGFP R): CGCGGATCCTGAGGGGCCACAGGCCGGGTC (SEQ ID NO: 30)

Primer (cPD-L1-EGFP F): GAAGATCTATGAGAATGTTTAGTGTC (SEQ ID NO: 31)

Primer (cPD-L1-EGFP R): GGAATTCTGTCTCTTCAAATTGTATATC (SEQ ID NO: 32)

COS-7 cells were subcultured at a density of 5×10^4 cells/cm² in 6-well plates, and then cultured overnight in RPMI 1640 medium containing 10% inactivated fetal bovine serum and 0.01% L-glutamine at 37°C in the presence of 5% CO₂. The pEGFP-N2-cPD-1,

pEGFP-N2-cPD-L1 or pEGFP-N2 (negative control) was introduced into COS-7 cells at 0.4 $\mu\text{g}/\text{cm}^2$ using Lipofectamine 2000 (Invitrogen). The cells were cultured for 48 hours (cPD-1-EGFP expressing cell and cPD-L1-EGFP expressing cell). In order to confirm the expression of canine PD-1 and PD-L1 in the thus prepared expressing cells, intracellular localization of enhanced green fluorescent protein (EGFP) was visualized with an inverted confocal laser microscope LSM700 (ZEISS) (Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S, Ohashi K. PLoS One. 2014 Jun 10;9(6):e98415).

2.4 Construction of Recombinant Canine PD-1, PD-L1 and CD80

In order to amplify the extracellular regions of canine PD-1, PD-L1 and CD80 estimated from their putative amino acid sequences, primers were designed. Briefly, primers having an *NheI* or *EcoRV* recognition sequence (PD-1 and PD-L1) added on the 5' side (cPD-1-Ig F and R; cPD-L1-Ig F and R) or having an *EcoRV* or *KpnI* (CD80) recognition sequence added on the 5' side (cCD80-Ig F and R) were designed. PCR was performed using a synthesized beagle PBMC-derived cDNA as a template. The PCR products were digested with *NheI* (Takara) and *EcoRV* (Takara) or with *EcoRV* (Takara) and *KpnI* (New England Biolabs) and purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics). The thus purified DNAs were individually cloned into pCXN2.1-Rabbit IgG Fc vector (Niwa et al., 1991; Zettlmeissl et al., 1990; kindly provided by Dr. T. Yokomizo, Juntendo University Graduate School of Medicine, and modified in the inventors' laboratory) treated with restriction enzymes in the same manner. The expression plasmids were purified with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmids are designated as pCXN2.1-cPD-1-Ig, pCXN2.1-cPD-L1-Ig and pCXN2.1-cCD80-Ig, respectively.

Primer (cPD-1-Ig F): CGCGGCTAGCATGGGGAGCCGGCGGGGGGCC (SEQ ID NO: 33)

Primer (cPD-1-Ig R): CGCGGATATCCAGCCCCTGCAACTGGCCGC (SEQ ID NO: 34)

Primer (cPD-L1-Ig F): CGCGGCTAGCATGAGAATGTTTAGTGTCTT (SEQ ID NO: 35)

Primer (cPD-L1-Ig R): CGCGGATATCAGTCCTCTCACTTGCTGGAA (SEQ ID NO: 36)

Primer (cCD80-Ig F): CGCGGATATCATGGATTACACAGCGAAGTG (SEQ ID NO: 129)

Primer (cCD80-Ig R): CGGGGTACCCAGAGCTGTTGCTGGTTAT (SEQ ID NO: 130)

These expression vectors were individually transfected into Expi293F cells (Life Technologies) to obtain a culture supernatant containing a recombinant Ig fusion protein. The recombinant protein produced was purified from the supernatant with Ab Capcher Extra (Protein A mutant; ProteNova). After buffer exchange with phosphate-buffered physiological

saline (PBS; pH 7.4) using PD-MidiTrap G-25 (GE Healthcare), each recombinant protein was stored at -30°C until use in experiments (cPD-1-Ig, cPD-L1-Ig and cCD80-Ig). The concentration of each protein was measured with Pierce BCA Protein Assay Kit (Thermo Fisher Scientific) before use in subsequent experiments.

2.5 Identification of Rat Anti-bovine PD-L1 Monoclonal Antibody Showing Cross-reactivity with Canine PD-L1

In order to identify rat anti-bovine PD-L1 monoclonal antibody showing cross-reactivity with canine PD-L1, flow cytometry was performed using the anti-bovine PD-L1 antibody prepared in 2.1 above. The anti-bovine PD-L1 antibody ($10\text{ }\mu\text{g/ml}$) was reacted with 2×10^5 - 1×10^6 cells at room temperature for 30 min. After washing, the anti-bovine PD-L1 antibody was detected with allophycocyanine-labeled anti-rat Ig goat antibody (Beckman Coulter). FACS Verse (Becton, Dickinson and Company) was used for analysis. As negative controls, rat IgG2a (κ) isotype control (BD Biosciences), rat IgG1 (κ) isotype control (BD Biosciences) and rat IgM (κ) isotype control (BD Biosciences) were used. For every washing operation and dilution of antibodies, 10% inactivated goat serum-supplemented PBS was used (Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S, Ohashi K. PLoS One. 2014 Jun 10;9(6):e98415 which is an article describing the use of three bovine PD-L1 monoclonal antibodies: 4G12 (Rat IgG2a (κ)), 5A2 (Rat IgG1 (κ)) and 6G7 (Rat IgM (κ)).

2.6 Selection Test of Variable Region for Establishment of Rat-Canine Chimeric Anti-PD-L1 Antibody

Out of 10 clones of rat anti-bovine PD-L1 monoclonal antibody which showed cross-reactivity with canine PD-L1, 4G12 (Rat IgG2a (κ)), 5A2 (Rat IgG1 (κ)) and 6G7 (Rat IgM (κ)) were selected and check was made to see whether these antibodies would inhibit canine PD-1/PD-L1 binding. Briefly, canine PD-1-Ig (prepared in 2.4 above) was immobilized on flat bottomed 96-well plates and blocked with 1% BSA and 0.05% Tween 20-containing PBS. Canine PD-L1-Ig (prepared in 2.4 above) was biotinylated using Lightning-Link Biotin Conjugation Kit (Innova Bioscience) and reacted with various concentrations (0, 2.5, 5 and $10\text{ }\mu\text{g/ml}$) of rat anti-bovine PD-L1 antibodies 4G12, 5A2 and 6G7 at 37°C for 30 min, followed by addition to the 96-well plates. The binding of cPD-L1-Ig to cPD-1-Ig was measured by color reaction using Neutravidin-HRP (Thermo Fisher Scientific) and TMB one component substrate (Bethyl Laboratories). As a result, rat anti-bovine PD-L1 monoclonal antibodies 4G12 and 6G7 showed a good inhibitory activity against canine PD-1/PD-L1 binding, whereas 5A2 showed no binding inhibitory activity (Fig. 1).

2.7 Preparation of Rat-Canine Chimeric Anti-PD-L1 Antibody Expressing Vector (Fig. 2)

Using rat anti-bovine PD-L1 monoclonal antibodies 4G12 and 6G7 which showed a good inhibitory activity against canine PD-1/PD-L1 binding (Fig. 1) as the variable region, two types of rat-canine chimeric anti-PD-L1 antibodies were established.

Briefly, heavy chain and light chain variable region genes were identified from hybridomas producing rat anti-bovine PD-L1 monoclonal antibodies 4G12 and 6G7. Further, the heavy chain and light chain variable region genes of the above rat antibodies were linked to the constant region of heavy chain IgG4 and the constant region of light chain Lambda of a known canine antibody, respectively, to prepare nucleotide sequences, followed by codon optimization (SEQ ID NOS: 9 and 10 (amino acid sequences), SEQ ID NOS: 19 and 20 (nucleotide sequences after codon optimization)). Then, synthesis of genes was performed so that *NotI* restriction enzyme recognition site, KOZAK sequence, chimeric antibody's light chain sequence, poly-A addition signal sequence (PABGH), promoter sequence (PCMV), *SacI* restriction enzyme recognition site, intron sequence (INRBG), KOZAK sequence, chimeric antibody's heavy chain sequence and *XbaI* restriction enzyme recognition site would be located in this order. The synthesized gene strands were individually incorporated into the cloning site (*NotI* and *XbaI* restriction enzyme recognition sequences downstream of PCMV and between INRBG and PABGH) of expression vector pDC6 (kindly provided by Prof. S. Suzuki, Hokkaido University Research Center for Zoonosis Control) using restriction enzyme recognition sequences so that the above-listed sequences would be located in the above-mentioned order (Fig. 2). Thus, rat-canine chimeric anti-PD-L1 antibody expressing vectors were constructed. Each of the expression vectors was transfected into Expi293F cells (Life Technologies) to obtain a culture supernatant containing a chimeric antibody. The chimeric antibody was purified from the supernatant with Ab Capcher Extra (Protein A mutant; ProteNova) and further purified by gel filtration chromatography. SDS-PAGE was performed under non-reducing conditions using 10% acrylamide gel. Bands were stained with Quick-CBB kit (Wako Pure Chemical) and decolorized in distilled water. Although contaminant proteins were observed after protein A purification alone, a highly purified antibody could be obtained by performing gel filtration chromatography (Fig. 3). It was confirmed by flow cytometry that the resultant purified antibodies specifically bound to canine PD-L1 expressing cells (data not shown). When the inhibitory activity of the two chimeric antibodies against canine PD-1/PD-L1 binding was examined by the method described in 2.6 above, rat-canine chimeric anti-PD-L1 antibody c4G12 showed a binding inhibitory activity similar to that of its original rat anti-bovine PD-L1 monoclonal antibody

4G12, whereas binding inhibition capacity was clearly attenuated in rat-canine chimeric anti-PD-L1 antibody c6G7 (Fig. 4). Therefore, rat-canine chimeric anti-PD-L1 antibody c4G12 was selected as a therapeutic antibody, which incorporated the variable region sequences of rat anti-bovine PD-L1 monoclonal antibody 4G12 (SEQ ID NOS: 2 and 1 (amino acid sequences) and SEQ ID NOS: 16 and 15 (nucleotide sequences after codon optimization)). The amino acid sequence and the nucleotide sequence (after codon optimization) of the light chain of c4G12 are shown in SEQ ID NOS: 9 and 19, and the amino acid sequence and the nucleotide sequence (after codon optimization) of the heavy chain of c4G12 are shown in SEQ ID NOS: 10 and 20.

2.8 Expression of Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12

Rat-canine chimeric anti-PD-L1 antibody c4G12 expressing vector pDC6 as used in 2.7 above was transfected into CHO-DG44 cells (CHO-DG44(dfhr^{-/-})) which were dihydrofolate reductase deficient cells and high expression clones were selected by dot blotting. Further, gene amplification treatment was performed by adding load on cells in a medium containing 60 nM methotrexate (Mtx). Cells stably expressing rat-canine chimeric anti-PD-L1 antibody c4G12 (clone name: 4.3F1) after gene amplification were transferred to Mtx-free Opti-CHO medium and cultured under shaking for 14 days (125 rpm, 37°C, 5% CO₂). Cell survival rate was calculated by trypan blue staining (Fig. 5). Chimeric antibody production in the culture supernatant was measured by ELISA (Fig. 5). The culture supernatant at day 14 was centrifuged at 10,000 g for 10 min to remove cells, then passed through a 0.22 µm filter before the process proceeded to purification steps for the antibody.

It should be noted that by exchanging the medium with Dynamis medium and doing appropriate feeding, antibody production was improved about two-fold compared to the conventional production (data not shown).

2.9 Purification of Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12

The culture supernatant provided as described above was purified with Ab Capcher Extra (ProteNova). An open column method was used for binding to resin; PBS pH 7.4 was used as equilibration buffer and wash buffer. As elution buffer, IgG Elution Buffer (Thermo Scientific) was used. As neutralization buffer, 1 M Tris was used. The purified antibody was concentrated and buffer-exchanged with PBS by ultrafiltration using Amicon Ultra-15 (50 kDa, Millipore). The resultant antibody was passed through a 0.22 µm filter for use in respective experiments.

2.10 Confirmation of Purification of Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12 (Fig.6)

In order to confirm the purity of the purified antibody, antibody proteins were detected by SDS-PAGE and CBB staining. Using SuperSep Ace 5-20% (Wako) gradient gel, rat anti-bovine PD-L1 monoclonal antibody 4G12 and rat-canine chimeric anti-PD-L1 antibody c4G12 were electrophoresed under reducing conditions and non-reducing conditions. Bands were stained with Quick-CBB kit (Wako) and decolored in distilled water. Bands were observed at positions of molecular weights corresponding to antibodies. No bands of contaminant proteins were recognized visually.

2.11 Measurement of Binding Avidities to cPD-L1-His of Rat Anti-Bovine PD-L1 Monoclonal Antibody 4G12 and Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12

In order to amplify the extracellular region of canine PD-L1 estimated from its putative amino acid sequence, primers were designed. Briefly, a primer having an *NheI* recognition sequence added on the 5' side (cPD-L1-His F) and a primer having an *EcoRV* recognition sequence and 6xHis tag sequence added on the 5' side (cPD-L1-His R) were designed. PCR was performed using a synthesized beagle PBMC-derived cDNA as a template. The PCR products were digested with *NheI* (Takara) and *EcoRV* (Takara) and purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics). The thus purified DNA was cloned into pCXN2.1 vector (Niwa et al., 1991; kindly provided by Dr. T. Yokomizo, Juntendo University Graduate School of Medicine) treated with restriction enzymes in the same manner. The expression plasmids were purified with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmid is designated as pCXN2.1-cPD-L1-His.

Primer (cPD-L1-His F): CGCGGCTAGCATGAGAATGTTTAGTGTCTT (SEQ ID NO: 131)

Primer (cPD-L1-His R): CGCGGATATCTTAATGGTGATGGTGATGGTGAGTCCTCTCACTTGCTGG (SEQ ID NO: 132)

The expression vector was transfected into Expi293F cells (Life Technologies) to obtain a culture supernatant containing a recombinant protein. The recombinant protein produced was purified from the supernatant using TALON Metal Affinity Resin (Clontech), and the buffer was exchanged with PBS using Amicon Ultra-4 Ultracel-3 (Merck Millipore). The thus obtained recombinant protein was stored at 4°C until use in experiments (cPD-L1-His). The protein concentration was measured with Pierce BCA Protein Assay Kit (Thermo Fisher Scientific) for use in subsequent experiments.

Using a biomolecular interaction analyzer (Biacore X100), the binding avidities to

cPD-L1-His of rat anti-bovine PD-L1 monoclonal antibody 4G12 and rat-canine chimeric anti-PD-L1 antibody c4G12 were assessed. Briefly, anti-histidine antibody was fixed on CM5 sensor chip, followed by capturing of cPD-L1-His. Subsequently, monoclonal antibodies were added as analyte to observe specific binding. Both antibodies exhibited specific binding and their avidities were almost comparable (Table 1). Further, the binding avidities of canine PD-1-Ig and CD80-Ig to cPD-L1-His were measured in the same manner and found to be clearly lower than that of rat-canine chimeric anti-PD-L1 antibody c4G12 (Table 1).

Table 1. Binding Avidity of Each Antibody and Recombinant Protein to Canine PD-L1-His

	$k_a (\times 10^6/\text{Ms})$	$k_d (\times 10^{-3}/\text{s})$	KD (nM)
4G12	2.42 ± 0.10	4.54 ± 0.19	1.88 ± 0.06
c4G12	3.14 ± 0.19	7.19 ± 0.26	2.30 ± 0.07
cPD-1			25.4 ± 4.89
cCD80			24.3 ± 0.89

2.12 Inhibitory Activity of Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12 against Canine PD-1/PD-L1 Binding and CD80/PD-L1 Binding (Fig. 7)

Using the canine PD-1-Ig, PD-L1-Ig and CD80-Ig (described above), anti-PD-L1 antibody was tested for its ability to inhibit canine PD-1/PD-L1 binding and CD80/PD-L1 binding. Briefly, canine PD-1-Ig or CD80-Ig was immobilized on flat-bottom 96-well plates. Canine PD-L1-Ig was reacted with various concentrations (0, 2.5, 5 and 10 $\mu\text{g}/\text{ml}$) of rat anti-bovine PD-L1 antibody 4G12 or rat-canine chimeric anti-PD-L1 antibody c4G12 according to the same procedures as described in 2.6 above, and the binding of canine PD-L1-Ig was assessed. No change in binding inhibition activity was observed due to the chimerization of antibody.

2.13. Canine Immune Cell Activating Effect of Rat-Canine Chimeric Anti-PD-L1 Antibody c4G12 (Fig. 8)

Canine PBMCs were cultured under stimulation with a super-antigen Staphylococcal Enterotoxin B (SEB) for three days, and changes in cytokine production by addition of rat-canine chimeric anti-PD-L1 antibody c4G12 were measured by ELISA using Duoset ELISA canine IL-2 or IFN- γ (R&D systems). Rat-canine chimeric anti-PD-L1 antibody c4G12 increased the production of IL-2 and IFN- γ from canine PBMCs. Further, nucleic acid analogue EdU was added to the culture medium at day 2 of the culture under SEB stimulation.

Two hours later, uptake of EdU was measured by flow cytometry using Click-iT Plus EdU flow cytometry assay kit (Life Technologies). As a result, EdU uptake in canine CD4⁺ and CD8⁺ lymphocytes was enhanced by addition of rat-canine chimeric anti-PD-L1 antibody c4G12, indicating an elevated cell proliferation capacity.

2.14 Selection of Tumor-Affected Dogs to be used in Canine Inoculation Test

Since the subject treatment is expected to manifest a higher efficacy when PD-L1 is being expressed in tumors, PD-L1 expression analysis at the tumor site of dogs was performed by immunohistochemical staining. Briefly, tumor tissue samples fixed with formaldehyde and embedded in paraffin were sliced into 4 µm thick sections with a microtome, attached to and dried on silane-coated slide glass (Matsunami Glass) and deparaffinized with xylene/alcohol. While the resultant sections were soaked in citrate buffer [citric acid (Wako Pure Chemical) 0.37 g, trisodium citrate dihydrate (Kishida Chemical) 2.4 g, distilled water 1000 ml], antigen retrieval treatment was performed for 10 min with microwave, followed by staining using a Nichirei automatic immuno-staining device. As pretreatment, sample sections were soaked in 0.3% hydrogen peroxide-containing methanol solution at room temperature for 15 min and washed with PBS. Then, anti-bovine PD-L1 monoclonal antibody was added and reaction was conducted at room temperature for 30 min. After washing with PBS, histofine simple stain MAX-PO (Rat) (Nichirei Bioscience) was added and reaction was carried at room temperature for 30 min, followed by coloring with 3,3'-diaminobenzidine tetrahydrochloride and observation with a light microscope. Dogs with oral melanoma or undifferentiated sarcoma in which tumor cells were PD-L1 positive were used in the following inoculation test (clinical trial). Anti-bovine PD-L1 monoclonal antibody was established from a rat anti-bovine PD-L1 monoclonal antibody producing hybridoma (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. *Immunology*. 2014 Aug;142(4):551-61).

2.15 Inoculation Test on Dogs

With respect to the rat-canine chimeric anti-PD-L1 antibody c4G12 to be inoculated into dogs in the clinical trial, the culture supernatant obtained by the procedures described in 2.8 above was purified by affinity chromatography using MabSelect SuRe LX (GE Healthcare) and then by hydroxyapatite chromatography using BioScale CHT20-I prepacked column (Bio-Rad) in order to remove contaminants and polymeric proteins. Aggregate-containing fractions were further purified by anion exchange chromatography using HiScreen Q-Sepharose HP prepacked column (GE Healthcare).

(1) Safety Test: The established rat-canine chimeric anti-PD-L1 antibody c4G12 was

administered intravenously into a dog (beagle, spayed female, 13-year-old, about 10 kg in body weight) at 2 mg/kg, every 2 weeks, 3 times in total. There was observed no anaphylaxis or other adverse effects that would cause any trouble in clinical trials. (2) Clinical Trial 1: The established rat-canine chimeric anti-PD-L1 antibody c4G12 was administered intravenously into a PD-L1 positive dog with relapsed oral melanoma (Fig. 9A) (miniature dachshund, male, 11-year-old, about 7.5 kg in body weight) at 2 mg/kg or 5 mg/kg, every 2 weeks, 22 times in total. At week 10 after the start of treatment, a remarkable reduction in tumor size was recognized. At week 34 after the start of treatment, a still further reduction was confirmed (Fig. 10). During the observation period of 44 weeks, no metastases to lymph nodes or the lung were observed. When 30% or more reduction in the longest diameter of tumor compared to that at the baseline is defined as PR (partial response), the criterion of PR was satisfied at weeks 16-20 and at week 34 and thereafter (Fig. 11).

(3) Clinical Trial 2: Rat-canine chimeric anti-PD-L1 antibody c4G12 was administered intravenously into a dog with undifferentiated sarcoma whose primary lesion was PD-L1 positive (Fig. 9B) and who had a plurality of metastatic lesions in muscles throughout the body (west highland white terrier, castrated male, 12-year-old, about 8 kg in body weight) at 5 mg/kg, every 2 weeks, 2 times in total. At week 3 from the start of treatment, a clear regression of tumor was recognized (Fig. 12).

(4) Clinical Trial 3: Rat-canine chimeric anti-PD-L1 antibody c4G12 was administered intravenously into a dog with oral melanoma whose primary lesion had been removed by surgery (beagle, spayed female, 11-year-old, about 10 kg in body weight) at 2 mg/kg or 5 mg/kg, every 2 weeks, 9 times in total. At week 18 after the start of treatment, a plurality of pulmonary metastatic lesions disappeared (Fig. 13),

(5) Clinical Trial 4: Rat-canine chimeric anti-PD-L1 antibody c4G12 was administered intravenously into 4 dogs with oral melanoma with pulmonary metastasis at 2 mg/kg or 5 mg/kg, every 2 weeks. Although no clear reduction in tumor size was observed during the observation period, the duration of the treated dogs' survival after confirmation of pulmonary metastasis tended to be longer than that of a control group (antibody not administered, historical control group: n=15) (Fig. 14). Therefore, the survival duration may have been extended by antibody administration.

2.16 CDR Analysis of Anti-PD-L1 Antibody

The complementarity-determining regions (CDRs) of rat anti-bovine PD-L1 antibody 4G12 were determined using NCBI IGBLAST (<http://www.ncbi.nlm.nih.gov/igblast/>). The results are shown in Fig. 15.

[Example 2] Application of Anti-PD-L1 Antibody to Other Animal Species

1.1 Identification of Ovine, Porcine and Water Buffalo PD-L1 Genes

In order to determine the full-lengths of the coding sequences (CDSs) of ovine, porcine and water buffalo PD-L1 cDNAs, primers for amplifying the full lengths of CDSs from the nucleotide sequences of ovine, porcine and water buffalo PD-L1 genes (GenBank accession number; XM_004004362, NM_001025221 and XM_613366) were first designed (ovPD-L1 CDS F and R; poPD-L1 CDS F and R; buPD-L1 CDS F1, R1, F2 and R2), and then PCR was performed. For the resultant amplified products, nucleotide sequences were determined with a capillary sequencer according to conventional methods (Mingala CN, Konnai S, Ikebuchi R, Ohashi K. *Comp. Immunol. Microbiol. Infect. Dis.* 2011 Jan; 34(1):55-63; Water buffalo PD-L1 gene was identified in this article).

Primer (ovPD-L1 CDS F): ATGAGGATATATAGTGTCTTAACAT (SEQ ID NO: 109)

Primer (ovPD-L1 CDS R): TTACGTCTCCTCAAATGTG (SEQ ID NO: 110)

Primer (poPD-L1 CDS F): ATGAGGATATGTAGTATCTTTACAT (SEQ ID NO: 111)

Primer (poPD-L1 CDS R): TTACGTCTCCTCAAATTGTGT (SEQ ID NO: 112)

Primer (buPD-L1 CDS F1): ATGAGGATATATAGTGTCTT (SEQ ID NO: 113)

Primer (buPD-L1 CDS R1): GCCACTCAGGACTTGGTGAT (SEQ ID NO: 114)

Primer (buPD-L1 CDS F2): GGGGGTTTACTGTTGCTTGA (SEQ ID NO: 115)

Primer (buPD-L1 CDS R2): TTACGTCTCCTCAAATTGT (SEQ ID NO: 116)

1.2 Construction of Ovine PD-1, Ovine PD-L1, Porcine PD-1 and Porcine PD-L1 Expressing COS-7 Cells

In order to prepare ovine PD-1, ovine PD-L1, porcine PD-1 and porcine PD-L1 expressing plasmids, PCR was performed using a synthesized ovine or porcine PBMC-derived cDNA as a template and primers designed by adding *Bgl*II and *Sma*I (ovine PD-1), *Hind*III and *Sma*I (porcine PD-1), or *Xho*I and *Sma*I (ovine and porcine PD-L1) recognition sites on the 5' side (ovPD-1-EGFP F and R; ovPD-L1-EGFP F and R; poPD-1-EGFP F and R; or poPD-L1-EGFP F and R). The resultant PCR products were digested with *Bgl*II (Takara) and *Sma*I (Takara) (ovine PD-1), *Hind*III (Takara) and *Sma*I (Takara) (porcine PD-1), and *Xho*I (Takara) and *Sma*I (Takara) (ovine and porcine PD-L1), then purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics) and cloned into pEGFP-N2 vector (Clontech) treated with restriction enzymes in the same manner. Expression plasmids were extracted using FastGene Xpress Plasmid PLUS Kit (NIPPON Genetics) and stored at -30°C

until use in experiments. Hereinafter, the thus prepared plasmid is designated as pEGFP-N2-ovPD-1, pEGFP-N2-ovPD-L1, pEGFP-N2-poPD-1 or pEGFP-N2-poPD-L1.

Primer (ovPD-1-EGFP F): GAAGATCTATGGGGACCCCGCGGGCGCCG (SEQ ID NO: 117)

Primer (ovPD-1-EGFP R): GACCCGGGGAGGGGCGCAGGAGCAGTGTCC (SEQ ID NO: 118)

Primer (ovPD-L1-EGFP F): CCGCTCGAGATGAGGATATATAGTGTCT (SEQ ID NO: 119)

Primer (ovPD-L1-EGFP R): ATCCCGGGCGTCTCCTCAAAATGTGTAG (SEQ ID NO: 120)

Primer (poPD-1-EGFP F): ACTAAGCTTATGGGGACCCCGCGGG (SEQ ID NO: 121)

Primer (poPD-1-EGFP R): ACTCCCGGGGAGGGGCGCAAGAGCAGT (SEQ ID NO: 122)

Primer (poPD-L1-EGFP F): CCGCTCGAGATGAGGATATGTAGTATCTT (SEQ ID NO: 123)

Primer (poPD-L1-EGFP R): ATCCCGGGCGTCTCCTCAAATTGTGTATC (SEQ ID NO: 124)

COS-7 cells were subcultured at a density of 5×10^4 cells/cm² in 6-well plates, and then cultured overnight in RPMI 1640 medium containing 10% inactivated fetal bovine serum and 0.01% L-glutamine at 37°C in the presence of 5% CO₂. The pEGFP-N2-ovPD-1, pEGFP-N2-ovPD-L1, pEGFP-N2-poPD-1, pEGFP-N2-poPD-L1 or pEGFP-N2 (negative control) was introduced into COS-7 cells at 0.4 µg/cm² using Lipofectamine 2000 (Invitrogen). The cells were cultured for 48 hours (ovPD-1-EGFP expressing cell, ovPD-L1-EGFP expressing cell, poPD-1-EGFP expressing cell, and poPD-L1-EGFP expressing cell). In order to confirm the expression of ovine PD-1, ovine PD-L1, porcine PD-1 and porcine PD-L1 in the thus prepared expressing cells, intracellular localization of EGFP was visualized with an inverted confocal laser microscope LSM700 (ZEISS) or an all-in-one fluorescence microscope BZ-9000 (KEYENCE).

1.3 Construction of Recombinant Ovine PD-L1 and Porcine PD-L1

In order to amplify the extracellular regions of ovine PD-L1 or porcine PD-L1 estimated from their putative amino acid sequences, primers were designed. Briefly, primers having an *Nhe*I or *Eco*RV recognition sequence added on the 5' side (ovPD-L1-Ig F and R, or poPD-L1-Ig F and R) were designed. PCR was performed using a synthesized ovine or porcine PBMC-derived cDNA as a template. The PCR products were digested with *Nhe*I (Takara) and *Eco*RV (Takara) and purified with FastGene Gel/PCR Extraction Kit (NIPPON

Genetics). The thus purified DNAs were individually cloned into pCXN2.1-Rabbit IgG Fc vector (Niwa et al., 1991; Zettlmeissl et al., 1990; kindly provided by Dr. T. Yokomizo, Juntendo University Graduate School of Medicine, and modified in the inventors' laboratory) treated with restriction enzymes in the same manner. The expression plasmids were purified with FastGene Xpress Plasmid PLUS Kit (NIPPON Genetics) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmids are designated as pCXN2.1-ovPD-L1-Ig and pCXN2.1-poPD-L1-Ig, respectively.

Primer (ovPD-L1-Ig F): GACGCTAGCATGAGGATATATAGTGTCT (SEQ ID NO: 125)

Primer (ovPD-L1-Ig R): GCTCTGATATCCCTCGTTTTTGCTGGAT (SEQ ID NO: 126)

Primer (poPD-L1-Ig F): GACGCTAGCATGAGGATATGTAGTATCTT (SEQ ID NO: 127)

Primer (poPD-L1-Ig R): AGCTTGATATCCCTCTTTCTTGCTGGATC (SEQ ID NO: 128)

Thirty micrograms of pCXN2.1-ovPD-L1-Ig or pCXN2.1-poPD-L1-Ig was introduced into 7.5×10^7 Expi293F cells (Life Technologies) using Expifectamin (Life Technologies). After 6-day shaking culture, a culture supernatant was collected. The culture supernatant contained an Fc fusion recombinant protein. The produced Fc recombinant protein was purified from the supernatant using Ab-Capcher Extra (ProteNova). After purification, the buffer was exchanged with PBS (pH 7.4) using PD-10 Desalting Column (GE Healthcare). The resultant recombinant protein was stored at -30°C until use in Experiment (ovine PD-L1-Ig). Concentrations of purified ovine PD-L1-Ig and porcine PD-L1-Ig were measured with Rabbit IgG ELISA Quantitation Set (BETHYL). For each washing operation in ELISA, Auto Palte Washer BIO WASHER 50 (DS Pharma Biomedical) was used. Absorbance was measured with Microplate Reader MTP-650FA (Corona Electric).

1.4 Reactivity of Rat Anti-Bovine PD-L1 Antibody 4G12 with Ovine and Porcine PD-L1

It was confirmed by flow cytometry that rat anti-bovine PD-L1 monoclonal antibody cross-reacts with ovine and porcine PD-L1. Ovine or Porcine PD-L1-EGFP expressing COS-7 cells were blocked with 10% inactivated goat serum supplemented PBS at room temperature for 15 min and reacted with 10 $\mu\text{g}/\text{ml}$ of rat anti-bovine PD-L1 antibody 4G12 at room temperature for 30 min. After washing, the cells were reacted with allophycocyanine-labeled anti-rat Ig goat antibody (Beckman Coulter) at room temperature for 30 min. For analysis, FACS Verse (BD Bioscience) was used. As a negative control antibody, rat IgG2a (κ) isotype control (BD Bioscience) was used. For every washing operation and dilution of antibodies, 1% bovine serum albumin supplemented PBS was used.

Experimental results are shown in Fig. 16. It was confirmed that rat anti-bovine PD-

L1 antibody 4G12 binds to ovine and porcine PD-L1.

1.5 Reactivity of Rat Anti-Bovine PD-L1 Antibody 4G12 with Water Buffalo Leukocytes

Peripheral blood of water buffalo (*Bubalus bubalis*; Asian water buffalo) was hemolyzed with ACK buffer to isolate leukocytes. After blocking with 10% inactivated goat serum supplemented PBS at room temperature for 15 min, reaction with rat anti-bovine PD-L1 antibody 4G12, peridinin-chlorophyll-protein complex/cyanin 5.5-labeled anti-bovine CD14 antibody (mouse IgG1, CAM36A, VMRD) and anti-bovine CD11b antibody (mouse IgG2b, CC126, AbD Serotec) was conducted at room temperature for 30 min. After washing, reaction with allophycocyanine-labelled anti-rat Ig goat antibody (Beckman Coulter) and fluorescein isothiocyanate-labeled anti-mouse IgG2 goat antibody (Beckman Coulter) was conducted at room temperature for 30 min. For analysis, FACS Calibur (BD Biosciences) was used. As a negative control antibody, rat IgG2a (κ) isotype control (BD Biosciences) was used. For every washing operation and dilution of antibodies, 10% inactivated goat serum supplemented PBS was used.

Experimental results are shown in Fig. 17. Rat anti-bovine PD-L1 antibody 4G12 strongly bound to blood macrophages ($CD14^+ CD11b^+$ cells) of water buffalo. On the other hand, rat anti-bovine PD-L1 antibody 4G12 weakly bound to lymphocytes ($CD14^- CD11b^-$ cells) of water buffalo. This difference in binding property is believed to reflect the expression levels of PD-L1 in macrophages and lymphocytes.

1.6 Inhibition Test on Ovine or Porcine PD-1/PD-L1 Binding with Rat Anti-Bovine PD-L1 Antibody 4G12

Using ovine PD-1-EGFP expressing COS-7 cells and ovine PD-L1-Ig recombinant protein, or porcine PD-1-EGFP expressing COS-7 cells and porcine PD-L1-Ig recombinant protein, inhibition of ovine or porcine PD-1/PD-L1 binding by rat anti-bovine PD-L1 antibody (4G12) was tested. Briefly, rat anti-bovine PD-L1 antibody 4G12 of various concentrations (0, 1, 5, 10, 20, 50 $\mu\text{g/ml}$) was reacted in advance with ovine PD-L1-Ig (final concentration 1 $\mu\text{g/ml}$) or porcine PD-L1-Ig (final concentration 5 $\mu\text{g/ml}$) at 37°C for 30 min. Subsequently, the antibody 4G12 was reacted with 2×10^5 ovine PD-1-EGFP expressing COS-7 cells or porcine PD-1-EGFP expressing COS-7 cells at 37 °C for 30 min. After washing, ovine PD-L1-Ig or porcine PD-L1-Ig bound to cell surfaces was detected with Alexa Fluor 647-labeled anti-rabbit IgG (H+L) goat F(ab')₂ (Life Technologies). For analysis, FACS Verse (BD Biosciences) was used. As a negative control antibody, rat IgG2a (κ) isotype control (BD Biosciences) was used. Taking the proportion of PD-L1-Ig bound cells without antibody addition as 100%, the proportion of PD-L1-Ig bound cells at each antibody

concentration was shown as relative value.

The results revealed that rat anti-bovine PD-L1 antibody 4G12 is capable of inhibiting ovine PD-1/PD-L1 and porcine PD-1/PD-L1 binding in a concentration dependent manner (Fig. 18).

[Example 3]

1. Introduction

Programmed cell death 1 (PD-1), an immunoinhibitory receptor, and its ligand programmed cell death ligand 1 (PD-L1) are molecules identified by Prof. Tasuku Honjo et al., Kyoto University, as factors which inhibit excessive immune response and are deeply involved in immunotolerance. Recently, it has been elucidated that these molecules are also involved in immunosuppression in tumors. In the subject Example, for the purpose of establishing a novel therapy for bovine infections, the present inventors have prepared a chimeric antibody gene by linking the variable region gene of rat anti-bovine PD-L1 monoclonal antibody (4G12) capable of inhibiting the binding of bovine PD-1 and PD-L1 to the constant region gene of a bovine immunoglobulin (IgG1 with mutations having been introduced into the putative binding sites for Fcγ receptors in CH2 domain to inhibit ADCC activity; see Fig. 19 for amino acid numbers and mutations: 250 E→P, 251 L→V, 252 P→A, 253 G→deletion, 347 A→S, 348 P→S; Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology 2014 Aug; 142(4):551-561). This chimeric antibody gene was introduced into Chinese hamster ovary cells (CHO cells). By culturing/proliferating the resultant cells, the present inventors have obtained a rat-bovine chimeric anti-bovine PD-L1 antibody (ch4G12) and confirmed its effect *in vitro* and *in vivo*.

2. Materials and Methods

Construction of Bovine PD-1 and PD-L1 Expressing Cells

The nucleotide sequences of the full length cDNAs of bovine PD-1 gene (GenBank accession number AB510901; Ikebuchi R, Konnai S, Sunden Y, Onuma M, Ohashi K. Microbiol. Immunol. 2010 May; 54(5):291-298) and bovine PD-L1 gene (GenBank accession number AB510902; Ikebuchi R, Konnai S, Shirai T, Sunden Y, Murata S, Onuma M, Ohashi K. Vet. Res. 2011 Sep. 26; 42:103) were determined. Based on the resultant genetic information, bovine PD-1 and bovine PD-L1 membrane expressing cells were prepared. First, for preparing bovine PD-1 or PD-L1 expressing plasmid, PCR was performed using a synthesized bovine PBMC-derived cDNA as a template and designed primers having *NotI* and *HindIII* (bovine PD-1) recognition sites and *NheI* and *XhoI* (bovine PD-L1) recognition

sites on the 5' side (boPD-1-myc F and R; boPD-L1-EGFP F and R). The PCR products were digested with *NotI* (Takara) and *HindIII* (Takara; bovine PD-1), *NheI* (Takara) and *XhoI* (Takara; bovine PD-L1), purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics) and cloned into pCMV-Tag1 vector (Agilent Technologies; bovine PD-1) or pEGFP-N2 vector (Clontech; bovine PD-L1) treated with restriction enzymes in the same manner. The resultant expression plasmid of interest was extracted with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmid is designated as pCMV-Tag1-boPD-1.

Primer (boPD-1-myc F): ATATGCGGCCGCATGGGGACCCCGCGGGCGCT (SEQ ID NO: 133)

Primer (boPD-1-myc R): GCGCAAGCTTTCAGAGGGGCCAGGAGCAGT (SEQ ID NO: 134)

Primer (boPD-L1-EGFP F): CTAGCTAGCACCATGAGGATATATAGTGTCTTAAC (SEQ ID NO: 135)

Primer (boPD-L1-EGFP R): CAATCTCGAGTTACAGACAGAAGATGACTGC (SEQ ID NO: 136)

Bovine PD-1 membrane expressing cells were prepared by the procedures described below. First, 2.5 μg of pCMV-Tag1-boPD-1 was introduced into 4×10^6 CHO-DG44 cells using Lipofectamine LTX (Invitrogen). Forty-eight hours later, the medium was exchanged with CD DG44 medium (Life Technologies) containing 800 $\mu\text{g}/\text{ml}$ G418 (Enzo Life Science), 20 ml/L GlutaMAX supplement (Life Technologies), and 18 ml/L 10% Pluronic F-68 (Life Technologies), followed by selection. The resultant expression cells were reacted with rat anti-bovine PD-1 antibody 5D2 at room temperature. After washing, the cells were further reacted with anti-rat IgG microbeads-labeled antibody (Miltenyi Biotec) at room temperature. Cells expressing bovine PD-1 at high levels were isolated with Auto MACS (Miltenyi Biotec). Subsequently, re-isolation was performed in the same manner to obtain still higher purity. The resultant expression cells were subjected to cloning by limiting dilution to thereby obtain a CHO DG44 cell clone expressing bovine PD-1 at high level (bovine PD-1 expressing cells).

Bovine PD-L1 membrane expressing cells were prepared by the procedures described below. First, 2.5 μg of pEGFP-N2-boPD-L1 or pEGFP-N2 (negative control) was introduced into 4×10^6 CHO-DG44 cells using Lipofectamine LTX (Invitrogen). Forty-eight hours later, the medium was exchanged with CD DG44 medium (Life Technologies) containing G418 (Enzo Life Science) 800 $\mu\text{g}/\text{ml}$, GlutaMAX supplement (Life Technologies) 20 ml/L, and

10% Pluronic F-68 (Life Technologies) 18 ml/L, followed by selection and cloning by limiting dilution (bovine PD-L1 expressing cell clone). In order to confirm the expression of bovine PD-L1 in the thus prepared expressing cell clone, intracellular localization of EGFP was visualized with an inverted confocal laser microscope LSM700 (ZEISS).

Construction of Soluble Bovine PD-1 and PD-L1

Bovine PD-1-Ig expressing plasmid was constructed by the procedures described below. Briefly, the signal peptide and the extracellular region of bovine PD-1 (GenBank accession number AB510901) were linked to the Fc domain of the constant region of a known bovine IgG1 (GenBank accession number X62916) to prepare a gene sequence. After codons were optimized for CHO cells, gene synthesis was performed in such a manner that *NotI* recognition sequence, KOZAK sequence, bovine PD-1 signal peptide sequence, bovine PD-1 gene extracellular region sequence, bovine IgG1 Fc region sequence, and *XbaI* recognition sequence would be located in the gene in this order. It should be noted here that bovine IgG1 was mutated to inhibit ADCC activity; more specifically, mutations were introduced into the putative binding sites for Fcγ receptors of CH2 domain (sites of mutation: 185 E→P, 186 L→V, 187 P→A, 189 G→deletion, 281 A→S, 282 P→S; Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology 2014 Aug; 142(4):551-561; the amino acid sequence of PD-1-Ig and the sites of mutation are disclosed in Figure 2 of this article). The synthesized gene strand was digested with *NotI* (Takara) and *XbaI* (Takara), purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics), and incorporated into the cloning site (*NotI* and *XbaI* restriction enzyme recognition sequences downstream of PCMV and between INRBG and PABGH) of expression vector pDN11 (kindly provided by Prof. S. Suzuki, Hokkaido University Research Center for Zoonosis Control) treated with restriction enzymes in the same manner, whereby bovine PD-1-Ig expressing vector was constructed. The expression plasmid was purified with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmid is designated as pDN11-boPD-1-Ig.

Bovine PD-L1-Ig expressing plasmid was constructed by the procedures described below. In order to amplify the signal peptide and the extracellular region of bovine PD-L1 (GenBank accession number AB510902), primers were designed that had *NheI* and *EcoRV* recognition sites added on the 5' side (boPD-L1-Ig F and R). PCR was performed using a synthesized bovine PBMC-derived cDNA as a template. The PCR products were digested with *NheI* (Takara) and *EcoRV* (Takara), purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics) and cloned into pCXN2.1-Rabbit IgG1 Fc vector (Niwa et al., 1991;

Zettlmeissl et al., 1990; kindly provided by Dr. T. Yokomizo, Juntendo University Graduate School of Medicine, and modified in the inventors' laboratory) treated with restriction enzymes in the same manner. The expression plasmid was purified with QIAGEN Plasmid Midi kit (Qiagen) or FastGene Xpress Plasmid PLUS Kit (NIPPON Genetics) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmid is designated as pCXN2.1-boPD-L1-Ig.

Primer (boPD-L1-Ig F): GCTAGCATGAGGATATATAGTGTCTTAAC (SEQ ID NO: 137)

Primer (boPD-L1-Ig R): GATATCATTCTCTTTTTTGCTGGAT (SEQ ID NO: 138)

Soluble bovine PD-1-Ig expressing cells were prepared by the procedures described below. Briefly, 2.5 μg of pDN11-boPD-1-Ig was introduced into 4×10^6 CHO-DG44 cells using Lipofectamine LTX (Invitrogen). Forty-eight hours later, the medium was exchanged with OptiCHO AGT medium (Life Technologies) containing 800 $\mu\text{g}/\text{ml}$ G418 (Enzo Life Science) and 20 ml/L GlutaMAX supplement (Life Technologies). After cultured for 3 weeks, the cells were subjected to selection. Briefly, the concentrations of the Fc fusion recombinant protein in the culture supernatants of the resultant cell clones were measured by ELISA using anti-bovine IgG F(c) rabbit polyclonal antibody (Rockland) to thereby select those cell clones that express the Fc fusion recombinant protein at high levels. The resultant highly expressing cell clone was transferred to a G418-free medium and cultured under shaking for 14 days, followed by collection of a culture supernatant. The culture supernatant containing the Fc fusion recombinants protein was ultrafiltered with Centricon Plus-70 (Millipore). Then, the Fc fusion recombinant protein was purified with Ab-Capcher Extra (ProteNova). After purification, the buffer was exchanged with phosphate-buffered physiological saline (PBS; pH 7.4) using PD-10 Desalting Column (GE Healthcare). The resultant protein was stored at -30°C until use in experiments (bovine PD-1-Ig). The concentration of the purified bovine PD-1-Ig was measured by ELISA using IgG F(c) rabbit polyclonal antibody (Rockland). For each washing operation in ELISA, Auto Plate Washer BIO WASHER 50 (DS Pharma Biomedical) was used. Absorbance was measured with Microplate Reader MTP-650FA (Corona Electric).

Soluble bovine PD-L1-Ig expressing cells were prepared by the procedures described below. Briefly, 30 μg of pCXN2.1-boPD-L1-Ig was introduced into 7.5×10^7 Expi293F cells (Life Technologies) using Expifectamine (Life Technologies). After 7-day culture under shaking, the culture supernatant was collected. The recombinant protein was purified from the supernatant using Ab-Capcher Extra (ProteNova; bovine PD-L1-Ig). After purification,

the buffer was exchanged with PBS (pH 7.4) using PD MiniTrap G-25 (GE Healthcare). The resultant protein was stored at -30°C until use in experiments (bovine PD-L1-Ig). The concentration of the purified bovine PD-L1-Ig was measured using Rabbit IgG ELISA Quantitation Set (Bethyl). For each washing operation in ELISA, Auto Plate Washer BIO WASHER 50 (DS Pharma Biomedical) was used. Absorbance was measured with Microplate Reader MTP-650FA (Corona Electric).

Preparation of Rat Anti-Bovine PD-L1 Monoclonal Antibody Producing Cells

Rat was immunized in the footpad with bovine PD-L1-Ig (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. *Immunology* 2014 Aug.; 142(4):551-561; bovine PD-L1-Ig was prepared by the method disclosed in this article and used for immunization). Hybridomas were established by the iliac lymph node method to thereby obtain rat anti-bovine PD-L1 monoclonal antibody producing hybridoma 4G12. With respect to the method of establishment of rat anti-bovine PD-L1 monoclonal antibody, details are disclosed in the following non-patent document (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. *Vet. Res.* 2013 Jul. 22; 44:59; Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. *Immunology* 2014 Aug.; 142(4):551-561).

Preparation of Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody Expressing Vector

Rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 was established by fusing the antibody constant regions of bovine IgG1 and Ig λ with rat anti-bovine PD-L1 antibody 4G12 being used as an antibody variable region.

First, the genes of heavy chain and light chain variable regions were identified from a hybridoma that would produce rat anti-bovine PD-L1 antibody 4G12. Subsequently, a gene sequence was prepared in which the heavy chain and the light chain variable regions of the antibody 4G12 were linked to known constant regions of bovine IgG1 (heavy chain; modified from GenBank Accession number X62916) and bovine Ig λ (light chain; GenBank Accession number X62917), respectively, and codon optimization was carried out [rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12: SEQ ID NOS: 105 and 106 (amino acid sequences), SEQ ID NOS: 107 and 108 (nucleotide sequences after codon optimization)]. It should be noted that in order to suppress the ADCC activity of bovine IgG1, mutations were added to the putative binding sites of Fc γ receptors in CH2 domain (See Fig. 19 for amino acid numbers and mutations: 250 E $\rightarrow$ P, 251 L $\rightarrow$ V, 252 P $\rightarrow$ A, 253 G $\rightarrow$ deletion, 347 A $\rightarrow$ S, 348 P $\rightarrow$ S; Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. *Immunology* 2014 Aug.; 142(4):551-561). Then, the gene was artificially

synthesized in such a manner that *NotI* recognition sequence, KOZAK sequence, chimeric antibody light chain sequence, poly-A addition signal sequence (PABGH), promoter sequence (PCMV), *SacI* recognition sequence, intron sequence (INRBG), KOZAK sequence, chimeric antibody heavy chain sequence and *XbaI* recognition sequence would be located in this order. The synthesized gene strand was digested with *NotI* (Takara) and *XbaI* (Takara), purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics) and cloned into the cloning site (*NotI* and *XbaI* restriction enzyme recognition sequences downstream of PCMV and between INRBG and PABGH) of expression plasmid pDC6 (kindly provided by Prof. S. Suzuki, Hokkaido University Research Center for Zoonosis Control) treated with restriction enzymes in the same manner (Fig. 20). The resultant plasmid was extracted with QIAGEN Plasmid Midi kit (Qiagen) and stored at -30°C until use in experiments. Hereinafter, the thus prepared expression plasmid is designated as pDC6-boPD-L1ch4G12.

Expression of Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody

The pDC6-boPD-L1ch4G12 was transfected into CHO-DG44 cells (CHO-DG44 (dfhr^{-/-})) which were a dihydrofolate reductase deficient cell. Forty-eight hours later, the medium was exchanged with OptiCHO AGT medium (Life Technologies) containing 20 ml/L GlutaMAX supplement (Life Technologies). After cultured for 3 weeks, the cells were subjected to selection and cloning by limiting dilution. Subsequently, the concentrations of the chimeric antibody in the culture supernatants were measured by dot blotting and ELISA using anti-bovine IgG F(c) rabbit polyclonal antibody (Rockland) to thereby select high expression clones. Further, the selected clones expressing rat-bovine chimeric anti-bovine PD-L1 antibody at high levels were subjected to gene amplification treatment by adding a load with 60 nM methotrexate (Mtx)-containing medium. The thus established cell clone stably expressing rat-bovine chimeric anti-bovine PD-L1 antibody was transferred into Mtx-free Opti-CHO AGT medium and cultured under shaking for 14 days (125 rpm, 37°C , 5% CO_2). Chimeric antibody production in the culture supernatant was measured by ELISA using anti-bovine IgG F(c) rabbit polyclonal antibody (Rockland). For each washing operation in ELISA, Auto Plate Washer BIO WASHER 50 (DS Pharma Biomedical) was used. Absorbance was measured with Microplate Reader MTP-650FA (Corona Electric). The culture supernatant at day 14 was centrifuged at 10,000 g for 10 min to remove cells, and the centrifugal supernatant was passed through a Steritop-GP 0.22 μm filter (Millipore) for sterilization and then stored at 4°C until it was subjected to purification.

Purification of Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody

From the culture supernatant prepared as described above, each chimeric antibody

was purified using Ab Capcher Extra (ProteNova). An open column method was used for binding to resin; PBS pH 7.4 was used as an equilibration buffer and a wash buffer. As an elution buffer, IgG Elution Buffer (Thermo Fisher Scientific) was used. As a neutralization buffer, 1M Tris (pH 9.0) was used. The purified antibody was subjected to buffer exchange with PBS (pH 7.4) using PD-10 Desalting Column (GE Healthcare) and concentrated using Amicon Ultra-15 (50 kDa, Millipore). The thus purified chimeric antibody was passed through a 0.22 μ m syringe filter (Millipore) for sterilization and stored at 4°C until use in experiments.

Confirmation of the Purity of Purified Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody (Fig. 21)

In order to confirm the purity of purified rat-bovine chimeric anti-bovine PD-L1 antibody, antibody proteins were detected by SDS-PAGE and CBB staining. Using 10% acrylamide gel, the purified rat-bovine chimeric antibody was electrophoresed under reducing conditions (reduction with 2-mercaptoethanol from Sigma-Aldrich) and non-reducing conditions. Bands were stained with Quick-CBB kit (Wako) and decolorized in distilled water. The results are shown in Fig. 21. Bands were observed at predicted positions, that is, at 25 kDa and 50 kDa under reducing conditions and at 150 kDa under non-reducing conditions.

Binding Specificity of Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody (Fig. 22)

It was confirmed by flow cytometry that the rat-bovine chimeric anti-bovine PD-L1 antibody specifically binds to the bovine PD-L1 expressing cells (described above). First, rat anti-bovine PD-L1 antibody 4G12 or rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 was reacted with bovine PD-L1 expressing cells at room temperature for 30 min. After washing, APC-labeled anti-rat Ig goat antibody (Southern Biotech) or Alexa Fluor 647-labeled anti-bovine IgG (H+L) goat F(ab')₂ (Jackson ImmunoResearch) was reacted at room temperature for 30 min. As negative control antibody, rat IgG2a (κ) isotype control (BD Biosciences) or bovine IgG1 antibody (Bethyl) was used. After washing, each rat antibody or rat-bovine chimeric antibody bound to cell surfaces was detected by FACS Verse (BD Biosciences). For every washing operation and dilution of antibody, PBS supplemented with 1% bovine serum albumin (Sigma-Aldrich) was used.

The experimental results are shown in Fig. 22. It was revealed that rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 binds to bovine PD-L1 expressing cells in the same manner as rat anti-bovine PD-L1 antibody 4G12.

Inhibitory Activity of Rat-Bovine Chimeric Anti-PD-L1 Antibody against Bovine PD-1/PD-L1 Binding

(1) Binding Inhibition Test on Bovine PD-L1 Expressing Cells and Soluble Bovine PD-1 (Fig. 23)

Using bovine PD-L1 expressing cells (described above) and bovine PD-1-Ig (described above), bovine PD-1/PD-L1 binding inhibition by anti-bovine PD-L1 antibody was tested. First, 2×10^5 bovine PD-L1 expressing cells were reacted with various concentrations (0, 0.32, 0.63, 1.25, 2.5, 5 or 10 $\mu\text{g/ml}$) of rat anti-bovine PD-L1 antibody 4G12 or rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 at room temperature for 30 min. As negative control antibody, rat IgG2a (κ) isotype control (BD Biosciences) or bovine IgG1 antibody (Bethyl) was used. After washing, bovine PD-1-Ig labeled with biotin using Lightning-Link Type A Biotin Labeling Kit (Innova Bioscience) was added to a final concentration of 2 $\mu\text{g/ml}$, followed by reaction for another 30 min at room temperature. Subsequently, after washing, bovine PD-1-Ig bound to cell surfaces was detected with APC-labeled streptavidin (BioLegend). For analysis, FACS Verse (BD Biosciences) was used. For every washing operation and dilution of antibody, PBS supplemented with 1% bovine serum albumin (Sigma-Aldrich) was used. Taking the proportion of PD-1-Ig bound cells without antibody addition as 100%, the proportion of PD-1-Ig bound cells at each antibody concentration was shown as relative value.

The experimental results are shown in Fig. 23. It was revealed that like rat anti-bovine PD-L1 antibody 4G12, rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 is capable of inhibiting bovine PD-1/PD-L1 binding in a concentration dependent manner.

(2) Binding Inhibition Test on Bovine PD-1 Expressing Cells and Soluble Bovine PD-L1 (Fig. 24)

Using bovine PD-1 expressing cells (described above) and bovine PD-L1-Ig (described above), bovine pD-1/PD-L1 binding inhibition by anti-bovine PD-L1 antibody was tested. First, rat anti-bovine PD-L1 antibody 4G12 or rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 at a final concentration of 0, 0.32, 0.63, 1.25, 2.5, 5 or 10 $\mu\text{g/ml}$ and bovine PD-L1-Ig at a final concentration of 1 $\mu\text{g/ml}$ were placed in 96-well plates, where they were reacted at room temperature for 30 min. The resultant mixture was reacted with 2×10^5 bovine PD-1 expressing cells at room temperature for 30 min. As negative control antibody, rat IgG2a (κ) isotype control (BD Biosciences) or bovine IgG1 antibody (Bethyl) was used. After washing, Alexa Fluor 647-labeled anti-rabbit IgG (H+L) goat F(ab')₂ (Life Technologies) was reacted at room temperature for 30 min to thereby detect bovine PD-L1-Ig bound to cell surfaces. For analysis, FACS Verse (BD Biosciences) was used. For every washing operation and dilution of antibody, PBS supplemented with 1% bovine serum

albumin (Sigma-Aldrich) was used. Taking the proportion of PD-L1-Ig bound cells without antibody addition as 100%, the proportion of PD-L1-Ig bound cells at each antibody concentration was shown as relative value.

The experimental results are shown in Fig. 24. It was revealed that like rat anti-bovine PD-L1 antibody 4G12, rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 is capable of inhibiting bovine PD-1/PD-L1 binding in a concentration dependent manner.

Biological Activity Test Using Rat-Bovine Chimeric Anti-Bovine PD-L1 Antibody

(1) Effect on Cell Proliferation (Fig. 25)

In order to confirm that bovine PD-1/PD-L1 binding inhibition by rat-bovine chimeric anti-PD-L1 antibody activates lymphocytes, a biological activity test was performed using cell proliferation as an indicator. Briefly, bovine PBMCs isolated from peripheral blood of healthy cattle were suspended in PBS to give a concentration of 10×10^6 cells/ml, and reacted with carboxyfluorescein succinimidyl ester (CFSE) at room temperature for 20 min. After washing twice with RPMI 1640 medium (Sigma-Aldrich) containing 10% inactivated fetal bovine serum (Cell Culture Technologies), antibiotics (streptomycin 200 μ g/ml, penicillin 200 U/ml) (Life Technologies) and 0.01% L-glutamine (Life Technologies), the PBMCs were reacted with anti-bovine CD3 mouse antibody (WSU Monoclonal Antibody Center) at 4°C for 30 min. After washing, the PBMCs were reacted with anti-mouse IgG1 microbeads (Miltenyi Biotec) at 4°C for 15 min, followed by isolation of CD3-positive T cells using autoMACSTM Pro (Miltenyi Biotec). To the isolated CD3-positive T cells, anti-bovine CD3 mouse antibody (WSU Monoclonal Antibody Center) and anti-bovine CD28 mouse antibody (Bio-Rad) were added. Then, the cells were co-cultured with bovine PD-L1 expressing cells (CD3-positive T cells: bovine PD-L1 expressing cells = 10:1) in the presence or absence of 10 μ g/ml of rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12. As a control for antibodies, serum-derived bovine IgG (Sigma-Aldrich) was used; as a control for PD-L1 expressing cells, EGFP expressing cells transfected with pEGFP-N2 were used. After a 6-day coculture, cells were harvested and reacted with anti-bovine CD4 mouse antibody and anti-bovine CD8 mouse antibody (Bio-Rad) at room temperature for 30 min. For the labeling of antibodies, Zenon Mouse IgG1 Labeling Kits (Life Technologies) or Lightning-Link Kit (Innova Biosciences) was used. For analysis, FACS Verse (BD Biosciences) was used. For washing operation after culturing and dilution of antibody, PBS supplemented with 1% bovine serum albumin (Sigma-Aldrich) was used.

The experimental results are shown in Fig. 25. Proliferation of CD4-positive and

CD8-positive T cells was significantly suppressed by co-culture with bovine PD-L1 expressing cells. It was revealed that rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 inhibits this suppression in CD4-positive T cells.

(2) Effect on IFN- γ Production (Fig. 26)

In order to confirm that bovine PD-1/PD-L1 binding inhibition by rat-bovine chimeric anti-PD-L1 antibody activates lymphocytes, a biological activity test was performed using IFN- γ production as an indicator. Briefly, PBMCs isolated from peripheral blood of BLV-infected cattle were suspended in RPMI medium (Sigma-Aldrich) containing 10% inactivated fetal bovine serum (Cell Culture Technologies), antibiotics (streptomycin 200 μ g/ml, penicillin 200 U/ml) (Life Technologies) and 0.01% L-glutamine (Life Technologies) to give a concentration of 4×10^6 cells/ml. To the PBMCs, 10 μ g/ml of rat anti-bovine PD-L1 antibody 4G12 or rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12, and 2% BLV-infected fetal lamp kidney cell (FLK-BLV) culture supernatant were added; culturing was then performed at 37 °C under 5% CO₂ for 6 days. As control antibodies, serum-derived rat IgG (Sigma-Aldrich) and serum-derived bovine IgG (Sigma-Aldrich) were used. After a 6-day culture, a culture supernatant was collected, and IFN- γ production was measured with Bovine IFN- γ ELISA Kit (BETYL). For each washing operation in ELISA, Auto Plate Washer BIO WASHER 50 (DS Pharma Biomedical) was used. Absorbance was measured with Microplate Reader MTP-650FA (Corona Electric).

The experimental results are shown in Fig. 26. It was revealed that rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 increases bovine PBMCs' IFN- γ response to BLV antigen in the same manner as rat anti-bovine PD-L1 antibody 4G12 (n=10).

CDR Analysis of Rat Anti-Bovine PD-L1 Antibody

The complementarity-determining regions (CDRs) of rat anti-bovine PD-L1 antibody 4G12 were determined using NCBI IGBLAST (<http://www.ncbi.nlm.nih.gov/igblast/>). The results are shown in Fig. 19.

Inoculation Test on Cattle

Established rat-bovine chimeric anti-bovine PD-L1 antibody ch4G12 (about 260 mg; 1 mg/kg) was intravenously administered into experimentally BLV-infected calf (Holstein, male, 7 months old, 267 kg). Blood samples were collected chronologically from the infected calf, followed by isolation of PBMCs by density gradient centrifugation.

(1) Cell Proliferation Response of T Cells to BLV Antigen (Fig. 27)

Bovine PBMCs were suspended in PBS and reacted with CFSE at room temperature for 20 min. After washing twice with RPMI 1640 medium (Sigma-Aldrich) containing 10%

inactivated fetal bovine serum (Cell Culture Technologies), antibiotics (streptomycin 200 µg/ml, penicillin 200 U/ml) (Life Technologies) and 0.01% L-glutamine (Life Technologies), the cell concentration was adjusted to 4×10^6 cells/ml using the same medium. Culture supernatant of 2% BLV-infected fetal lamp kidney cells (FLK-BLV) was added to the PBMCs, which were then cultured at 37°C under 5% CO₂ for 6 days. As a control, culture supernatant of 2% BLV-not-infected fetal lamp kidney cells (FLK) was used. After a 6-day culture, PBMCs were collected and reacted with anti-bovine CD4 mouse antibody, anti-bovine CD8 mouse antibody and anti-bovine IgM mouse antibody (Bio-Rad) at 4°C for 20 min. For the labeling of antibodies, Zenon Mouse IgG1 Labeling Kits (Life Technologies) or Lightning-Link Kit (Innova Biosciences) was used. For analysis, FACS Verse (BD Biosciences) was used. For every washing operation and dilution of antibody, PBS supplemented with 1% bovine serum albumin (Sigma-Aldrich) was used.

The experimental results are shown in Fig. 27. As a result of antibody administration, BLV-specific cell proliferation response of CD4-positive T cells increased compared to the response before administration.

(2) Changes in the BLV Provirus Load (Fig. 28)

DNA was extracted from isolated bovine PBMCs using Wizard DNA Purification kit (Promega). The concentration of the extracted DNA was quantitatively determined, taking the absorbance (260 nm) measured with Nanodrop 8000 Spectrophotometer (Thermo Fisher Scientific) as a reference. In order to measure the BLV provirus load in PBMCs, real time PCR was performed using Cycleave PCR Reaction Mix SP (TaKaRa) and Probe/Primer/Positive control for bovine leukemia virus detection (TaKaRa). Light Cycler 480 System II (Roche Diagnosis) was used for measurement.

The experimental results are shown in Fig. 28. The BLV provirus load significantly decreased until the end of test period compared to the load before administration.

All publications, patents and patent applications cited herein are incorporated herein by reference in their entirety.

INDUSTRIAL APPLICABILITY

The anti-PD-L1 antibody of the present invention is applicable to prevention and/or treatment of cancers and infections in animals.

SEQUENCE LISTING FREE TEXT

<SEQ ID NO: 1>

SEQ ID NO: 1 shows the amino acid sequence of the light chain variable region (VL) of rat anti-bovine PD-L1 antibody.

MESQTHVLISLLLSVSGTYGDIAITQSPSSVAVSVGETVTLSCKSSQSLLYSENQKDYL
GWYQQKPGQTPKPLIYWATNRHTGVPDRFTGSGSGTDFTLISSVQAEDLADYYCGQ
YLVYPFTFGPGTKLELK

<SEQ ID NO: 2>

SEQ ID NO: 2 shows the amino acid sequence of the heavy chain variable region (VH) of rat anti-bovine PD-L1 antibody.

MGWSQIILFLVAAATCVHSQVQLQQSGAELVKPGSSVKISCKASGYTFTSNFMHWVK
QQPGNGLEWIGWIYPEYGNTKYNQKFDGKATLTADKSSSTAYMQLSSLTSEDSAVYF
CASEEAVISLVYWGGQGLTVTVSS

<SEQ ID NO: 3>

SEQ ID NO: 3 shows the amino acid sequence of the light chain constant region (CL) of a canine antibody.

QPKASPSVTLFPPSSEELGANKATLVCLISDFYPSGVTVAWKASGSPVTQGVETTKPSK
QSNNKYAASSYLSLTPDKWKSHSSFCLVTHEGSTVEKKVAPAECS

<SEQ ID NO: 4>

SEQ ID NO: 4 shows the amino acid sequence of the heavy chain constant region (CH) of a canine antibody.

ASTTAPSVFPLAPSCGSTSGSTVALACLVSGYFPEPVTVSWNSGSLTSGVHTFPSVLQS
SGLYSLSSTVTVPSSRWPSETFTCNVVHPASNTKVDKVPKESTCKCISPCVPPELGG
PSVFIFPPKPKDILRITRTPETCVVLDLGREDPEVQISWFVDGKEVHTAKTQPREQQFN
STYRVVSVLPIEHQDWLTGKEFKCRVNHIGLPSPIERTISKARGQAHQPSVYVLPPSPK
ELSSSDTVTLTCLIKDFFPPEIDVEWQSNQPEPESEKYHTTAPQLDEDGSYFLYSKLSV
DKSRWQQGDTFTCAVMHEALQNHYTDLSSLHSPGK

<SEQ ID NO: 5>

SEQ ID NO: 5 shows the nucleotide sequence of the VL of rat anti-bovine PD-L1 antibody.

ATGGAATCACAGACGCATGTCCTCATTTCCCTTCTGCTCTCGGTATCTGGTACCTAT
GGGGACATTGCGATAACCCAGTCTCCATCCTCTGTGGCTGTGTCAGTAGGAGAGA

CGGTCACTCTGAGCTGCAAGTCCAGTCAGAGTCTTTTATACAGTGAAAACCAAAA
 GGACTATTTGGGCTGGTACCAGCAGAAACCAGGGCAGACTCCTAAACCCCTTATCT
 ACTGGGCAACCAACCGGCACACTGGGGTCCCTGATCGCTTCACAGGTAGTGGATC
 CGGGACAGACTTCACTCTGATCATCAGCAGTGTGCAGGCTGAAGACCTGGCTGAT
 TATTACTGTGGGCAGTACCTTGTCTATCCGTTACGTTTGGACCTGGGACCAAGCT
 GGAAGTGAAG

The nucleotide sequence of SEQ ID NO: 5 after codon optimization is shown in <SEQ ID NO: 15>.

ATGGAATCTCAAACCTCATGTTTTGATTTCACTTCTGAGTGTTTCCGGAACCTAC
 GGTGATATCGCTATCACTCAATCTCCCTCCTCTGTTGCTGTGTCTGTGGGCGAAAC
 CGTTACCTGTCTGCAAGTCCAGTCAGTCTCTTCTCTACTCCGAGAATCAAAAGG
 ACTACCTGGGCTGGTACCAACAGAAGCCCGGCCAGACCCCAAAGCCACTGATATA
 CTGGGCAACCAACAGGCACACCGGAGTGCCCGACAGGTTACAGGCAGTGGATC
 TGGCACCGACTTTACCTTGATCATTTCAAGCGTGCAGGCTGAAGATCTGGCCGACT
 ACTACTGTGGTCAGTATCTGGTGTATCCTTTCACTTTCGGGCCAGGGACAAAATTG
 GAATTGAAG

<SEQ ID NO: 6>

SEQ ID NO: 6 shows the nucleotide sequence of the VH of rat anti-bovine PD-L1 antibody.

ATGGGATGGAGCCAGATCATCCTCTTTCTGGTGGCAGCAGCTACATGTGTTCCTC
 CCAGGTACAGCTGCAGCAATCTGGGGCTGAATTAGTGAAGCCTGGGTCCTCAGTG
 AAAATTTCTGCAAGGCTTCTGGCTACACCTTCACCAGTAACTTTATGCACTGGGT
 AAAGCAGCAGCCTGGAAATGGCCTTGAGTGGATTGGGTGGATTTATCCTGAATATG
 GTAATACTAAGTACAATCAAAAGTTCGATGGGAAGGCAACACTCACTGCAGACAA
 ATCCTCCAGCACAGCCTATATGCAGCTCAGCAGCCTGACATCTGAGGACTCTGCAG
 TCTATTTCTGTGCAAGTGAGGAGGCAGTTATATCCCTTGTTTACTGGGGCCAAGGC
 ACTCTGGTCACTGTCTCTTCA

The nucleotide sequence of SEQ ID NO: 6 after codon optimization is shown in <SEQ ID NO: 16>.

ATGGGTTGGTCTCAAATTATCTTGTTTTTGGTTGCTGCAGCCACTTGTGTTCACTCT
 CAGGTGCAGCTGCAACAAAGCGGCGCAGAACTGGTGAAACCTGGCAGCAGCGTG
 AAAATATCTTGTAAGGCCAGCGGATATACTTTCACCTCCAATTCATGCATTGGGTC

AAACAGCAGCCCGGCAACGGACTCGAGTGGATCGGCTGGATCTACCCCGAGTATG
GCAACACAAAATATAACCAAAAATTTGATGGAAAGGCTACCCTGACTGCCGATAA
GTCCTCCAGCACCGCATACATGCAACTCTCCTCCCTGACCTCCGAGGATAGCGCTG
TCTACTTCTGTGCTTCCGAAGAGGCTGTCATATCCTTGGTCTATTGGGGCCAAGGA
ACTCTGGTGACCGTCTCATCT

<SEQ ID NO: 7>

SEQ ID NO: 7 shows the nucleotide sequence of the CL of a canine antibody.

CAGCCCAAGGCCTCCCCCTCGGTCACACTCTTCCCGCCCTCCTCTGAGGAGCTCG
GCGCCAACAAGGCCACCCTGGTGTGCCTCATCAGCGACTTCTACCCAGCGGCGT
GACGGTGGCCTGGAAGGCAAGCGGCAGCCCCGTCACCCAGGGCGTGGAGACCAC
CAAGCCCTCCAAGCAGAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCT
GACGCCTGACAAGTGGAAATCTCACAGCAGCTTCAGCTGCCTGGTCACGCACGA
GGGGAGCACCGTGGAGAAGAAGGTGGCCCCCGCAGAGTGCTCTTAG

The nucleotide sequence of SEQ ID NO: 7 after codon optimization is shown in <SEQ ID NO: 17>.

CAGCCCAAAGCCTCTCCCAGCGTCACCTCTTCCCACCTTCCAGTGAGGAGCTGG
GGGCAAACAAAGCCACTTTGGTGTGTCTCATCTCCGATTTTTTACCCCTCCGGGGTC
ACAGTCGCATGGAAGGCCTCCGGATCCCCTGTGACACAGGGAGTGGAGACAACA
AAACCTAGCAAGCAGAGTAACAATAAGTATGCCGCCTCAAGCTATCTCAGCCTTAC
TCCTGATAAGTGGAAAGTCATAGCAGTTTTAGTTGCCTCGTAACACATGAGGGTT
CAACTGTGGAGAAAAAAGTAGCTCCAGCTGAGTGCTCATGA

<SEQ ID NO: 8>

SEQ ID NO: 8 is the nucleotide sequence of the CH of a canine antibody.

GCCTCCACCACGGCCCCCTCGGTTTTCCeCACTGGCCCCCAGCTGCGGGTCCACTT
CCGGCTCCACGGTGGCCCTGGCCTGCCTGGTGTGAGGCTACTTCCCCGAGCCTGT
AACTGTGTCCTGGAATTCCGGCTCCTTGACCAGCGGTGTGCACACCTTCCCGTCC
GTCCTGCAGTCCTCAGGGCTCTACTCCCTCAGCAGCACGGTGACAGTGCCCTCCA
GCAGGTGGCCCAGCGAGACCTTCACCTGCAACGTGGTCCACCCGGCCAGCAACA
CTAAAGTAGACAAGCCAGTGCCCAAAGAGTCCACCTGCAAGTGTATATCCCCATG
CCCAGTCCCTGAATCACTGGGAGGGCCTTCGGTCTTCATCTTTCCCCCGAAACCCA
AGGACATCCTCAGGATTACCCGAACACCCGAGATCACCTGTGTGGTGTAGATCTG

GGCCGTGAGGACCCTGAGGTGCAGATCAGCTGGTTCGTGGATGGTAAGGAGGTG
CACACAGCCAAGACGCAGCCTCGTGAGCAGCAGTTCAACAGCACCTACCGTGTG
GTCAGCGTCCTCCCCATTGAGCACCAGGACTGGCTCACCGGAAAGGAGTTCAAGT
GCAGAGTCAACCACATAGGCCTCCCGTCCCCCATCGAGAGGACTATCTCCAAAGC
CAGAGGGCAAGCCCATCAGCCCAGTGTGTATGTCCTGCCACCATCCCCAAAGGAG
TTGTCATCCAGTGACACGGTCACCCTGACCTGCCTGATCAAAGACTTCTTCCCACC
TGAGATTGATGTGGAGTGGCAGAGCAATGGACAGCCGGAGCCCGAGAGCAAGTA
CCACACGACTGCGCCCCAGCTGGACGAGGACGGGTCTTCTTCTGTACAGCAAG
CTCTCTGTGGACAAGAGCCGCTGGCAGCAGGGAGACACCTTCACATGTGCGGTGA
TGCATGAAGCTCTACAGAACCACTACACAGATCTATCCCTCTCCATTCTCCGGGT
AAATGA

The nucleotide sequence of SEQ ID NO: 8 after codon optimization is shown in <SEQ ID NO: 18>.

GCTAGCACAACCGCTCCCTCCGTTTTTCCCCTCGCCCCATCCTGCGGGTCAACCAG
CGGATCCACCGTCGCTCTGGCTTGTCTGGTGTGTCAGGATACTTCCCCGAGCCTGTCA
CCGTTTCTTGGAATAGCGGCAGCCTTACTTCCGGCGTGCATACCTTCCCTAGCGTG
CTTCAGTCCTCCGGTCTGTATTCCCTCAGCTCCACCGTAACTGTCCCAAGCTCAAG
GTGGCCCTCTGAGACATTTACCTGCAATGTGGTCCATCCTGCTTCAAATACCAAAG
TGGACAAGCCCGTCCCAAAAGAGTCTACCTGCAAATGTATCAGTCCTTGTCCCGT
GCCCCGAGTCTCTGGGCGGACCCTCAGTCTTTATCTTCCCACCCAAGCCAAAGGAC
ATATTGCGCATTACACGGACACCCGAAATCACCTGTGTTGTGTTGGATCTCGGCCG
GGAAGATCCTGAGGTGCAGATTAGTTGGTTTGTGTTGATGGCAAGGAGGTGCACACA
GCAAAAACACAGCCCAGAGAACAGCAGTTCAACAGTACTTATAGAGTAGTGAGT
GTGTTGCCTATAGAGCATCAGGACTGGCTGACAGGCAAAGAATTCAAATGTAGGG
TTAACCACATTGGCCTCCCTAGTCCAATCGAGAGGACAATCTCTAAAGCCCGAGG
CCAGGCTCATCAGCCTTCTGTGTACGTTCTGCCTCCTAGTCCTAAGGAACTGTCTT
CTTCAGACACAGTAACACTCACTTGCCTGATTAAGGACTTTTTTCCCTCCAGAGATT
GATGTGGAATGGCAGTCTAACGGGCAGCCAGAGCCAGAATCTAAGTACCACACTA
CTGCACCACAGCTGGATGAGGATGGGTCTTACTTCCTGTACAGTAAGCTGAGTGT
GGACAAGTCTCGATGGCAGCAGGGGGATACTTTTACTTGCGCAGTAATGCACGAA
GCATTGCAGAACCACTACACTGACCTGTCACTTAGTCACTCACCAGGGAAGTAA

<SEQ ID NO: 9>

SEQ ID NO: 9 shows the amino acid sequence of a chimeric light chain consisting of the VL of rat anti-bovine PD-L1 antibody and the CL of a canine antibody.

MESQTHVLISLLLSVSGTYGDIAITQSPSSVAVSVGETVTLSCSSQSLLYSENQKDYL
GWYQQKPGQTPKPLIYWATNRHTGVPDRFTGSGSGTDFTLISSVQAEDLADYYCGQ
YLVYPFTFGPGTKLELKQPKASPSVTLFPPSSEELGANKATLVCLISDFYPSGVTVAWK
ASGSPVTQGVETTKPSKQSNNKYAASSYLSLTPDKWKSHSSFCLVTHEGSTVEKKV
APA ECS

<SEQ ID NO: 10>

SEQ ID NO: 10 shows the amino acid sequence of a chimeric heavy chain consisting of the VH of rat anti-bovine PD-L1 antibody and the CH of a canine antibody.

MGWSQIILFLVAAATCVHSQVQLQQSGAELVKPGSSVKISCKASGYTFTSNFMHWVK
QQPGNGLEWIGWIYPEYGNTKYNQKFDGKATLTADKSSSTAYMQLSSLTSEDSAVYF
CASEEAVISLVYWGGQGLTVTVSSASTTAPSVFPLAPSCGSTSGSTVALACLVSGYFPEP
VTVSWNSGSLTSGVHTFPSVLQSSGLYLSSTVTVPSSRWPSETFTCNV VHPASNTKV
DKPVPKESTCKCISPCVPESLGGPSVFIFPPKPKDILRITRTPEITCVVLDLGREDPEVQ
ISWFVDGKEVHTAKTQPREQQFNSTYRVVSVLPIEHQDWLTGKEFKCRVNHIGLPSPI
ERTISKARGQAHQPSVYVLPPSPKELSSSDTVTLTCLIKDFFPPEIDVEWQSNGQPEPES
KYHTTAPQLDEDGSYFLYSKLSVDKSRWQQGDTFTCAVMHEALQNHYTDLSLSHSP
GK

<SEQ ID NO: 19>

This sequence shows the nucleotide sequence (after codon optimization) of a chimeric light chain consisting of the VL of rat anti-bovine PD-L1 antibody and the CL of a canine antibody.

ATGGAATCTCAAACATCATGTTTTGATTTCACTTCTGAGTGTTTCCGGAACCTAC
GGTGATATCGCTATCACTCAATCTCCCTCCTCTGTTGCTGTGTCTGTGGGCGAAAC
CGTTACCCTGTCCTGCAAGTCCAGTCAGTCTCTTCTCTACTCCGAGAATCAAAAGG
ACTACCTGGGCTGGTACCAACAGAAGCCCGGCCAGACCCCAAAGCCACTGATATA
CTGGGCAACCAACAGGCACACCGGAGTGCCCGACAGGTTACAGGCAGTGGATC
TGGCACCGACTTTACCTTGATCATTTCAAGCGTGCAGGCTGAAGATCTGGCCGACT
ACTACTGTGGTCAGTATCTGGTGTATCCTTTCACTTTCCGGGCCAGGGACAAAATTG
GAATTGAAGCAGCCCAAAGCCTCTCCAGCGTCACCCTCTTCCACCTTCCAGTG
AGGAGCTGGGGGCAAACAAAGCCACTTTGGTGTGTCTCATCTCCGATTTTTACCC

CTCCGGGGTTCACAGTCGCATGGAAGGCCTCCGGATCCCCTGTGACACAGGGAGTG
 GAGACAACAAAACCTAGCAAGCAGAGTAACAATAAGTATGCCGCCTCAAGCTATC
 TCAGCCTTACTCCTGATAAGTGGAAGTCACATAGCAGTTTTAGTTGCCTCGTAACA
 CATGAGGGTTCAACTGTGGAGAAAAAAGTAGCTCCAGCTGAGTGCTCATGA

<SEQ ID NO: 20>

SEQ ID NO: 20 shows the nucleotide sequence (after codon optimization) of a chimeric heavy chain consisting of the VH of rat anti-bovine PD-L1 antibody and the CH of a canine antibody.

ATGGGTTGGTCTCAAATTATCTTGTTTTTGGTTGCTGCAGCCACTTGTGTTTCATTCT
 CAGGTGCAGCTGCAACAAAGCGGCGCAGAAGTGGTGAAACCTGGCAGCAGCGTG
 AAAATATCTTGTAAGGCCAGCGGATATACTTTACCTCCAATTCATGCATTGGGTC
 AAACAGCAGCCCGGCAACGGACTCGAGTGGATCGGCTGGATCTACCCCGAGTATG
 GCAACACAAAATATAACCAAAAATTTGATGGAAAGGCTACCCTGACTGCCGATAA
 GTCTCCAGCACCGCATACATGCAACTCTCCTCCCTGACCTCCGAGGATAGCGCTG
 TCTACTTCTGTGCTTCCGAAGAGGCTGTCATATCCTTGGTCTATTGGGGCCAAGGA
 ACTCTGGTGACCGTCTCATCTGCTAGCACAACCGCTCCCTCCGTTTTTCCCCTCGC
 CCCATCCTGCGGGTCAACCAGCGGATCCACCGTCGCTCTGGCTTGTCTGGTGTCA
 GGATACTTCCCCGAGCCTGTCACCGTTTCTTGAATAGCGGCAGCCTTACTTCCGG
 CGTGCATACCTTCCCTAGCGTGCTTCAGTCCTCCGGTCTGTATTCCCTCAGCTCCAC
 CGTAACTGTCCCAAGCTCAAGGTGGCCCTCTGAGACATTTACCTGCAATGTGGTCC
 ATCCTGCTTCAAATACCAAAAGTGGACAAGCCCGTCCCAAAAGAGTCTACCTGCAA
 ATGTATCAGTCCTTGTCCCGTGCCCGAGTCTCTGGGCGGACCCTCAGTCTTTATCTT
 CCCACCCAAGCCAAAGGACATATTGCGCATTACACGGACACCCGAAATCACCTGT
 GTTGTGTTGGATCTCGGCCGGGAAGATCCTGAGGTGCAGATTAGTTGGTTTGTGTA
 TGGCAAGGAGGTGCACACAGCAAAAACACAGCCCAGAGAACAGCAGTTCAACA
 GTACTTATAGAGTAGTGAGTGTGTTGCCTATAGAGCATCAGGACTGGCTGACAGGC
 AAAGAATTCAAATGTAGGGTTAACCACATTGGCCTCCCTAGTCCAATCGAGAGGA
 CAATCTCTAAAGCCCCGAGGCCAGGCTCATCAGCCTTCTGTGTACGTTCTGCCTCCT
 AGTCCTAAGGAAGTGTCTTCTTCAGACACAGTAACACTCACTTGCTGATTAAGG
 ACTTTTTTCTCCTCCAGAGATTGATGTGGAATGGCAGTCTAACGGGCAGCCAGAGCC
 AGAATCTAAGTACCACACTACTGCACCACAGCTGGATGAGGATGGGTCTTACTTCC
 TGTACAGTAAGCTGAGTGTGGACAAGTCTCGATGGCAGCAGGGGGATACTTTTAC
 TTGCGCAGTAATGCACGAAGCATTGCAGAACCCTACACTGACCTGTCACTTAGT

CACTCACCAGGGAAGTAA

<SEQ ID NO: 11>

SEQ ID NO: 11 shows the amino acid sequence of the CL of a human antibody.

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

<SEQ ID NO: 12>

SEQ ID NO: 12 shows the amino acid sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 1).

STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQKTYTCNVDPKPSNTKVDKRVESKYGPPCPSCPAPEFLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE
QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR
LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK

<SEQ ID NO: 13>

SEQ ID NO: 13 shows the nucleotide sequence of the CL of a human antibody.

ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

<SEQ ID NO: 14>

SEQ ID NO: 14 shows the nucleotide sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 1).

TCCACCAAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCG
AGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA
CGGTGTCGTGGAAGTCAAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGT
CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACC

AAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCATGCCCAG
CACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCAAACCCAAGGA
CACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGC
CAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATA
ATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCA
GCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA
AGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAA
AGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGAT
GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC
GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTG
GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGG
CTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAATGA

<SEQ ID NOS: 21-36>

SEQ ID NOS: 21-36 show the nucleotide sequences of primers cPD-1 inner F, cPD-1 inner R, cPD-L1 inner F, cPD-L1 inner R, cPD-1 5' GSP, cPD-1 3' GSP, cPD-L1 5' GSP, cPD-L1 3' GSP, cPD-1-EGFP F, cPD-1-EGFP R, cPD-L1-EGFP F, cPD-L1-EGFP R, cPD-1-Ig, cPD-1-Ig R, cPD-L1-Ig F and cPD-L1-Ig R in this order.

<SEQ ID NO: 37>

SEQ ID NO: 37 shows the amino acid sequence (QSLLYSENQKDY) of CDR1 of the VL of rat anti-bovine PD-L1 antibody 4G12.

<SEQ ID NO: 38>

SEQ ID NO: 38 shows the amino acid sequence (QSLLYSENQKDY) of CDR3 of the VL of rat anti-bovine PD-L1 antibody 4G12.

<SEQ ID NO: 39>

SEQ ID NO: 39 shows the amino acid sequence (GYTFTSNF) of CDR1 of the VH of rat anti-bovine PD-L1 antibody 4G12.

<SEQ ID NO: 40>

SEQ ID NO: 40 shows the amino acid sequence (IYPEYGNT) of CDR2 of the VH of rat anti-bovine PD-L1 antibody 4G12.

<SEQ ID NO: 41>

SEQ ID NO: 41 shows the amino acid sequence (ASEEAVISLVY) of CDR3 of the VH of rat

anti-bovine PD-L1 antibody 4G12.

<SEQ ID NO: 42>

SEQ ID NO: 42 shows the amino acid sequence of the CH (CH1-CH3) of ovine antibody (IgG1).

<SEQ ID NO: 43>

SEQ ID NO: 43 shows the nucleotide sequence of the CH (CH1-CH3) of ovine antibody (IgG1).

<SEQ ID NO: 44>

SEQ ID NO: 44 he amino acid sequence of the CH (CH1-CH3) of ovine antibody (IgG2).

<SEQ ID NO: 45>

SEQ ID NO: 45 shows the nucleotide sequence of the CH (CH1-CH3) of ovine antibody (IgG2).

<SEQ ID NO: 46>

SEQ ID NO: 46 shows the amino acid sequence of the light chain (Ig kappa(CK)) constant region of an ovine antibody.

<SEQ ID NO: 47>

SEQ ID NO: 47 shows the nucleotide sequence of the light chain (Ig kappa(CK)) constant region of an ovine antibody.

<SEQ ID NO: 48>

SEQ ID NO: 48 shows the amino acid sequence of the light chain (Ig lambda(CL)) constant region of an ovine antibody.

<SEQ ID NO: 49>

SEQ ID NO: 49 shows the nucleotide sequence of the light chain (Ig lambda(CL)) constant region of an ovine antibody.

<SEQ ID NO: 50>

SEQ ID NO: 50 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG1^a).

<SEQ ID NO: 51>

SEQ ID NO: 51 shows the nucleotide acid sequence of the CH (CH1-CH3) of porcine antibody (IgG1^a).

<SEQ ID NO: 52>

SEQ ID NO: 52 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG1^b).

<SEQ ID NO: 53>

SEQ ID NO: 53 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG1^b).

<SEQ ID NO: 54>

SEQ ID NO: 54 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG2^a).

<SEQ ID NO: 55>

SEQ ID NO: 55 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG2^a).

<SEQ ID NO: 56>

SEQ ID NO: 56 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG2^b).

<SEQ ID NO: 57>

SEQ ID NO: 57 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG2^b).

<SEQ ID NO: 58>

SEQ ID NO: 58 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG3).

<SEQ ID NO: 59>

SEQ ID NO: 59 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG3).

<SEQ ID NO: 60>

SEQ ID NO: 60 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG4^a).

<SEQ ID NO: 61>

SEQ ID NO: 61 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG4^a).

<SEQ ID NO: 62>

SEQ ID NO: 62 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG4^b).

<SEQ ID NO: 63>

SEQ ID NO: 63 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG4^b).

<SEQ ID NO: 64>

SEQ ID NO: 64 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody

(IgG5^a).

<SEQ ID NO: 65>

SEQ ID NO: 65 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG5^a).

<SEQ ID NO: 66>

SEQ ID NO: 66 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG5^b).

<SEQ ID NO: 67>

SEQ ID NO: 67 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG5^b).

<SEQ ID NO: 68>

SEQ ID NO: 68 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG6^a).

<SEQ ID NO: 69>

SEQ ID NO: 69 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG6^a).

<SEQ ID NO: 70>

SEQ ID NO: 70 shows the amino acid sequence of the CH (CH1-CH3) of porcine antibody (IgG6^b).

<SEQ ID NO: 71>

SEQ ID NO: 71 shows the nucleotide sequence of the CH (CH1-CH3) of porcine antibody (IgG6^b).

<SEQ ID NO: 72>

SEQ ID NO: 72 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG1).

<SEQ ID NO: 73>

SEQ ID NO: 73 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG1).

<SEQ ID NO: 74>

SEQ ID NO: 74 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG2).

<SEQ ID NO: 75>

SEQ ID NO: 75 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG2).

<SEQ ID NO: 76>

SEQ ID NO: 76 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG3).

<SEQ ID NO: 77>

SEQ ID NO: 77 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG3).

<SEQ ID NO: 78>

SEQ ID NO: 78 shows the amino acid sequence of the light chain (estimated to be Ig lambda) constant region (CL) of a water buffalo antibody.

<SEQ ID NO: 79>

SEQ ID NO: 79 shows the nucleotide sequence of the light chain (estimated to be Ig lambda) constant region (CL) of a water buffalo antibody.

<SEQ ID NO: 80>

SEQ ID NO: 80 shows the amino acid sequence of the CH (CH1-CH3) of human antibody (IgG4 variant 2).

<SEQ ID NO: 81>

SEQ ID NO: 81 shows the nucleotide sequence of the CH (CH1-CH3) of human antibody (IgG4 variant 2).

<SEQ ID NO: 82>

SEQ ID NO: 82 shows the amino acid sequence of the CH (CH1-CH3) of human antibody (IgG4 variant 3).

<SEQ ID NO: 83>

SEQ ID NO: 83 shows the nucleotide sequence of the CH (CH1-CH3) of human antibody (IgG4 variant 3).

<SEQ ID NO: 84>

SEQ ID NO: 84 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 1).

<SEQ ID NO: 85>

SEQ ID NO: 85 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 2).

<SEQ ID NO: 86>

SEQ ID NO: 86 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 3).

<SEQ ID NO: 87>

SEQ ID NO: 87 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 1).

<SEQ ID NO: 88>

SEQ ID NO: 88 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 2).

<SEQ ID NO: 89>

SEQ ID NO: 89 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 3).

<SEQ ID NO: 90>

SEQ ID NO: 90 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG3 variant 1).

<SEQ ID NO: 91>

SEQ ID NO: 91 shows the amino acid sequence of the CH (CH1-CH3) of bovine antibody (IgG3 variant 2).

<SEQ ID NO: 92>

SEQ ID NO: 92 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 1).

<SEQ ID NO: 93>

SEQ ID NO: 93 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 2).

<SEQ ID NO: 94>

SEQ ID NO: 94 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG1 variant 3).

<SEQ ID NO: 95>

SEQ ID NO: 95 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 1).

<SEQ ID NO: 96>

SEQ ID NO: 96 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 2).

<SEQ ID NO: 97>

SEQ ID NO: 97 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG2 variant 3).

<SEQ ID NO: 98>

SEQ ID NO: 98 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody

(IgG3 variant 1).

<SEQ ID NO: 99>

SEQ ID NO: 99 shows the nucleotide sequence of the CH (CH1-CH3) of bovine antibody (IgG3 variant 2).

<SEQ ID NO: 100>

SEQ ID NO: 100 shows the amino acid sequence of the CL of a bovine antibody (bovine Ig lambda, GenBank: X62917).

QPKSPPSVTLFPPSTEELNGNKATLVCLISDFYPGSVTVVWKADGSTITRNVETTRASK
QNSKYAASSYLSLTSSDWKSKGSYSCEVTHEGSTVTKTVKPSECS

<SEQ ID NO: 101>

SEQ ID NO: 101 shows the nucleotide sequence of the CL of a bovine antibody (bovine Ig lambda, GenBank: X62917).

CAGCCCAAGTCCCCACCCTCGGTCACCCTGTTCCCGCCCTCCACGGAGGAGCTCA
ACGGCAACAAGGCCACCCTGGTGTGTCTCATCAGCGACTTCTACCCGGGTAGCGT
GACCGTGGTCTGGAAGGCAGACGGCAGCACCATCACCCGCAACGTGGAGACCAC
CCGGGCCTCCAAACAGAGCAACAGCAAGTACGCGGCCAGCAGCTACCTGAGCCT
GACGAGCAGCGACTGGAAATCGAAAGGCAGTTACAGCTGCGAGGTCACGCACGA
GGGGAGCACCGTGACGAAGACAGTGAAGCCCTCAGAGTGTTCTTAG

The nucleotide sequence of SEQ ID NO: 101 after codon optimization is shown in <SEQ ID NO: 104>.

CAGCCTAAGAGTCCTCCTTCTGTAACACTCTTTCCCCCTCTACCGAGGAACTCAA
CGGCAATAAAGCTACCTTGGTTTGCCTTATTTCTGATTTCTACCCCGGGTCTGTGAC
CGTGGTGTGGAAAGCTGATGGGTCCACCATTACTCGGAATGTGGAAACCACCCGG
GCTTCTAAGCAGTCCAACCTCTAAATACGCAGCATCCTCCTATTTGAGTCTTACTAGT
AGTGACTGGAAGTCAAAGGGTAGTTACAGTTGCGAAGTCACACATGAAGGTTCA
ACAGTGACAAAGACAGTCAAGCCCTCAGAGTGCTCATAG

<SEQ ID NO: 102>

SEQ ID NO: 102 shows the amino acid sequence of the CH of a bovine antibody (bovine IgG1, modified from GenBank: X62916). The sites of mutation are underlined. Amino acid numbers and mutations: 113E→P, 114L→V, 115P→A, 116G→deletion, 209A→S, 210P→S
ASTTAPKVYPLSSCCGDKSSSTVTLGCLVSSYMPEPVTVTWNSGALKSGVHTFPAVL
QSSGLYSLSSMVTVPGSTSGQTFTCNVAHPASSTKVDKAVDPTCKPSPCDCCPPPVA
GPSVFIFPPKPKDTLTISGTPEVTCVVVDVGHDDPEVKFSWFVDDVEVNTATTKPREE
QFNSTYRVVSALRIQHQQDWTGGKEFKCKVHNEGLPSIVRTISRTKGPAREPQVYVLA

PPQEELSKSTVSLTCMVTSFYPDYIAVEWQRNGQPESEDKYGTTPPQLDADSSYFLYS
KLRVDRNSWQEGDTYTCVVMHEALHNHYTQKSTSKSAGK

<SEQ ID NO: 103>

SEQ ID NO: 103 shows the nucleotide sequence (after codon optimization) of the CH of a bovine antibody (bovine IgG1, modified from GenBank: X62916).

GCTAGCACAACTGCTCCTAAGGTGTACCCCCTGAGCTCTTGCTGCGGCGACAAGT
CTAGCAGCACCGTGACCCTCGGATGCCTCGTCAGCAGCTATATGCCTGAGCCAGTT
ACAGTGACATGGAATTCTGGTGCCCTTAAGTCCGGCGTCCATACCTTCCCTGCTGT
GCTGCAGTCCTCTGGCCTGTACAGTTTGTCTCTATGGTGACAGTACCCGGTTCCA
CCTCCGGACAGACCTTTACCTGTAATGTGGCTCATCCCGCCTCCTCCACAAAGGTG
GATAAGGCTGTTGACCCTACCTGTAAACCCAGTCCATGCGACTGCTGTCCCCCCCC
TCCAGTTGCCGGACCCTCAGTCTTTATTTTCCACCCAAACCCAAAGACACCCTGA
CAATCTCTGGAACACCAGAAGTCACCTGCGTCGTCGTGGATGTGGGCCACGACGA
TCCTGAGGTAAAATTCTCATGGTTCGTCGACGATGTGGAAGTGAATACAGCTACTA
CAAAACCTCGCGAAGAGCAGTTTAACTCTACCTATCGAGTGGTTTCTGCTTTGCGG
ATTCAGCATCAGGATTGGACAGGCGGCAAAGAGTTTAAATGTAAAGTCCATAACG
AGGGACTTCCTTCTAGTATCGTGCGCACTATCAGTAGAACTAAAGGGCCTGCTCGG
GAACCTCAGGTGTACGTCCTGGCACCTCCACAGGAAGAGCTGAGTAAGTCTACAG
TTTCTCTGACTTGTATGGTAACATCTTTTATCCAGATTACATCGCAGTTGAATGGC
AGAGGAACGGGCAGCCAGAGAGTGAGGATAAGTACGGGACTACTCCACCACAGC
TGGACGCAGACTCAAGTTACTTCCTGTACTCAAAGCTGAGGGTTGACAGAACTC
ATGGCAGGAGGGGGACACTTACACTTGCGTAGTTATGCACGAGGCACTTCACAAC
CACTACACTCAGAAGAGTACTTCAAAGAGTGCAGGGAAGTAA

<SEQ ID NO: 105>

SEQ ID NO: 105 shows the amino acid sequence of a chimeric light chain consisting of the VL of rat anti-bovine PD-L1 antibody and the CL of a bovine antibody.

MESQTHVLISLLLSVSGTYGDIAITQSPSSVAVSVGETVTLSCSSQSLLYSENQKDYL
GWYQQKPGQTPKPLIYWATNRHTGVPDRFTGSGSGTDFTLISSVQAEDLADYYCGQ
YLVYPFTFGPGTKLELKQPKSPPSVTLPFPSTEELNGNKATLVCLISDFYPGSVTVVWK
ADGSTITRNVETTRASKQSNISKYAASSYLSLTSSDWKSKGSYSCEVTHEGSTVTKTV
KPSECS

<SEQ ID NO: 106>

SEQ ID NO: 106 shows the amino acid sequence of a chimeric heavy chain consisting of the VH of rat anti-bovine PD-L1 antibody and the CH of a bovine antibody (bovine IgG1,

modified from GenBank: X62916).

MGWSQIILFLVAAATCVHSQVQLQQSGAELVKPGSSVKISCKASGYTFTSNFMHWVK
 QQPGNGLEWIGWIYPEYGNTKYNQKFDGKATLTADKSSSTAYMQLSSLTSEDSAVYF
 CASEEAVISLVYWGGTLTVSSASTTAPKVYPLSSCCGDKSSSTVTLGCLVSSYMPE
 PVTVTWNSGALKSGVHTFPAVLQSSGLYSLSSMVTVPGSTSGQTFTCNVAHPASSTKV
 DKAVDPTCKPSPCDCCPPPPVAGPSVFIFPPKPKDTLTISGTPEVTCVVVDVGHDDPEV
 KFSWFVDDVEVNTATTKPREEQFNSTYRVVSALRIQHQDWTGGKEFKCKVHNEGLP
 SSIVRTISRTKGPAEPQVYVLAPPQEELSKSTVSLTCMVTSFYDPDYIAVEWQRNGQPE
 SEDKYGTTPPQLDADSSYFLYSKLRVDRNSWQEGDTYTCVVMHEALHNHYTQKSTS
 KSAGK

<SEQ ID NO: 107>

This sequence shows the nucleotide sequence (after codon optimization) of a chimeric light chain consisting of the VL of rat anti-bovine PD-L1 antibody and the CL of a bovine antibody.

ATGGAATCTCAAACCTCATGTTTTGATTTCACTTCTGAGTGTTTCCGGAACCTAC
 GGTGATATCGCTATCACTCAATCTCCCTCCTCTGTTGCTGTGTCTGTGGGCGAAAC
 CGTTACCCTGTCCTGCAAGTCCAGTCAGTCTCTTCTCTACTCCGAGAATCAAAAGG
 ACTACCTGGGCTGGTACCAACAGAAGCCCGGCCAGACCCCAAAGCCACTGATATA
 CTGGGCAACCAACAGGCACACCGGAGTGCCCGACAGGTTACAGGCAGTGGATC
 TGGCACCGACTTTACCTTGATCATTTCAGCGTGCAGGCTGAAGATCTGGCCGACT
 ACTACTGTGGTCAGTATCTGGTGTATCCTTTCACTTTCCGGGCCAGGGACAAAATC
 GAGCTCAAACAGCCTAAGAGTCCTCCTTCTGTAACTCTTTCCCCCTCTACCGA
 GGAATCAACGGCAATAAAGCTACCTTGGTTTGCCTTATTTCTGATTTCTACCCCG
 GGTCTGTGACCGTGGTGTGGAAAGCTGATGGGTCCACCATTACTCGGAATGTGGA
 AACCACCCGGGCTTCTAAGCAGTCCAATCTAAATACGCAGCATCCTCCTATTTGA
 GTCTTACTAGTAGTACTGGAAGTCAAAGGGTAGTTACAGTTGCGAAGTCACACA
 TGAAGGTTCAACAGTGACAAAGACAGTCAAGCCCTCAGAGTGCTCATAG

<SEQ ID NO: 108>

This sequence shows the nucleotide sequence (after codon optimization) of a chimeric heavy chain consisting of the VH of rat anti-bovine PD-L1 antibody and the CH of a bovine antibody (bovine IgG1, modified from GenBank: X62916).

ATGGGGTGGTCCCAGATTATATTGTTCCCTCGTCGCCGCCGCCACTTGCGTACACAG
 CCAAGTGCAACTTCAACAAAGCGGTGCAGAACTGGTAAAGCCCGGTAGCTCTGT
 GAAAATATCCTGTAAAGCCAGTGGCTACACATTTACCAGCAACTTTATGCACTGGG

TGAAGCAACAGCCCGGAAATGGCTTGGAGTGGATTGGCTGGATCTATCCCGAATAT
 GGTAACACCAAGTATAATCAGAAGTTCGACGGTAAGGCCACCCTCACCGCCGATA
 AGTCATCCTCCACCGCCTATATGCAGCTCAGCAGCCTGACCAGCGAGGATTCCGCT
 GTGTA CT TCTGTGCCAGCGAAGAGGCTGTGATCTCATTGGTGTATTGGGGACAGG
 GCACCCTCGTCACCGTGTCCAGCGCTAGCACAACTGCTCCTAAGGTGTACCCCT
 GAGCTCTTGCTGCGGCGACAAGTCTAGCAGCACCGTGACCCTCGGATGCCTCGTC
 AGCAGCTATATGCCTGAGCCAGTTACAGTGACATGGAATTCTGGTGCCCTTAAGTC
 CGGCGTCCATACCTTCCCTGCTGTGCTGCAGTCCTCTGGCCTGTACAGTTTGTCT
 CTATGGTGACAGTACCCGGTTCCACCTCCGGACAGACCTTTACCTGTAATGTGGCT
 CATCCCGCCTCCTCCACAAAGGTGGATAAGGCTGTTGACCCTACCTGTAAACCCA
 GTCCATGCGACTGCTGTCCCCCCCCCTCCAGTTGCCGGACCCTCAGTCTTTATTTTC
 CCACCCAAACCCAAAGACACCCTGACAATCTCTGGAACACCAGAAGTCACCTGC
 GTCGTCGTGGATGTGGGGCCACGACGATCCTGAGGTAAAATTCTCATGGTTCGTCGA
 CGATGTGGAAGTGAATACAGCTACTACAAAACCTCGCGAAGAGCAGTTTAACTCT
 ACCTATCGAGTGGTTTCTGCTTTGCGGATTCAGCATCAGGATTGGACAGGCGGCAA
 AGAGTTTAAATGTAAAGTCCATAACGAGGGACTTCCTTCTAGTATCGTGCGCACTA
 TCAGTAGAACTAAAGGGCCTGCTCGGGAACCTCAGGTGTACGTCCTGGCACCTCC
 ACAGGAAGAGCTGAGTAAGTCTACAGTTTCTCTGACTTGTATGGTAACATCTTTTT
 ATCCAGATTACATCGCAGTTGAATGGCAGAGGAACGGGCAGCCAGAGAGTGAGG
 ATAAGTACGGGACTACTCCACCACAGCTGGACGCAGACTCAAGTTACTTCCTGTA
 CTCAAAGCTGAGGGTTGACAGAACTCATGGCAGGAGGGGGACACTTACACTTG
 CGTAGTTATGCACGAGGCACTTCACAACCACTACACTCAGAAGAGTACTTCAAAG
 AGTGCAGGGAAGTAA

<SEQ ID NOS: 109-132>

SEQ ID NOS: 109-132 show the nucleotide sequences of primers ovPD-L1 CDS F, ovPD-L1 CDS R, poPD-L1 CDS F, poPD-L1 CDS R, buPD-L1 CDS F1, buPD-L1 CDS R1, buPD-L1 CDS F2, buPD-L1 CDS R2, ovPD-1-EGFP F, ovPD-1-EGFP R, ovPD-L1-EGFP F, ovPD-L1-EGFP R, poPD-1-EGFP F, poPD-1-EGFP R, poPD-L1-EGFP F, poPD-L1-EGFP R, ovPD-L1-Ig F, ovPD-L1-Ig R, poPD-L1-Ig F, poPD-L1-Ig R, cCD80-Ig F, cCD80-Ig R, cPD-L1-His F and cPD-L1-His R in this order.

<SEQ ID NOS: 133-138>

SEQ ID NOS: 133-138 show nucleotide sequences of primers boPD-1-myc F, boPD-1-myc R, boPD-L1-EGFP F, boPD-L1-EGFP R, boPD-L1-Ig F and boPD-L1-Ig R in this order.

SEQUENCE LISTING

<110> NATIONAL UNIVERSITY CORPORATION HOKKAIDO UNIVERSITY

<120> Anti-PD-L1 antibodies

<130> FP-221PCT

<150> JP P2016-159088

<151> 2016-08-15

<150> JP P2016-159089

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Gly Thr Tyr Gly Asp Ile Ala Ile Thr Gln Ser Pro Ser Ser Val Ala
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Val Ser Val Gly Glu Thr Val Thr Leu Ser Cys Lys Ser Ser Gln Ser
 35 40 45

Leu Leu Tyr Ser Glu Asn Gln Lys Asp Tyr Leu Gly Trp Tyr Gln Gln
 50 55 60

Lys Pro Gly Gln Thr Pro Lys Pro Leu Ile Tyr Trp Ala Thr Asn Arg
65 70 75 80

His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
 85 90 95

Phe Thr Leu Ile Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr
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Lys Leu Glu Leu Lys
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 20 25 30

Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 40 45

Thr Ser Asn Phe Met His Trp Val Lys Gln Gln Pro Gly Asn Gly Leu
 50 55 60

Glu Trp Ile Gly Trp Ile Tyr Pro Glu Tyr Gly Asn Thr Lys Tyr Asn
 65 70 75 80

Gln Lys Phe Asp Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
 85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 105 110

Tyr Phe Cys Ala Ser Glu Glu Ala Val Ile Ser Leu Val Tyr Trp Gly
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Gln Gly Thr Leu Val Thr Val Ser Ser
 130 135

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 20 25 30

Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Ser Gly Ser Pro Val
 35 40 45

Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys
 50 55 60

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
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 85 90 95

Lys Lys Val Ala Pro Ala Glu Cys Ser
 100 105

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 20 25 30

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 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Ser Ser Gly Leu Tyr Ser

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Pro Val Pro Lys Glu Ser Thr Cys Lys Cys Ile Ser Pro Cys Pro Val					
	100	105	110		
Pro Glu Ser Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro					
	115	120	125		
Lys Asp Ile Leu Arg Ile Thr Arg Thr Pro Glu Ile Thr Cys Val Val					
	130	135	140		
Leu Asp Leu Gly Arg Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val					
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Asp Gly Lys Glu Val His Thr Ala Lys Thr Gln Pro Arg Glu Gln Gln					
	165	170	175		
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile Glu His Gln					
	180	185	190		
Asp Trp Leu Thr Gly Lys Glu Phe Lys Cys Arg Val Asn His Ile Gly					
	195	200	205		
Leu Pro Ser Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala					
	210	215	220		
His Gln Pro Ser Val Tyr Val Leu Pro Pro Ser Pro Lys Glu Leu Ser					
	225	230	235	240	
Ser Ser Asp Thr Val Thr Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro					
	245	250	255		
Pro Glu Ile Asp Val Glu Trp Gln Ser Asn Gly Gln Pro Glu Pro Glu					
	260	265	270		

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Phe Leu Tyr Ser Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Gln Gly
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<213> Canis lupus

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tggaaggcaa gcggcagccc cgtcaccag ggcgtggaga ccaccaagcc ctccaagcag 180

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gagtcacct gcaagtgtat atcccatgc ccagtcctg aatcactggg agggcctteg 360

gtcttcatct ttccccgaa acccaaggac atcctcagga ttaccgaac accgagatc 420

acctgtgtgg tgtagatct gggccgtgag gaccctgagg tgcagatcag ctggttcgtg 480

gatggttaagg aggtgcacac agccaagacg cagcctcgtg agcagcagtt caacagcacc 540

taccgtgtgg tcagcgtcct cccattgag caccaggact ggctcaccgg aaaggagttc 600

aagtgcagag tcaaccacat aggctcccg tccccatcg agaggactat ctcaaagcc 660

agagggaag cccatcagcc cagtgtgtat gtctgccac catccccaaa ggagttgtca 720

tccagtgaca cggtcacct gacctgcctg atcaaagact tcttcccacc tgagattgat 780

gtggagtggc agagcaatgg acagccggag cccgagagca agtaccacac gactgcgccc 840

cagctggacg aggacgggtc ctacttctg tacagcaagc tctctgtgga caagagccgc 900

tggcagcagg gagacacctt cacatgtgcg gtgatgcatg aagctctaca gaaccactac 960

acagatctat ccctctccca ttctccgggt aaatga 996

<210> 9

<211> 238

<212> PRT

<213> Artificial Sequence

<220>

<223> chimeric L chain

<400> 9

Met Glu Ser Gln Thr His Val Leu Ile Ser Leu Leu Leu Ser Val Ser
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Gly Thr Tyr Gly Asp Ile Ala Ile Thr Gln Ser Pro Ser Ser Val Ala
20 25 30

Val Ser Val Gly Glu Thr Val Thr Leu Ser Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu Tyr Ser Glu Asn Gln Lys Asp Tyr Leu Gly Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Thr Pro Lys Pro Leu Ile Tyr Trp Ala Thr Asn Arg
65 70 75 80

His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Ile Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr
100 105 110

Tyr Cys Gly Gln Tyr Leu Val Tyr Pro Phe Thr Phe Gly Pro Gly Thr
115 120 125

Lys Leu Glu Leu Lys Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
130 135 140

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys

145 150 155 160
 Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
 165 170 175
 Ser Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
 180 185 190
 Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
 195 200 205
 Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
 210 215 220
 Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
 225 230 235

 <210> 10
 <211> 468
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> chimeric H chain

 <400> 10

 Met Gly Trp Ser Gln Ile Ile Leu Phe Leu Val Ala Ala Ala Thr Cys
 1 5 10 15

 Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys
 20 25 30

 Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 40 45

 Thr Ser Asn Phe Met His Trp Val Lys Gln Gln Pro Gly Asn Gly Leu
 50 55 60

 Glu Trp Ile Gly Trp Ile Tyr Pro Glu Tyr Gly Asn Thr Lys Tyr Asn
 65 70 75 80

 Gln Lys Phe Asp Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
 85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 105 110

Tyr Phe Cys Ala Ser Glu Glu Ala Val Ile Ser Leu Val Tyr Trp Gly
 115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser
 130 135 140

Val Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr Val
 145 150 155 160

Ala Leu Ala Cys Leu Val Ser Gly Tyr Phe Pro Glu Pro Val Thr Val
 165 170 175

Ser Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser
 180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Thr Val Thr Val
 195 200 205

Pro Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Val His
 210 215 220

Pro Ala Ser Asn Thr Lys Val Asp Lys Pro Val Pro Lys Glu Ser Thr
 225 230 235 240

Cys Lys Cys Ile Ser Pro Cys Pro Val Pro Glu Ser Leu Gly Gly Pro
 245 250 255

Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Ile Leu Arg Ile Thr
 260 265 270

Arg Thr Pro Glu Ile Thr Cys Val Val Leu Asp Leu Gly Arg Glu Asp
 275 280 285

Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys Glu Val His Thr
 290 295 300

Ala Lys Thr Gln Pro Arg Glu Gln Gln Phe Asn Ser Thr Tyr Arg Val

305 310 315 320

Val Ser Val Leu Pro Ile Glu His Gln Asp Trp Leu Thr Gly Lys Glu
 325 330 335

Phe Lys Cys Arg Val Asn His Ile Gly Leu Pro Ser Pro Ile Glu Arg
 340 345 350

Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro Ser Val Tyr Val
 355 360 365

Leu Pro Pro Ser Pro Lys Glu Leu Ser Ser Ser Asp Thr Val Thr Leu
 370 375 380

Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Glu Ile Asp Val Glu Trp
 385 390 395 400

Gln Ser Asn Gly Gln Pro Glu Pro Glu Ser Lys Tyr His Thr Thr Ala
 405 410 415

Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Ser
 420 425 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asp Thr Phe Thr Cys Ala Val
 435 440 445

Met His Glu Ala Leu Gln Asn His Tyr Thr Asp Leu Ser Leu Ser His
 450 455 460

Ser Pro Gly Lys
 465

<210> 11
 <211> 106
 <212> PRT
 <213> Homo sapiens

<400> 11

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 12

<211> 326

<212> PRT

<213> Homo sapiens

<400> 12

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
1 5 10 15

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
20 25 30

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
35 40 45

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
50 55 60

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr
65 70 75 80

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
85 90 95

Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu

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

Ser Leu Ser Leu Gly Lys
325

<210> 13
<211> 321
<212> DNA
<213> Homo sapiens

<400> 13
actgtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacagaaaa 240
caciaagtct acgcctgcga agtcacccat cagggcctga gctcgcccg caciaagagc 300
ttcaacaggg gagagtgtta g 321

<210> 14
<211> 981
<212> DNA
<213> Homo sapiens

<400> 14
tccaccaagg gcccatccgt cttccccctg gcgcctgct ccaggagcac ctccgagagc 60
acagccgccc tgggtgcct ggtcaaggac tacttccccg aaccgggtgac ggtgtcgtgg 120
aactcaggcg cctgaccag cggcgtgcac accttccccg ctgtctaca gtctcagga 180
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac gaagacctac 240
acctgcaacg tagatcacia gccagcaac accaaggtgg acaagagagt tgagtcaaaa 300
tatggteccc catgcccate atgccagca cctgagttcc tgggggggacc atcagtcttc 360
ctgttcccc caaaaccaa ggacactctc atgatctccc ggaccctga ggtaacgtgc 420
gtggtggtgg acgtgagcca ggaagacccc gaggtccagt tcaactggta cgtggatggc 480
gtggaggtgc ataatgcaa gacaaagccg cgggaggagc agttcaacag cacgtaccgt 540
gtggtcagcg tcctaccgt cctgcaccag gactggctga acggcaagga gtacaagtgc 600
aaggtctcca acaaaggcct cccgtctctc atcgagaaaa ccatctcaa agccaaaggg 660
cagccccgag agccacaggt gtacacctg ccccatccc aggaggagat gaccaagaac 720
caggtcagcc tgacctgcct ggtcaaagge ttctaccca gcgacatgc cgtggagtgg 780

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 840
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 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc 960
 tcctgtctc tgggtaaata a 981

<210> 15
 <211> 399
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 15
 atggaatctc aaactcatgt ttgatttca ttacttctga gtgtttccgg aacctacggt 60
 gatategcta tcaactcaatc tccctcctct gttgctgtgt ctgtgggcga aaccgttacc 120
 ctgtctgca agtcagtcg gtctcttctc tactccgaga atcaaaagga ctacctgggc 180
 tggtagcaac agaagcccg ccagaccca aagccactga tatactgggc aaccaacagg 240
 cacaccggag tgcccacag gtacacaggc agtggatctg gcaccgactt taccttgatc 300
 atttcaagcg tgcaggctga agatctggcc gactactact gtggtcagta tctggtgtat 360
 cctttcactt tcgggccagg gacaaaattg gaattgaag 399

<210> 16
 <211> 411
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 16
 atgggttggc ctcaaattat cttgtttttg gttgctgcag ccacttgtgt tcattctcag 60
 gtgcagctgc aacaaagcgg cgcagaactg gtgaaacctg gcagcagcgt gaaaatatct 120
 tgtaaggcca gcggatatac tttcacctcc aatttcatgc attgggtcaa acagcagccc 180
 ggcaacggac tcgagtggat cggctggatc taccgccagt atggcaacac aaaatataac 240
 caaaaatttg atggaaaggc taccctgact gccgataagt cctccagcac cgcatacatg 300
 caactctcct ccctgacctc cgaggatage gctgtctact tetgtgttc cgaagaggct 360
 gtcatatcct tgggtctattg gggccaagga actctggtga ccgtctcatc t 411

<210> 17
 <211> 318
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 17
 cagcccaaag cctctcccag cgtcaccctc ttccacctt ccagtgagga gctgggggca 60
 aacaaagcca ctttgggtgtg tctcatctcc gatttttacc cctccgggggt cacagtcgca 120
 tggaaggcct ccgcatcccc tgtgacacag ggagtggaga caacaaaacc tagcaagcag 180
 agtaacaata agtatgccgc ctcaagctat ctacgcctta ctctgataa gtggaagtca 240
 catagcagtt ttagttgcct cgtaacacat gaggggtcaa ctgtggagaa aaaagtagct 300
 ccagctgagt gctcatga 318

<210> 18
 <211> 996
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 18
 gctagcaciaa ccgtccctc cgtttttccc ctgcgcccat cctgcggggtc aaccagcgga 60
 tccaccgtcg ctctggcttg tctgggtgtca ggatacttcc ccgagcctgt caccgtttct 120
 tggaatagcg gcagccttac ttccggcgtg cataccttcc ctagectgct tcagtcctcc 180
 ggtctgtatt cctcagctc caccgtaact gtcccaagct caaggtggcc ctctgagaca 240
 tttacctgca atgtgtgtcca tctgttcca aataccaaag tggacaagcc cgtcccaaaa 300
 gagtctacct gcaaatgtat cagtccttgt cccgtgcccg agtctctggg cggaccctca 360
 gtctttatct tcccaccaa gccaaaggac atattgcgca ttacacggac acccgaaatc 420
 acctgtgttg tgttgatct cggccgggaa gatcctgagg tgcagattag ttggtttgtt 480
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cgagccagg ctcacagcc ttctgtgtac gttctgcctc ctagtcttaa ggaactgtct 720
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 gtggaatggc agtctaacgg gcagccagag ccagaatcta agtaccacac tactgcacca 840
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 tggcagcagg gggatacttt tacttgcgca gtaatgcacg aagcattgca gaaccactac 960
 actgacctgt cacttagtca ctcaccaggg aagtaa 996

<210> 19
 <211> 717
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 19
 atggaatctc aaactcatgt ttgatttca ttacttctga gtgtttccgg aacctacgg 60
 gatatcgcta tcaactcaatc tccctctctt gttgctgtgt ctgtgggcga aaccgttacc 120
 ctgtctgca agtcagtcga gtctcttctc tactccgaga atcaaaagga ctacctgggc 180
 tggtagcaac agaagcccg ccagaccca aagccactga tatactgggc aaccaacagg 240
 cacaccggag tgcccagacag gttcacaggc agtggatctg gcaccgactt taccttgatc 300
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 gtcacctct tccaccttc cagtgaggag ctgggggcaa acaaagccac tttggtgtgt 480
 ctcactcccg atttttacc ctcgggggtc acagtgcga ggaaggcctc cggatccct 540
 gtgacacagg gagtggagac aacaaaacct agcaagcaga gtaacaataa gtatgccgc 600
 tcaagctatc tcagccttac tctgataag tggaagtcac atagcagttt tagttgcctc 660
 gtaacacatg agggttcaac tgtggagaaa aaagtagctc cagctgagtg ctcatga 717

<210> 20
 <211> 1407
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> codon-optimized sequence

<400> 20

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 gtgcagctgc aacaaagcgg cgcagaactg gtgaaacctg gcagcagcgt gaaaatatct 120
 tgtaaggcca gcggatatac tttcacctcc aatttcatgc attgggtcaa acagcagccc 180
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 caactctcct ccctgacctc cgaggatagc gctgtctact tctgtgcttc cgaagagget 360
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 ggggatactt ttacttgctc agtaatgcac gaagcattgc agaaccacta cactgacctg 1380
 tcacttagtc actcaccagg gaagtaa 1407

<210> 21

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> primer

<400> 21

aggatggctc ctagactccc

20

<210> 22

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> primer

<400> 22

agacgatggt ggcatactcg

20

<210> 23

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> primer

<400> 23

atgagaatgt ttagtgtctt

20

<210> 24

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> primer

<400> 24

ttatgtctct tcaaattgta tadc

24

<210> 25

<211> 16

<212> DNA

<213> Artificial Sequence

<220>

<223> primer

<400> 25

gttgatctgt gtgttg

16

<210> 26
 <211> 20
 <212> DNA
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<220>
 <223> primer

<400> 26
 cgggacttcc acatgagcat 20

<210> 27
 <211> 17
 <212> DNA
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<220>
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<400> 27
 ttttagacag aaagtga 17

<210> 28
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<400> 28
 gaccagctct tcttggggaa 20

<210> 29
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<400> 29
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<210> 30
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<210> 32 <211> 28 <212> DNA <213> Artificial Sequence	
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<400> 35
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<210> 36
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<220>
 <223> primer

<400> 36
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<210> 37
 <211> 12
 <212> PRT
 <213> Rattus norvegicus

<400> 37

Gln Ser Leu Leu Tyr Ser Glu Asn Gln Lys Asp Tyr
 1 5 10

<210> 38
 <211> 9
 <212> PRT
 <213> Rattus norvegicus

<400> 38

Gly Gln Tyr Leu Val Tyr Pro Phe Thr
 1 5

<210> 39
 <211> 8
 <212> PRT
 <213> Rattus norvegicus

<400> 39

Gly Tyr Thr Phe Thr Ser Asn Phe
 1 5

<210> 40
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 <213> Rattus norvegicus

<400> 40

Ile Tyr Pro Glu Tyr Gly Asn Thr
 1 5

<210> 41
 <211> 11
 <212> PRT
 <213> Rattus norvegicus

<400> 41

Ala Ser Glu Glu Ala Val Ile Ser Leu Val Tyr
 1 5 10

<210> 42
 <211> 331
 <212> PRT
 <213> Ovis aries

<400> 42

Ala Ser Thr Thr Pro Pro Lys Val Tyr Pro Leu Thr Ser Cys Cys Gly
 1 5 10 15

Asp Thr Ser Ser Ser Ile Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Ile Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ala Ser Thr Ser Gly Ala Gln Thr
 65 70 75 80

Phe Ile Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
 85 90 95

Arg Val Glu Pro Gly Cys Pro Asp Pro Cys Lys His Cys Arg Cys Pro
 100 105 110

Pro Pro Glu Leu Pro Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys
 115 120 125

Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val
 130 135 140

Val Val Asp Val Gly Gln Asp Asp Pro Glu Val Gln Phe Ser Trp Phe
 145 150 155 160

Val Asp Asn Val Glu Val Arg Thr Ala Arg Thr Lys Pro Arg Glu Glu
 165 170 175

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Ala Leu Pro Ile Gln His
 180 185 190

Gln Asp Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Asn Glu
 195 200 205

Ala Leu Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Gln
 210 215 220

Ala Arg Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu
 225 230 235 240

Ser Lys Ser Thr Leu Ser Val Thr Cys Leu Val Thr Gly Phe Tyr Pro
 245 250 255

Asp Tyr Ile Ala Val Glu Trp Gln Lys Asn Gly Gln Pro Glu Ser Glu
 260 265 270

Asp Lys Tyr Gly Thr Thr Thr Ser Gln Leu Asp Ala Asp Gly Ser Tyr
 275 280 285

Phe Leu Tyr Ser Arg Leu Arg Val Asp Lys Asn Ser Trp Gln Glu Gly
 290 295 300

Asp Thr Tyr Ala Cys Val Val Met His Glu Ala Leu His Asn His Tyr
 305 310 315 320

Thr Gln Lys Ser Ile Ser Lys Pro Pro Gly Lys

325

330

<210> 43

<211> 996

<212> DNA

<213> Ovis aries

<400> 43

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ggatgcccgg acccatgcaa acattgccga tgcccacccc ctgagctccc cggaggaccg    360
tctgtcttca tcttcccacc gaaaccaag gacacctta caatctctgg aacgcccag    420
gtcacgtgtg tgggtgtgga cgtgggccag gatgaccccg aggtgcagtt ctctgggtc    480
gtggacaacg tggaggtgcg cacggccagg acaaagccga gagaggagca gttcaacagc    540
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ttcaagtga aggtccacaa cgaagccctc ccggcccca tcgtgaggac catctccagg    660
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agcaaaagca cgtcagcgt cacctgcctg gtcaccggct tctaccaga ctacatgcc    780
gtggagtggc agaaaaatgg gcagcctgag tcggaggaca agtacggcac gaccacatcc    840
cagctggacg ccgacggctc ctacttcctg tacagcaggc tcagggtgga caagaacagc    900
tggaagaag gagacaccta cgcgtgtgtg gtgatgcacg aggctctgca caaccactac    960
acacagaagt cgatctctaa gcctccgggt aatga                                996

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<210> 44

<211> 329

<212> PRT

<213> Ovis aries

<400> 44

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Thr Ser Cys Cys Gly

1

5

10

15

Asp Thr Ser Ser Ser Ser Ser Ile Val Thr Leu Gly Cys Leu Val Ser
 20 25 30

Ser Tyr Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu
 35 40 45

Thr Ser Gly Val His Thr Phe Pro Ala Ile Leu Gln Ser Ser Gly Leu
 50 55 60

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ala Ser Thr Ser Gly Ala
 65 70 75 80

Gln Thr Phe Ile Cys Asn Val Ala His Pro Ala Ser Ser Ala Lys Val
 85 90 95

Asp Lys Arg Val Gly Ile Ser Ser Asp Tyr Ser Lys Cys Ser Lys Pro
 100 105 110

Pro Cys Val Ser Arg Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Ser Leu Met Ile Thr Gly Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Gly Gln Gly Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp
 145 150 155 160

Asn Val Glu Val Arg Thr Ala Arg Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Phe Arg Val Val Ser Ala Leu Pro Ile Gln His Asp His
 180 185 190

Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Ser Lys Gly Leu
 195 200 205

Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Ala Lys Gly Gln Ala Arg
 210 215 220

Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys
 225 230 235 240

Ser Thr Leu Ser Val Thr Cys Leu Val Thr Gly Phe Tyr Pro Asp Tyr
 245 250 255

Ile Ala Val Glu Trp Gln Arg Ala Arg Gln Pro Glu Ser Glu Asp Lys
 260 265 270

Tyr Gly Thr Thr Thr Ser Gln Leu Asp Ala Asp Gly Ser Tyr Phe Leu
 275 280 285

Tyr Ser Arg Leu Arg Val Asp Lys Ser Ser Trp Gln Arg Gly Asp Thr
 290 295 300

Tyr Ala Cys Val Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 305 310 315 320

Lys Ser Ile Ser Lys Pro Pro Gly Lys
 325

<210> 45

<211> 990

<212> DNA

<213> Ovis aries

<400> 45

gcctccacca cagcccgaa agtctaccet ctgacttctt gctgcgggga cacgtccagc	60
tccagctcca tcgtgacctt gggctgcctg gtctccagct atatgcccga gccggtgacc	120
gtgacctgga actctggtgc cctgaccagc ggcgtgcaca ccttcccggc catcctgcag	180
tcctccgggc tctactctct cagcagcgtg gtgaccgtgc cggccagcac ctcaggagcc	240
cagaccttca tctgcaacgt agcccacccg gccagcagcg ccaaggtgga caagcgtgtt	300
gggatctcca gtgactactc caagtgttct aaaccgcctt gcgtgagccg accgtctgtc	360
ttcatcttcc ccccgaaacc caaggacagc ctcatgatca caggaacgcc cgaggtcacg	420
tgtgtggtgg tggacgtggg ccagggtgac ccgaggtgc agttctctg gttcgtggac	480
aacgtggagg tgcgcacggc caggacaaag ccgagagagg agcagttcaa cagcaccttc	540
cgcgtggtca gcgcctgcc catccagcac gaccactgga ctggaggaaa ggagttcaag	600
tgcaaggtec acagcaaagg cctcccggcc cccatcgtga ggaccatctc cagggccaaa	660
gggcaggccc gggagccgca ggtgtacgtc ctggccccac ccaggaaga gtcagcaaa	720

agcacgetca gcgtcacctg cctggtcacc ggetttctacc cagactacat cgccgtggag 780
 tggcagagag cgcggcagcc tgagtcggag gacaagtacg gcacgaccac atcccagctg 840
 gacgccgacg gctcctactt cctgtacagc aggtcaggg tggacaagag cagctggcaa 900
 agaggagaca cctacgcgtg tgtggtgatg cagcaggctc tgcacaacca ctacacacag 960
 aagtcgatct ctaagcctcc gggtaaatga 990

<210> 46
 <211> 102
 <212> PRT
 <213> Ovis aries

<400> 46

Pro Ser Val Phe Leu Phe Lys Pro Ser Glu Glu Gln Leu Arg Thr Gly
 1 5 10 15

Thr Val Ser Val Val Cys Leu Val Asn Asp Phe Tyr Pro Lys Asp Ile
 20 25 30

Asn Val Lys Val Lys Val Asp Gly Val Thr Gln Asn Ser Asn Phe Gln
 35 40 45

Asn Ser Phe Thr Asp Gln Asp Ser Lys Lys Ser Thr Tyr Ser Leu Ser
 50 55 60

Ser Thr Leu Thr Leu Ser Ser Ser Glu Tyr Gln Ser His Asn Ala Tyr
 65 70 75 80

Ala Cys Glu Val Ser His Lys Ser Leu Pro Thr Ala Leu Val Lys Ser
 85 90 95

Phe Asn Lys Asn Glu Cys
 100

<210> 47
 <211> 309
 <212> DNA
 <213> Ovis aries

<400> 47

ccatccgtct tcctcttcaa accatctgag gaacagctga ggaccggaac tgtctctgtc 60
 gtgtgcttgg tgaatgattt ctaccccaaa gatatcaatg tcaaggtgaa agtggatggg 120

gttaccaga acagcaactt ccagaacagc ttacagacc aggacagcaa gaaaagcacc 180
 tacagcctca gcagcaccct gacactgtcc agctcagagt accagagcca taacgcctat 240
 gcgtgtgagg tcagccacaa gagcctgccc accgcctcg tcaagagctt caataagaat 300
 gaatgttag 309

<210> 48
 <211> 106
 <212> PRT
 <213> Ovis aries

<400> 48

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

Glu Glu Leu Ser Thr Asn Lys Ala Thr Val Val Cys Leu Ile Asn Asp
 20 25 30

Phe Tyr Pro Gly Ser Val Asn Val Val Trp Lys Ala Asp Gly Ser Thr
 35 40 45

Ile Asn Gln Asn Val Lys Thr Thr Gln Ala Ser Lys Gln Ser Asn Ser
 50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Thr Leu Thr Gly Ser Glu Trp Lys
 65 70 75 80

Ser Lys Ser Ser Tyr Thr Cys Glu Val Thr His Glu Gly Ser Thr Val
 85 90 95

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

<210> 49
 <211> 321
 <212> DNA
 <213> Ovis aries

<400> 49

ggtcagccca agtcgcacc ctcggtcacc ctgttccgc ctccacgga ggagctcagt 60

accaacaagg ccaccgtggt gtgtctcatc aacgacttct acccggttag cgtgaacgtg 120

gtctggaagg cagatggcag caccatcaat cagaacgtga agaccacca ggcctccaaa 180
cagagcaaca gcaagtacgc ggccagcagc tacctgaccc tgacgggcag cgagtggaag 240
tctaagagca gttacacctg cgaggtcacg cacgagggga gcaccgtgac gaagacagtg 300
aagccctcag agtgttctta g 321

<210> 50
<211> 328
<212> PRT
<213> Sus scrofa

<400> 50

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
20 25 30

Phe Pro Glu Pro Val Thr Met Thr Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser
65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Lys
85 90 95

Arg Val Gly Thr Lys Thr Lys Pro Pro Cys Pro Ile Cys Pro Gly Cys
100 105 110

Glu Val Ala Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Gln Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser Lys Glu His Ala Glu Val Gln Phe Ser Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Thr Ala Glu Thr Arg Pro Lys Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gln His Gln Asp Trp
 180 185 190

Leu Lys Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Val Asp Leu Pro
 195 200 205

Ala Pro Ile Thr Arg Thr Ile Ser Lys Ala Ile Gly Gln Ser Arg Glu
 210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Pro Ala Glu Glu Leu Ser Arg Ser
 225 230 235 240

Lys Val Thr Val Thr Cys Leu Val Ile Gly Phe Tyr Pro Pro Asp Ile
 245 250 255

His Val Glu Trp Lys Ser Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr
 260 265 270

Arg Thr Thr Pro Pro Gln Gln Asp Val Asp Gly Thr Phe Phe Leu Tyr
 275 280 285

Ser Lys Leu Ala Val Asp Lys Ala Arg Trp Asp His Gly Glu Thr Phe
 290 295 300

Glu Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 305 310 315 320

Ser Ile Ser Lys Thr Gln Gly Lys
 325

<210> 51

<211> 987

<212> DNA

<213> Sus scrofa

<400> 51

gcccccaaga cggccccatc ggtetacct ctggccccct gcggcaggga cacgtctggc 60

cctaacgtgg ccttgggctg cctggcctca agctacttcc ccgagccagt gaccatgacc 120

tggaaactcgg gcgccctgac cagtggcgtg cataccttcc catccgtcct gcagccgtca 180
 gggctctact ccctcagcag catggtgacc gtgccggcca gcagcctgtc cagcaagagc 240
 tacacctgca atgtcaacca cccggccacc accaccaagg tggacaagcg tgttggaaca 300
 aagaccaaac caccatgtcc catatgccca ggctgtgaag tggccgggcc ctcggtcttc 360
 atcttcctc caaaacccaa ggacaccctc atgatctccc agacccccga ggtcacgtgc 420
 gtggtgggtg acgtcagcaa ggagcacgcc gaggtccagt tctctggta cgtggacggc 480
 gtagagggtc acacggccga gacgagacca aaggaggagc agttcaacag cacctaccgt 540
 gtggtcagcg tctgccccat ccagcaccag gactggctga aggggaagga gttcaagtgc 600
 aaggtcaaca acgtagacct ccagccccc atcacgagga ccatctcaa ggctataggg 660
 cagagccggg agccgcaggt gtacacctg cccccaccg ccgaggagct gtccaggagc 720
 aaagtcaccg taacctgcct ggtcattggc ttctaccac ctgacatcca tgttgagtgg 780
 aagagcaacg gacagccgga gccagagggc aattaccgca ccacccgcc ccagcaggac 840
 gtggacggga ccttcttct gtacagcaag ctgcggtgg acaaggcaag atgggacat 900
 ggagaaacat ttgagtgtgc ggtgatgcac gaggtctgc acaaccacta caccagaag 960
 tccatctcca agactcagg taaatga 987

<210> 52
 <211> 328
 <212> PRT
 <213> Sus scrofa

<400> 52

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Val Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser

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

Ser Lys Leu Ala Val Asp Lys Ala Arg Trp Asp His Gly Asp Lys Phe
 290 295 300

Glu Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 305 310 315 320

Ser Ile Ser Lys Thr Gln Gly Lys
 325

<210> 53

<211> 987

<212> DNA

<213> Sus scrofa

<400> 53

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gcccccaaga cggccccatc ggtctaccct ctggccccct gcggcaggga cgtgtctggc    60
cctaacgtgg ccttgggctg cctggcctca agctacttcc ccgagccagt gaccgtgacc    120
tggaactcgg gcgcctgac cagtggcgtg cacaccttcc catecgtcct gcagccgtca    180
gggctctact ccctcagcag catggtgacc gtgccggcca gcagcctgtc cagcaagagc    240
tacacctgca atgtcaacca cccggccacc accaccaagg tggacaagcg tgttgaata    300
caccagccgc aaacatgtcc catatgccc ggctgtgaag tggccgggcc ctcggtcttc    360
atcttcctc caaaacccaa ggacaccctc atgatctccc agacccccga ggtcacgtgc    420
gtggtggtgg acgtcagcaa ggagcacgcc gaggtccagt tctctggta cgtggacggc    480
gtagaggtgc acacggccga gacgagacca aaggaggagc agttcaacag cacctaccgt    540
gtggtcagcg tctgcccac ccagcaccag gactggctga aggggaagga gttcaagtgc    600
aaggtcaaca acgtagacct ccagcccc atcacgagga ccatctcaa ggctataggg    660
cagagccggg agccgcaggt gtacacctg cccccaccg ccgaggagct gtccaggagc    720
aaagtcaagc taacctgcct ggtcattggc ttctaccac ctgacatcca tgttgagtgg    780
aagagcaacg gacagccgga gccagagaac acataccgca ccacccgcc ccagcaggac    840
gtggacggga ctttcttct gtacagcaaa ctgcggtgg acaaggcaag atgggacat    900
ggagacaaat ttgagtgtgc ggtgatgcac gaggtctgc acaaccacta caccagaag    960
tccatctcca agactcaggg taaatga                                     987

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<210> 54

<211> 328

<212> PRT

<213> Sus scrofa

<400> 54

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Ser Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser
 65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Lys
 85 90 95

Arg Val Gly Thr Lys Thr Lys Pro Pro Cys Pro Ile Cys Pro Ala Cys
 100 105 110

Glu Ser Pro Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
 115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Gln Val Thr Cys Val Val Val Asp
 130 135 140

Val Ser Gln Glu Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly
 145 150 155 160

Val Glu Val His Thr Ala Gln Thr Arg Pro Lys Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gln His Gln Asp Trp
 180 185 190

Leu Asn Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro
 195 200 205

Ala Pro Ile Thr Arg Ile Ile Ser Lys Ala Lys Gly Gln Thr Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro His Ala Glu Glu Leu Ser Arg Ser
225 230 235 240

Lys Val Ser Ile Thr Cys Leu Val Ile Gly Phe Tyr Pro Pro Asp Ile
245 250 255

Asp Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr
260 265 270

Arg Thr Thr Pro Pro Gln Gln Asp Val Asp Gly Thr Tyr Phe Leu Tyr
275 280 285

Ser Lys Phe Ser Val Asp Lys Ala Ser Trp Gln Gly Gly Gly Ile Phe
290 295 300

Gln Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
305 310 315 320

Ser Ile Ser Lys Thr Pro Gly Lys
325

<210> 55

<211> 987

<212> DNA

<213> Sus scrofa

<400> 55

gcccccaaga cggcccccac ggtctaccct ctggcccccct gcagcaggga cacgtctggc 60

cctaaactgg ccttgggctg cctggcctca agctaacttc ccgagccagt gaccgtgacc 120

tggaactcgg gcgcctgtc cagtggcgtg cataccttcc catccgtcct gcagccgtca 180

gggtcttact cctcagcag catggtgacc gtgccggcca gcagcctgtc cagcaagagc 240

tacactgca atgtcaacca cccggccacc accaccaagg tggacaagcg tgttggaaca 300

aagaccaaac caccatgtcc catatgccca gcctgtgaat caccagggcc ctcggtcttc 360

atcttccttc caaaaccaa ggacaccctc atgatctccc ggacaccca ggtcacgtgc 420

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gtagagggtgc acacggccca gacgaggcca aaggaggagc agttcaacag cacctaccgc 540
 gtggtcagcg tcctacccat ccagcaccag gactgggtga acgggaagga gttcaagtgc 600
 aaggtcaaca acaaagacct ccagccccc atcacaagga tcattctcaa ggccaaaggg 660
 cagaccgggg agccgcaggt gtacacctg cccccacacg ccgaggagct gtccaggagc 720
 aaagtcagea taacctgcct ggtcattggc ttctaccac ctgacatcga tgtcgagtgg 780
 caaagaaacg gacagccgga gccagagggc aattaccgca ccacccgcc ccagcaggac 840
 gtggacggga cctacttct gtacagcaag ttctcggtgg acaaggccag ctggcagggt 900
 ggaggcatat tccagtgtgc ggtgatgcac gaggtctgc acaaccacta caccagaag 960
 tctatctcca agactccggg taaatga 987

<210> 56

<211> 328

<212> PRT

<213> *Sus scrofa*

<400> 56

Ala Pro Lys Thr Ala Pro Leu Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser
 65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Lys
 85 90 95

Arg Val Gly Thr Lys Thr Lys Pro Pro Cys Pro Ile Cys Pro Ala Cys
 100 105 110

Glu Ser Pro Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
 115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Gln Val Thr Cys Val Val Val Asp
 130 135 140

Val Ser Gln Glu Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly
 145 150 155 160

Val Glu Val His Thr Ala Gln Thr Arg Pro Lys Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gln His Gln Asp Trp
 180 185 190

Leu Asn Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro
 195 200 205

Ala Pro Ile Thr Arg Ile Ile Ser Lys Ala Lys Gly Gln Thr Arg Glu
 210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro His Ala Glu Glu Leu Ser Arg Ser
 225 230 235 240

Lys Val Ser Ile Thr Cys Leu Val Ile Gly Phe Tyr Pro Pro Asp Ile
 245 250 255

Asp Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr
 260 265 270

Arg Thr Thr Pro Pro Gln Gln Asp Val Asp Gly Thr Tyr Phe Leu Tyr
 275 280 285

Ser Lys Phe Ser Val Asp Lys Ala Ser Trp Gln Gly Gly Gly Ile Phe
 290 295 300

Gln Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 305 310 315 320

Ser Ile Ser Lys Thr Pro Gly Lys
 325

<210> 57
 <211> 987
 <212> DNA
 <213> *Sus scrofa*

<400> 57
 gcccccaaga cggccccatt ggtctaccct ctggccccct gcggcaggga cacgtctggc 60
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 tggaactcgg gcgcctgac cagtggcgtg cataccttcc catccgtcct gcagccgtca 180
 gggctctact cctcagcag catggtgacc gtgccggcca gcagcctgtc cagcaagagc 240
 tacacctgca atgtcaacca cccggccacc accaccaagg tggacaagcg tgttgaaca 300
 aagaccaaac caccatgtcc catatgccca gcctgtgaat cgccagggcc ctcggtcttc 360
 atcttcctc caaaaccaa ggacacctc atgatctccc ggacaccca ggtcacgtgc 420
 gtggtagttg atgtgagcca ggagaaccg gaggtccagt tctctggta cgtggacggc 480
 gtagaggtgc acacggccca gacgaggcca aaggaggagc agttcaacag cacctaccgc 540
 gtggtcagcg tctgccccat ccagcaccag gactggctga acgggaagga gttcaagtgc 600
 aaggtcaaca acaaagacct ccagccccc atcacaagga tcattctcaa ggccaaaggg 660
 cagaccgggg agccgcaggt gtacacctg cccccacag ccgaggagct gtccaggagc 720
 aaagtcagca taacctgcct ggtcattggc ttetaccac ctgacatcga tgtcagtggt 780
 caaagaaacg gacagccgga gccagagggc aattaccgca ccacccgcc ccagcaggac 840
 gtggacggga cctacttct gtacagcaag ttctcggtgg acaaggccag ctggcagggt 900
 ggaggcatat tccagtgtgc ggtgatgcac gaggtctgc acaaccacta caccagaag 960
 tctatctcca agactccggg taaatga 987

<210> 58
 <211> 333
 <212> PRT
 <213> *Sus scrofa*

<400> 58

Ala Tyr Asn Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Val Ser Asp His Asn Val Ala Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Ser Arg
 35 40 45

Val Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Ile Val Ala Ala Ser Ser Leu Ser Thr Leu Ser
 65 70 75 80

Tyr Thr Cys Asn Val Tyr His Pro Ala Thr Asn Thr Lys Val Asp Lys
 85 90 95

Arg Val Asp Ile Glu Pro Pro Thr Pro Ile Cys Pro Glu Ile Cys Ser
 100 105 110

Cys Pro Ala Ala Glu Val Leu Gly Ala Pro Ser Val Phe Leu Phe Pro
 115 120 125

Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Lys Val Thr
 130 135 140

Cys Val Val Val Asp Val Ser Gln Glu Glu Ala Glu Val Gln Phe Ser
 145 150 155 160

Trp Tyr Val Asp Gly Val Gln Leu Tyr Thr Ala Gln Thr Arg Pro Met
 165 170 175

Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile
 180 185 190

Gln His Gln Asp Trp Leu Lys Gly Lys Glu Phe Lys Cys Lys Val Asn
 195 200 205

Asn Lys Asp Leu Leu Ser Pro Ile Thr Arg Thr Ile Ser Lys Ala Thr
 210 215 220

Gly Pro Ser Arg Val Pro Gln Val Tyr Thr Leu Pro Pro Ala Trp Glu
 225 230 235 240

Glu Leu Ser Lys Ser Lys Val Ser Ile Thr Cys Leu Val Thr Gly Phe

245 250 255
 Tyr Pro Pro Asp Ile Asp Val Glu Trp Gln Ser Asn Gly Gln Gln Glu
 260 265 270
 Pro Glu Gly Asn Tyr Arg Thr Thr Pro Pro Gln Gln Asp Val Asp Gly
 275 280 285
 Thr Tyr Phe Leu Tyr Ser Lys Leu Ala Val Asp Lys Val Arg Trp Gln
 290 295 300
 Arg Gly Asp Leu Phe Gln Cys Ala Val Met His Glu Ala Leu His Asn
 305 310 315 320
 His Tyr Thr Gln Lys Ser Ile Ser Lys Thr Gln Gly Lys
 325 330

<210> 59

<211> 1002

<212> DNA

<213> Sus scrofa

<400> 59

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 cataacgtgg ccttgggctg cettgtctca agctacttcc ccgagccagt gaccgtgacc 120
 tggaactcgg gtgccctgtc cagagtcgtg cataccttcc catecgtcct gcagccgtca 180
 gggctctact ccctcagcag catggtgata gtggcggcca gcagcctgtc caccctgagc 240
 tacacgtgca acgtctacca cccggccacc aacaccaagg tggacaagcg tgttgacatc 300
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 tccaaggcta cagggccgag ccgggtgccg caggtgtaca cctgcccc agctgggaa 720
 gagctgtcca agagcaaagt cagcataacc tgctgtgtca ctggcttcta cccacctgac 780

atcgatgtcg agtggcagag caacggacaa caagagccag agggcaatta ccgcaccacc 840
 ccgccccage aggacgtgga tgggacctac ttctgtaca gcaagctgc ggtggacaag 900
 gtcaggtggc agcgtggaga cctattccag tgtgcggtga tgcacgaggc tctgcacaac 960
 cactacacc agaagtcac ctccaagact cagggtaaat ga 1002

<210> 60
 <211> 277
 <212> PRT
 <213> Sus scrofa

<400> 60

Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser Leu Ser Ser
 1 5 10 15

Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser Tyr Thr Cys
 20 25 30

Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Lys Arg Val Gly
 35 40 45

Thr Lys Thr Lys Pro Pro Cys Pro Ile Cys Pro Ala Cys Glu Gly Pro
 50 55 60

Gly Pro Ser Ala Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 65 70 75 80

Ile Ser Arg Thr Pro Lys Val Thr Cys Val Val Val Asp Val Ser Gln
 85 90 95

Glu Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly Val Glu Val
 100 105 110

His Thr Ala Gln Thr Arg Pro Lys Glu Glu Gln Phe Asn Ser Thr Tyr
 115 120 125

Arg Val Val Ser Val Leu Pro Ile Gln His Gln Asp Trp Leu Asn Gly
 130 135 140

Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile
 145 150 155 160

Thr Arg Ile Ile Ser Lys Ala Lys Gly Gln Thr Arg Glu Pro Gln Val
 165 170 175

Tyr Thr Leu Pro Pro Pro Thr Glu Glu Leu Ser Arg Ser Lys Val Thr
 180 185 190

Leu Thr Cys Leu Val Thr Gly Phe Tyr Pro Pro Asp Ile Asp Val Glu
 195 200 205

Trp Gln Arg Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr Arg Thr Thr
 210 215 220

Pro Pro Gln Gln Asp Val Asp Gly Thr Tyr Phe Leu Tyr Ser Lys Leu
 225 230 235 240

Ala Val Asp Lys Ala Ser Trp Gln Arg Gly Asp Thr Phe Gln Cys Ala
 245 250 255

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Phe
 260 265 270

Lys Thr Pro Gly Lys
 275

<210> 61

<211> 834

<212> DNA

<213> Sus scrofa

<400> 61

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 accaaggtgg acaagcgtgt tggaacaaag accaaaccac catgtcccat atgccagacc 180
 tgtgaagggc ccgggccttc gcccttcac ttccctcaa aaccaagga caccctcatg 240
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 gtccagttct cctggtacgt ggacggcgta gaggtgcaca cggcccagac gaggccaaag 360
 gaggagcagt tcaacagcac ctaccgcgtg gtcagcgtcc tgcccatcca gcaccaggac 420
 tggetgaacg ggaaggagtt caagtgaag gtcaacaaca aagacctccc agccccatc 480

acaaggatca tctccaaggc caaagggcag acccgggagc cgcaggtgta caccctgccc 540
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 taccgcacca cccgcacca gcaggacgtg gacgggacct acttctgta cagcaagctc 720
 gcggtggaca aggccagctg gcagcgtgga gacacattcc agtgtgcggt gatgcacgag 780
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<210> 62

<211> 318

<212> PRT

<213> Sus scrofa

<400> 62

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Val Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser
 65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Lys
 85 90 95

Arg Val Gly Ile His Gln Pro Gln Thr Cys Pro Ile Cys Pro Ala Cys
 100 105 110

Glu Gly Pro Gly Pro Ser Ala Phe Ile Phe Pro Pro Lys Pro Lys Asp
 115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Lys Val Thr Cys Val Val Val Asp
 130 135 140

Val Ser Gln Glu Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly
 145 150 155 160

Val Glu Val His Thr Ala Gln Thr Arg Pro Lys Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Tyr Arg Val Val Ser Val Leu Leu Ile Gln His Gln Asp Trp
 180 185 190

Leu Asn Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro
 195 200 205

Ala Pro Ile Thr Arg Ile Ile Ser Lys Ala Lys Gly Gln Thr Arg Glu
 210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Pro Thr Glu Glu Leu Ser Arg Ser
 225 230 235 240

Lys Val Thr Leu Thr Cys Leu Val Thr Gly Phe Tyr Pro Pro Asp Ile
 245 250 255

Asp Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr
 260 265 270

Arg Thr Thr Pro Pro Gln Gln Asp Val Asp Gly Thr Tyr Phe Leu Tyr
 275 280 285

Ser Lys Leu Ala Val Asp Lys Ala Ser Trp Gln Arg Gly Asp Thr Phe
 290 295 300

Gln Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315

<210> 63

<211> 955

<212> DNA

<213> Sus scrofa

<400> 63

gcccccaaga cggccccatc ggtetacct ctggccccct gcggcaggga cgtgtctggc 60

cctaacgtgg ccttgggctg cctggcctca agctacttcc ccgagccagt gaccgtgacc 120

tggaaactcgg gcgccctgac cagtggcgtg cacaccttc catccgtcct gcagccgtca 180
 gggctctact ccctcagcag catggtgacc gtgccggcca gcagcctgtc cagcaagagc 240
 tacacctgca atgtcaacca cccggccacc accaccaagg tggacaagcg tgttggaata 300
 caccagccgc aaacatgtcc catatgccca gcctgtgaag ggcccgggcc ctcggccttc 360
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 gtggtgggtg atgtgagcca ggagaacctg gaggtccagt tctctggta cgtggacggc 480
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 gtggtcagcg tctgtctcat ccagcaccag gactggctga acgggaagga gttcaagtgc 600
 aaggtcaaca acaaagacct ccagccccc atcacaagga tcctctcaa ggccaaaggg 660
 cagaccgggg agccgcaggt gtacacctg cccccacca ccgaggagct gtccaggagc 720
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 caaagaaacg gacagccgga gccagagggc aattaccgca ccacccgcc ccagcaggac 840
 gtggacggga cctacttctt gtacagcaag ctgcgggtgg acaaggccag ctggcagcgt 900
 ggagacacat tccagtgtgc ggtgatgcac gaggtctgc acaaccacta cacc 955

<210> 64

<211> 323

<212> PRT

<213> Sus scrofa

<400> 64

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala His Ser Leu Ser Ser Lys Arg
 65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Lys Thr Lys Val Asp Leu
85 90 95

Cys Val Gly Arg Pro Cys Pro Ile Cys Pro Gly Cys Glu Val Ala Gly
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Ile Leu Met Ile
115 120 125

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Lys Glu
130 135 140

His Ala Glu Val Gln Phe Ser Trp Tyr Val Asp Gly Glu Glu Val His
145 150 155 160

Thr Ala Glu Thr Arg Pro Lys Glu Glu Gln Phe Asn Ser Thr Tyr Arg
165 170 175

Val Val Ser Val Leu Pro Ile Gln His Glu Asp Trp Leu Lys Gly Lys
180 185 190

Glu Phe Glu Cys Lys Val Asn Asn Glu Asp Leu Pro Gly Pro Ile Thr
195 200 205

Arg Thr Ile Ser Lys Ala Lys Gly Val Val Arg Ser Pro Glu Val Tyr
210 215 220

Thr Leu Pro Pro Pro Ala Glu Glu Leu Ser Lys Ser Ile Val Thr Leu
225 230 235 240

Thr Cys Leu Val Lys Ser Ile Phe Pro Phe Ile His Val Glu Trp Lys
245 250 255

Ile Asn Gly Lys Pro Glu Pro Glu Asn Ala Tyr Arg Thr Thr Pro Pro
260 265 270

Gln Glu Asp Glu Asp Arg Thr Tyr Phe Leu Tyr Ser Lys Leu Ala Val
275 280 285

Asp Lys Ala Arg Trp Asp His Gly Glu Thr Phe Glu Cys Ala Val Met
290 295 300

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Ser Lys Thr
 305 310 315 320

Gln Gly Lys

<210> 65
 <211> 975
 <212> DNA
 <213> Sus scrofa

<220>
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 <222> (748)..(748)
 <223> n is a, c, g, or t

<400> 65
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 tggaaactcgg gcgcctgac cagtggcgtg cacaccttcc catccgtcct gcagccgtca 180
 gggctctact ccctcagcag catggtgacc gtgccggccc acagcttgtc cagcaagcgc 240
 tatacgtgca atgtcaacca cccagccacc aaaaccaagg tggacctgtg tgttggaaga 300
 ccatgtccca tatgcccagg ctgtgaagtg gccgggccct cgggttctcat ctccctcca 360
 aaaccaagg acatcctcat gatctcccg acccccgagg tcacgtgcgt ggtggtggac 420
 gtcagcaagg agcacgccga ggtccagttc tcttggtacg tggacggcga agaggtgcac 480
 acggccgaga cgaggccaaa ggaggagcag ttcaacagca cctaccgctg ggtcagcgtc 540
 ctgcccattc agcagagga ctggctgaag gggaaggagt tcgagtcaa ggtcaacaac 600
 gaagacctcc caggcccat cagaggacc atctccaagg ccaaaggggt ggtacggagc 660
 ccggaggtgt acacctgcc cccaccgcc gaggagctgt ccaagagcat agtcacgta 720
 acctgcctgg taaaagcat ctcccgnc tcatccatg ttgagtggaa aatcaacgga 780
 aaaccagagc cagagaacgc atatgcacc acccgcctc aggaggacga ggacaggacc 840
 tacttctgt acagcaagct cgcggtggac aaggcaagat gggaccatgg agaaacattt 900
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 actcagggtg aatga 975

<210> 66
 <211> 317
 <212> PRT
 <213> Sus scrofa

<400> 66

Ala Tyr Asn Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Val Ser Asp His Asn Val Ala Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Trp Gly Ala Gln Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Thr Val Thr Val Pro Ala His Ser Leu Ser Ser Lys Cys
 65 70 75 80

Phe Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Leu
 85 90 95

Cys Val Gly Lys Lys Thr Lys Pro Arg Cys Pro Ile Cys Pro Gly Cys
 100 105 110

Glu Val Ala Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
 115 120 125

Ile Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 130 135 140

Val Ser Lys Glu His Ala Glu Val Gln Phe Ser Trp Tyr Val Asp Gly
 145 150 155 160

Glu Glu Val His Thr Ala Glu Thr Arg Pro Lys Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gln His Glu Asp Trp
 180 185 190

Leu Lys Gly Lys Glu Phe Glu Cys Lys Val Asn Asn Glu Asp Leu Pro
 195 200 205

Gly Pro Ile Thr Arg Thr Ile Ser Lys Ala Lys Gly Val Val Arg Ser
 210 215 220

Pro Glu Val Tyr Thr Leu Pro Pro Pro Ala Glu Glu Leu Ser Lys Ser
 225 230 235 240

Ile Val Thr Leu Thr Cys Leu Val Lys Ser Phe Phe Pro Pro Phe Ile
 245 250 255

His Val Glu Trp Lys Ile Asn Gly Lys Pro Glu Pro Glu Asn Ala Tyr
 260 265 270

Arg Thr Thr Pro Pro Gln Glu Asp Glu Asp Gly Thr Tyr Phe Leu Tyr
 275 280 285

Ser Lys Phe Ser Val Glu Lys Phe Arg Trp His Ser Gly Gly Ile His
 290 295 300

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315

<210> 67

<211> 952

<212> DNA

<213> Sus scrofa

<400> 67

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tggaactggg gcgcccagac cagtggcgtg cacaccttcc catccgtcct gcagccgtca	180
gggtcttact cctcagcag cacggtgacc gtgccggccc acagcttgtc cagcaagtgc	240
ttcacgtgca atgtcaacca cccggccacc accaccaagg tggacctgtg tgttggaana	300
aagaccaagc ctcatgttcc catatgccca ggctgtgaag tggccgggcc ctcatgttcc	360
atcttccctc caaaaccaa ggacatcttc atgatctccc ggacccccga ggtcacgtgc	420
gtggtggtgg acgtcagcaa ggagcacgcc gaggtccagt tctctggta cgtggacggc	480

gaagaggtgc acacggccga gacgagacca aaggaggagc agttcaacag cacttaccgc 540
gtggtcagcg tctgccccat ccagcacgag gactggctga aggggaagga gttcgagtgc 600
aaggtcaaca acgaagacct cccaggcccc atcacgagga ccatctcaa ggccaaaggg 660
gtggtacgga gcccggaggt gtacaccctg cccccaccg ccgaggagct gtccaagagc 720
atagtcacgc taacctgcct ggtcaaaagc ttcttccgc ctttcatcca tgttgagtgg 780
aaaatcaacg gaaaaccaga gccagagaac gcataccgca ccaccccgcc ccaggaggac 840
gaggacggga cctacttctt gtacagcaag ttctcggtgg aaaagttcag gtggcacagt 900
ggaggcatcc actgtgcggt gatgcacgag gctctgcaca accactacac cc 952

<210> 68

<211> 314

<212> PRT

<213> Sus scrofa

<400> 68

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
20 25 30

Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Leu Ser Ser Lys Ser
65 70 75 80

Tyr Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Leu
85 90 95

Cys Val Gly Arg Pro Cys Pro Ile Cys Pro Ala Cys Glu Gly Pro Gly
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
115 120 125

Ser Arg Thr Pro Gln Val Thr Cys Val Val Val Asp Val Ser Gln Glu
130 135 140

Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly Val Glu Val His
145 150 155 160

Thr Ala Gln Thr Arg Pro Lys Glu Ala Gln Phe Asn Ser Thr Tyr Arg
165 170 175

Val Val Ser Val Leu Pro Ile Gln His Glu Asp Trp Leu Lys Gly Lys
180 185 190

Glu Phe Glu Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Thr
195 200 205

Arg Ile Ile Ser Lys Ala Lys Gly Pro Ser Arg Glu Pro Gln Val Tyr
210 215 220

Thr Leu Ser Pro Ser Ala Glu Glu Leu Ser Arg Ser Lys Val Ser Ile
225 230 235 240

Thr Cys Leu Val Thr Gly Phe Tyr Pro Pro Asp Ile Asp Val Glu Trp
245 250 255

Lys Ser Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr Arg Thr Thr Pro
260 265 270

Pro Gln Gln Asp Val Asp Gly Thr Tyr Phe Leu Tyr Ser Lys Leu Ala
275 280 285

Val Asp Lys Ala Ser Trp Gln Arg Gly Asp Pro Phe Gln Cys Ala Val
290 295 300

Met His Glu Ala Leu His Asn His Tyr Thr
305 310

<210> 69

<211> 943

<212> DNA

<213> Sus scrofa

<400> 69

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 tggaaactcgg gcgccttgac cagtggcgtg cataccttcc catccgtcct gcagccgtca 180
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 tacactgca atgtcaacca cccggccacc accaccaagg tggacctgtg tgttggacga 300
 ccatgtcca tatgcccagc ctgtgaaggg cccgggccct cggcttctcat ctccctcca 360
 aaaccaagg acaccctcat gatctcccgg acaccccagg tcacgtgcgt ggtggtagat 420
 gtgagccagg aaaacccgga ggtccagttc tcttggtatg tggacggtgt agaggtgcac 480
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 ctgcccattc agcagagga ctggctgaag gggaaggagt tcgagtcaa ggtcaacaac 600
 aaagacctcc cagccccat cacaaggatc atctccaagg ccaaagggcc gagccgggag 660
 ccgcaggtgt acacctgtc cccatccgcc gaggagctgt ccaggagcaa agtcagcata 720
 acctgcctgg tctactggctt ctaccacct gacatcgatg tcgagtggaa gagcaacgga 780
 cagccggagc cagagggcaa ttaccgcacc accccgcccc agcaggacgt ggacgggacc 840
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<210> 70

<211> 320

<212> PRT

<213> Sus scrofa

<400> 70

Ala Pro Lys Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Cys Gly Arg
 1 5 10 15

Asp Thr Ser Gly Pro Asn Val Ala Leu Gly Cys Leu Ala Ser Ser Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ser Val Leu Gln Pro Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Thr Val Thr Val Pro Ala Arg Ser Ser Ser Arg Lys Cys
65 70 75 80

Phe Thr Cys Asn Val Asn His Pro Ala Thr Thr Thr Lys Val Asp Leu
 85 90 95

Cys Val Gly Arg Pro Cys Pro Ile Cys Pro Ala Cys Glu Gly Asn Gly
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 115 120 125

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
 130 135 140

Asn Pro Glu Val Gln Phe Ser Trp Tyr Val Asp Gly Glu Glu Val His
145 150 155 160

Thr Ala Glu Thr Arg Pro Lys Glu Glu Gln Phe Asn Ser Thr Tyr Arg
 165 170 175

Val Val Ser Val Leu Pro Ile Gln His Gln Asp Trp Leu Lys Gly Lys
 180 185 190

Glu Phe Glu Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Thr
 195 200 205

Arg Ile Ile Ser Lys Ala Lys Gly Pro Ser Arg Glu Pro Gln Val Tyr
 210 215 220

Thr Leu Ser Pro Ser Ala Glu Glu Leu Ser Arg Ser Lys Val Ser Ile
225 230 235 240

Thr Cys Leu Val Thr Gly Phe Tyr Pro Pro Asp Ile Asp Val Glu Trp
 245 250 255

Lys Ser Asn Gly Gln Pro Glu Pro Glu Gly Asn Tyr Arg Ser Thr Pro
 260 265 270

Pro Gln Glu Asp Glu Asp Gly Thr Tyr Phe Leu Tyr Ser Lys Leu Ala

275 280 285

Val Asp Lys Ala Arg Leu Gln Ser Gly Gly Ile His Cys Ala Val Met
290 295 300

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Ser Lys Thr
305 310 315 320

<210> 71

<211> 960

<212> DNA

<213> Sus scrofa

<400> 71

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ccatgtccca tatgccagc ctgtgaaggg aacgggccct cggcttcat ctccctcca    360
aaaccaagg acacctcat gatctcccgg acccccgagg tcacgtgcgt ggtggtagat    420
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acggccgaga cgaggccaaa ggaggagcag ttcaacagca cctaccgtgt ggtcagcgtc    540
ctgcccattc agcaccagga ctggctgaag ggaaaggagt tcgagtgcaa ggtcaacaac    600
aaagacctcc cagccccat cacaaggatc atctccaagg ccaaagggcc gagccgggag    660
ccgcaggtgt acacctgtc cccatccgcc gaggagctgt ccaggagcaa agtcagcata    720
acctgctgg tcactggctt ctaccacct gacatgatg tcgagtggaa gagcaacgga    780
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tacttctgt acagcaaact cgcggtggac aaggcgaggt tgcagagtgg aggcattcac    900
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<210> 72

<211> 266

<212> PRT

<213> Bubalus bubalis

<400> 72

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 1 5 10 15

Ser Leu Ser Ser Thr Val Thr Ala Pro Ala Ser Ala Thr Lys Ser Gln
 20 25 30

Thr Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp
 35 40 45

Lys Ala Val Val Pro Pro Cys Arg Pro Lys Pro Cys Asp Cys Cys Pro
 50 55 60

Pro Pro Glu Leu Pro Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys
 65 70 75 80

Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val
 85 90 95

Val Val Asp Val Gly His Asp Asp Pro Glu Val Lys Phe Ser Trp Phe
 100 105 110

Val Asp Asp Val Glu Val Asn Thr Ala Arg Thr Lys Pro Arg Glu Glu
 115 120 125

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Ala Leu Pro Ile Gln His
 130 135 140

Asn Asp Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val Tyr Asn Glu
 145 150 155 160

Gly Leu Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Gln
 165 170 175

Ala Arg Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Asp Glu Leu
 180 185 190

Ser Lys Ser Thr Val Ser Ile Thr Cys Met Val Thr Gly Phe Tyr Pro
 195 200 205

Asp Tyr Ile Ala Val Glu Trp Gln Lys Asp Gly Gln Pro Glu Ser Glu

210	215	220	
Asp Lys Tyr Gly Thr Thr Pro Pro Gln Leu Asp Ser Asp Gly Ser Tyr			
225	230	235	240
Phe Leu Tyr Ser Arg Leu Arg Val Asn Lys Asn Ser Trp Gln Glu Gly			
	245	250	255
Gly Ala Tyr Thr Cys Val Val Met His Glu			
	260	265	

<210> 73

<211> 801

<212> DNA

<213> Bubalus bubalis

<400> 73

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cccggccagc agcaccaagg tggacaaggc tgttgttccc ccatgcagac cgaaaccctg      180
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acccaaggac accctcaca tctctggaac tctgaggtc acgtgtgtgg tggaggacgt      300
gggccaagat gaccccgagg tgaagttctc ctggttcgtg gacgatgtgg aggtaaacac      360
agccaggacg aagccaagag aggagcagtt caacagcacc taccgctgg tcagcgcct      420
gccatccag cacaacgact ggactggagg aaaggagttc aagtgcaagg tctacaatga      480
aggcctccca gcccctatcg tgaggacat ctccaggacc aaagggcagg cccgggagcc      540
gcaggtgtac gtctggccc caccacagga cgagctcagc aaaagcacgg tcagcatcac      600
ttgcatggtc actggcttct acccagacta catcgccgta gagtggcaga aagatgggca      660
gcctgagtca gaggacaaat atggcacgac ccgccccag ctggacagcg atggctcta      720
cttctgtac agcaggctca ggtgaacaa gaacagctgg caagaaggag ggcctacac      780
gtgtgtagtg atgcatgagg c

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801

<210> 74

<211> 309

<212> PRT

<213> Bulalus bubalis

<400> 74

Ala Ser Ile Thr Ala Pro Lys Val Tyr Pro Leu Thr Ser Cys Arg Gly
 1 5 10 15

Glu Thr Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Thr Val Thr Ala Pro Ala Ser Ala Thr Lys Ser Gln Thr
 65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Thr
 85 90 95

Ala Val Gly Phe Ser Ser Asp Cys Cys Lys Phe Pro Lys Pro Cys Val
 100 105 110

Arg Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu
 115 120 125

Met Ile Thr Gly Asn Pro Glu Val Thr Cys Val Val Val Asp Val Gly
 130 135 140

Arg Asp Asn Pro Glu Val Gln Phe Ser Trp Phe Val Gly Asp Val Glu
 145 150 155 160

Val His Thr Gly Arg Ser Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
 165 170 175

Tyr Arg Val Val Ser Thr Leu Pro Ile Gln His Asn Asp Trp Thr Gly
 180 185 190

Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Gly Leu Pro Ala Pro
 195 200 205

Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Gln Ala Arg Glu Pro Gln

210 215 220
 Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys Ser Thr Val
 225 230 235 240
 Ser Val Thr Cys Met Val Thr Gly Phe Tyr Pro Asp Tyr Ile Ala Val
 245 250 255
 Glu Trp His Arg Asp Arg Gln Ala Glu Ser Glu Asp Lys Tyr Arg Thr
 260 265 270
 Thr Pro Pro Gln Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Arg
 275 280 285
 Leu Lys Val Asn Lys Asn Ser Trp Gln Glu Gly Gly Ala Tyr Thr Cys
 290 295 300
 Val Val Met His Glu
 305

<210> 75
 <211> 929
 <212> DNA
 <213> Bubalus bubalis

<400> 75
 gctccatca cagccccgaa agttaccct ctgacttctt gccgcgggga aacgtccage 60
 tccaccgtga ccctgggctg cctggtctcc agctacatgc ccgagccggt gaccgtgacc 120
 tggaactcgg gtgcctgaa gageggcgtg cacaccttc cggccgtcct tcagtcctct 180
 gggtctact ctctcagcag cacggtgacc gcgccgcca gcgccacaaa aagccagacc 240
 ttcacctgca acgtagccca cccggccagc agcaccaagg tggacacggc tgttgggttc 300
 tccagtgact gtgcaagtt tctaagcct tgtgtgaggg gaccatctgt cttcatcttc 360
 ccgccgaac ccaaagacac cctgatgatc acaggaaatc ccgaggtcac atgtgtggtg 420
 gtggacgtgg gccgggataa ccccgaggtg cagttctcct ggttcgtggg tgatgtggag 480
 gtgcacacgg gcaggtcgaa gccgagagag gagcagttca acagcaccta ccgcgtggtc 540
 agcacctgc ccatccagca caatgactgg actggaggaa aggagttaa gtgcaaggtc 600
 aacaacaaag gctccccagc cccatcgtg aggaccatct ccaggaccaa agggcaggcc 660

cgggagccgc aggtgtacgt cctggcccca cccaggaag agctcagcaa aagcacggtc 720
 agcgtcactt gcatggtcac tggcttctac ccagactaca tcgccgtaga gtggcataga 780
 gaccggcagg ctgagtcgga ggacaagtac cgcacgaccc cgccccagct ggacagcgat 840
 ggctctact tctgtacag caggctcaag gtgaacaaga acagctggca agaaggaggc 900
 gcctacacgt gtgtagtgat gcatgaggc 929

<210> 76

<211> 352

<212> PRT

<213> Bubalus bubalis

<400> 76

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ala Ser Ser Cys Gly
 1 5 10 15

Asp Thr Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Asn
 35 40 45

Gly Val His Thr Phe Pro Ala Val Arg Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Met Pro Thr Ser Thr Ala Gly Thr Gln Thr
 65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Thr
 85 90 95

Ala Val Thr Ala Arg His Pro Val Pro Lys Thr Pro Glu Thr Pro Ile
 100 105 110

His Pro Val Lys Pro Pro Thr Gln Glu Pro Arg Asp Glu Lys Thr Pro
 115 120 125

Cys Gln Cys Pro Lys Cys Pro Glu Pro Leu Gly Gly Leu Ser Val Phe
 130 135 140

Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr Pro

145 150 155 160
 Glu Val Thr Cys Val Val Val Asp Val Gly Gln Asp Asp Pro Glu Val
 165 170 175
 Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Arg Met
 180 185 190
 Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Ala
 195 200 205
 Leu Pro Ile Gln His Gln Asp Trp Leu Arg Glu Lys Glu Phe Lys Cys
 210 215 220
 Lys Val Asn Asn Lys Gly Leu Pro Ala Pro Ile Val Arg Thr Ile Ser
 225 230 235 240
 Arg Thr Lys Gly Gln Ala Arg Glu Pro Gln Val Tyr Val Leu Ala Pro
 245 250 255
 Pro Arg Glu Glu Leu Ser Lys Ser Thr Leu Ser Leu Thr Cys Leu Ile
 260 265 270
 Thr Gly Phe Tyr Pro Glu Glu Val Asp Val Glu Trp Gln Arg Asn Gly
 275 280 285
 Gln Pro Glu Ser Glu Asp Lys Tyr His Thr Thr Pro Pro Gln Leu Asp
 290 295 300
 Ala Asp Gly Ser Tyr Phe Leu Tyr Ser Arg Leu Arg Val Asn Arg Ser
 305 310 315 320
 Ser Trp Gln Glu Gly Asp His Tyr Thr Cys Ala Val Met His Glu Ala
 325 330 335
 Leu Arg Asn His Tyr Lys Glu Lys Pro Ile Ser Arg Ser Pro Gly Lys
 340 345 350

<210> 77

<211> 1059

<212> DNA

<213> Bubalus bubalis

<400> 77

gcctccacca cagccccgaa agtctaccct ctggcatcca gctgcgggga cacgtccage 60
 tccaccgtga cctggggtg cctggtctcc agctacatgc ccgagccggt gaccgtgacc 120
 tggaactcgg gtgccctgaa gaacggcgtg cacaccttc cgcccgccg gcagtectcc 180
 gggctctact ctctcagcag catggtgacc atgccacca gcaccgcagg aaccagacc 240
 ttcacctgca acgtagccca cccggccagc agcaccaagg tggacacggc tgtcactgca 300
 aggcacccgg tccgaagac accagagaca cctatccatc ctgtaaaacc cccaaccag 360
 gagcccagag atgaaaagac accctgccag tgtcccaa at gccagaacc tctgggagga 420
 ctgtctgtct tcattctccc accgaaacc aaggacacc tcacaatctc tggaacgccc 480
 gaggtcacgt gtgtgggtgt ggacgtgggc caggatgacc ccgaagtga gttctcctgg 540
 ttcgtggatg acgtggaggt gcacacagcc aggatgaagc caagagagga gcagttcaac 600
 agcacctacc gcgtggtcag cgcctgccc atccagcacc aggactggct gcgggaaaag 660
 gaggttcaagt gcaaggtaaa caacaaaggc ctcccgccc ccatcgtgag gaccatctcc 720
 aggacaaaag ggcaggcccc ggagccacag gtgtatgtcc tggccccacc ccgggaagag 780
 ctacgcaaaa gcacgtcag cctcacctgc ctaatcacc gttctaccc agaagaggta 840
 gacgtggagt ggcagagaaa tgggcagcct gagtcagagg acaagtacca cagacccca 900
 cccagctgg acgtgacgg ctctacttc ctgtacagca ggctcagggt gaacaggagc 960
 agctggcagg aaggagacca ctacacgtgt gcagtgatgc atgaagcttt acggaatcac 1020
 taaaagaga agcccatctc gaggtctccg ggtaaatga 1059

<210> 78

<211> 105

<212> PRT

<213> Bubalus bubalis

<400> 78

Gln Pro Lys Ser Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Thr Glu
 1 5 10 15

Glu Leu Ser Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 20 25 30

Tyr Pro Gly Ser Met Thr Val Ala Arg Lys Ala Asp Gly Ser Thr Ile

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
 50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
 65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
 85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
 100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
 130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 145 150 155 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 165 170 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
 180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
 195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 210 215 220

Leu Ser Leu Gly Lys
 225

<210> 81

<211> 690

<212> DNA

<213> Homo sapiens

<400> 81
gagtccaaat atgggtcccc gtgcccata tgcccagcac ctgagttcct ggggggacca 60
tcagtcttcc tgttcccccc aaaaccaag gacactctca tgatctcccg gaccctgag 120
gtcacgtgcg tgggtggtgga cgtgagccag gaagaccccg aggtccagtt caactggtac 180
gtggatggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gttcaacagc 240
acgtaccgtg tggtcagcgt cctcaccgtc gtgcaccagg actggctgaa cggcaaggag 300
tacaagtgca aggtctccaa caaaggcctc ccgtcctcca tcgagaaaac catctccaaa 360
gccaaagggc agccccgaga gccacaggtg tacaccctgc ccccatccca ggaggagatg 420
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctacccag cgacatcgcc 480
gtggagtggg agagcaatgg gcagccggag acaactaca agaccagcc tcccgctgtg 540
gactccgacg gctccttctt cctctacagc aggctaaccg tggacaagag caggtggcag 600
gaggggaatg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 660
aagagcctct ccctgtctct gggtaaatga 690

<210> 82
<211> 217
<212> PRT
<213> Homo sapiens

<400> 82

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
 115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 195 200 205

Lys Ser Leu Ser Leu Ser Leu Gly Lys
 210 215

<210> 83

<211> 654

<212> DNA

<213> Homo sapiens

<400> 83

gcacctgagt tctggtgggg accatcagtc ttctgttcc ccccaaaacc caaggacact 60

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac 120

cccagggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagttcaa cagcacgtac cgtgtgttca gcgtctcac cgtcctgcac 240

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc 300

tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc 360

ctgccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacaagacca cgctcccggt gctggactcc gacggctcct tcttctcteta cagcaagctc 540

accgtggaca agagcaggtg gcaggagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctctgggtaa atga 654

<210> 84

<211> 329

<212> PRT

<213> Bos taurus

<400> 84

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
1 5 10 15

Asp Lys Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Gly Ser Thr Ser Gly Gln Thr Phe
65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Ala
85 90 95

Val Asp Pro Thr Cys Lys Pro Ser Pro Cys Asp Cys Cys Pro Pro Pro
100 105 110

Glu Leu Pro Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Gly His Asp Asp Pro Glu Val Lys Phe Ser Trp Phe Val Asp
145 150 155 160

Asp Val Glu Val Asn Thr Ala Thr Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Ala Leu Arg Ile Gln His Gln Asp
 180 185 190

Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Asn Glu Gly Leu
 195 200 205

Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Pro Ala Arg
 210 215 220

Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys
 225 230 235 240

Ser Thr Val Ser Leu Thr Cys Met Val Thr Ser Phe Tyr Pro Asp Tyr
 245 250 255

Ile Ala Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Ser Glu Asp Lys
 260 265 270

Tyr Gly Thr Thr Pro Pro Gln Leu Asp Ala Asp Ser Ser Tyr Phe Leu
 275 280 285

Tyr Ser Lys Leu Arg Val Asp Arg Asn Ser Trp Gln Glu Gly Asp Thr
 290 295 300

Tyr Thr Cys Val Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 305 310 315 320

Lys Ser Thr Ser Lys Ser Ala Gly Lys
 325

<210> 85

<211> 329

<212> PRT

<213> Bos taurus

<400> 85

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
 1 5 10 15

Asp Lys Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Gly Ser Thr Ser Gly Gln Thr Phe
 65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Ala
 85 90 95

Val Asp Pro Thr Cys Lys Pro Ser Pro Cys Asp Cys Cys Pro Pro Pro
 100 105 110

Glu Leu Pro Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Gly His Asp Asp Pro Glu Val Lys Phe Ser Trp Phe Val Asp
 145 150 155 160

Asp Val Glu Val Asn Thr Ala Thr Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Ala Leu Arg Ile Gln His Gln Asp
 180 185 190

Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Asn Glu Gly Leu
 195 200 205

Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Pro Ala Arg
 210 215 220

Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys
 225 230 235 240

Ser Thr Val Ser Leu Thr Cys Met Val Thr Ser Phe Tyr Pro Asp Tyr
 245 250 255

Ile Ala Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Ser Glu Asp Lys
 260 265 270

Tyr Gly Thr Thr Pro Pro Gln Leu Asp Ala Asp Ser Ser Tyr Phe Leu
 275 280 285

Tyr Ser Lys Leu Arg Val Asp Arg Asn Ser Trp Gln Glu Gly Asp Thr
 290 295 300

Tyr Thr Cys Val Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 305 310 315 320

Lys Ser Thr Ser Lys Ser Ala Gly Lys
 325

<210> 86

<211> 329

<212> PRT

<213> Bos taurus

<400> 86

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
 1 5 10 15

Asp Lys Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Gly Ser Thr Ser Gly Thr Gln Thr
 65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
 85 90 95

Ala Val Asp Pro Arg Cys Lys Thr Thr Cys Asp Cys Cys Pro Pro Pro
 100 105 110

Glu Leu Pro Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Gly His Asp Asp Pro Glu Val Lys Phe Ser Trp Phe Val Asp
 145 150 155 160

Asp Val Glu Val Asn Thr Ala Thr Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Ala Leu Arg Ile Gln His Gln Asp
 180 185 190

Trp Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Asn Glu Gly Leu
 195 200 205

Pro Ala Pro Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Pro Ala Arg
 210 215 220

Glu Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys
 225 230 235 240

Ser Thr Val Ser Leu Thr Cys Met Val Thr Ser Phe Tyr Pro Asp Tyr
 245 250 255

Ile Ala Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Ser Glu Asp Lys
 260 265 270

Tyr Gly Thr Thr Pro Pro Gln Leu Asp Ala Asp Gly Ser Tyr Phe Leu
 275 280 285

Tyr Ser Arg Leu Arg Val Asp Arg Asn Ser Trp Gln Glu Gly Asp Thr
 290 295 300

Tyr Thr Cys Val Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 305 310 315 320

Lys Ser Thr Ser Lys Ser Ala Gly Lys
325

<210> 87
<211> 326
<212> PRT
<213> Bos taurus

<400> 87

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ala Ser Ser Cys Gly
1 5 10 15

Asp Thr Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Ser Gly Gln Thr Phe
65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Ala
85 90 95

Val Gly Val Ser Ile Asp Cys Ser Lys Cys His Asn Gln Pro Cys Val
100 105 110

Arg Glu Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu
115 120 125

Met Ile Thr Gly Thr Pro Glu Val Thr Cys Val Val Val Asn Val Gly
130 135 140

His Asp Asn Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145 150 155 160

Val His Thr Ala Arg Ser Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
165 170 175

Tyr Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Thr Gly
 180 185 190

Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Gly Leu Ser Ala Pro
 195 200 205

Ile Val Arg Ile Ile Ser Arg Ser Lys Gly Pro Ala Arg Glu Pro Gln
 210 215 220

Val Tyr Val Leu Asp Pro Pro Lys Glu Glu Leu Ser Lys Ser Thr Leu
 225 230 235 240

Ser Val Thr Cys Met Val Thr Gly Phe Tyr Pro Glu Asp Val Ala Val
 245 250 255

Glu Trp Gln Arg Asn Arg Gln Thr Glu Ser Glu Asp Lys Tyr Arg Thr
 260 265 270

Thr Pro Pro Gln Leu Asp Thr Asp Arg Ser Tyr Phe Leu Tyr Ser Lys
 275 280 285

Leu Arg Val Asp Arg Asn Ser Trp Gln Glu Gly Asp Ala Tyr Thr Cys
 290 295 300

Val Val Met His Glu Ala Leu His Asn His Tyr Met Gln Lys Ser Thr
 305 310 315 320

Ser Lys Ser Ala Gly Lys
 325

<210> 88

<211> 326

<212> PRT

<213> Bos taurus

<400> 88

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
 1 5 10 15

Asp Lys Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Gly Ser Thr Ser Gly Gln Thr Phe
 65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Ala
 85 90 95

Val Gly Val Ser Ser Asp Cys Ser Lys Pro Asn Asn Gln His Cys Val
 100 105 110

Arg Glu Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu
 115 120 125

Met Ile Thr Gly Thr Pro Glu Val Thr Cys Val Val Val Asn Val Gly
 130 135 140

His Asp Asn Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
 145 150 155 160

Val His Thr Ala Arg Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
 165 170 175

Tyr Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Thr Gly
 180 185 190

Gly Lys Glu Phe Lys Cys Lys Val Asn Ile Lys Gly Leu Ser Ala Ser
 195 200 205

Ile Val Arg Ile Ile Ser Arg Ser Lys Gly Pro Ala Arg Glu Pro Gln
 210 215 220

Val Tyr Val Leu Asp Pro Pro Lys Glu Glu Leu Ser Lys Ser Thr Val
 225 230 235 240

Ser Val Thr Cys Met Val Ile Gly Phe Tyr Pro Glu Asp Val Asp Val

245 250 255
 Glu Trp Gln Arg Asp Arg Gln Thr Glu Ser Glu Asp Lys Tyr Arg Thr
 260 265 270

Thr Pro Pro Gln Leu Asp Ala Asp Arg Ser Tyr Phe Leu Tyr Ser Lys
 275 280 285

Leu Arg Val Asp Arg Asn Ser Trp Gln Arg Gly Asp Thr Tyr Thr Cys
 290 295 300

Val Val Met His Glu Ala Leu His Asn His Tyr Met Gln Lys Ser Thr
 305 310 315 320

Ser Lys Ser Ala Gly Lys
 325

<210> 89

<211> 327

<212> PRT

<213> Bos taurus

<400> 89

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
 1 5 10 15

Asp Lys Ser Ser Ser Gly Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Ser Gly Thr Gln Thr
 65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
 85 90 95

Ala Val Gly Val Ser Ser Asp Cys Ser Lys Pro Asn Asn Gln His Cys

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

Thr Ser Lys Ser Ala Gly Lys
325

<210> 90
<211> 352
<212> PRT
<213> Bos taurus

<400> 90

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ala Ser Ser Cys Gly
1 5 10 15

Asp Thr Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Arg Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Ser Ser Glu Thr Gln Thr
65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
85 90 95

Ala Val Thr Ala Arg Arg Pro Val Pro Thr Thr Pro Lys Thr Thr Ile
100 105 110

Pro Pro Gly Lys Pro Thr Thr Pro Lys Ser Glu Val Glu Lys Thr Pro
115 120 125

Cys Gln Cys Ser Lys Cys Pro Glu Pro Leu Gly Gly Leu Ser Val Phe
130 135 140

Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr Pro
145 150 155 160

Glu Val Thr Cys Val Val Val Asp Val Gly Gln Asp Asp Pro Glu Val
165 170 175

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Arg Thr
 180 185 190

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Ala
 195 200 205

Leu Arg Ile Gln His Gln Asp Trp Leu Gln Gly Lys Glu Phe Lys Cys
 210 215 220

Lys Val Asn Asn Lys Gly Leu Pro Ala Pro Ile Val Arg Thr Ile Ser
 225 230 235 240

Arg Thr Lys Gly Gln Ala Arg Glu Pro Gln Val Tyr Val Leu Ala Pro
 245 250 255

Pro Arg Glu Glu Leu Ser Lys Ser Thr Leu Ser Leu Thr Cys Leu Ile
 260 265 270

Thr Gly Phe Tyr Pro Glu Glu Ile Asp Val Glu Trp Gln Arg Asn Gly
 275 280 285

Gln Pro Glu Ser Glu Asp Lys Tyr His Thr Thr Ala Pro Gln Leu Asp
 290 295 300

Ala Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Arg Val Asn Lys Ser
 305 310 315 320

Ser Trp Gln Glu Gly Asp His Tyr Thr Cys Ala Val Met His Glu Ala
 325 330 335

Leu Arg Asn His Tyr Lys Glu Lys Ser Ile Ser Arg Ser Pro Gly Lys
 340 345 350

<210> 91

<211> 352

<212> PRT

<213> Bos taurus

<400> 91

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ala Ser Arg Cys Gly
 1 5 10 15

Asp Thr Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
 20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Met Val Thr Val Pro Ala Ser Thr Ser Glu Thr Gln Thr
 65 70 75 80

Phe Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
 85 90 95

Ala Val Thr Ala Arg Arg Pro Val Pro Thr Thr Pro Lys Thr Thr Ile
 100 105 110

Pro Pro Gly Lys Pro Thr Thr Gln Glu Ser Glu Val Glu Lys Thr Pro
 115 120 125

Cys Gln Cys Ser Lys Cys Pro Glu Pro Leu Gly Gly Leu Ser Val Phe
 130 135 140

Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr Pro
 145 150 155 160

Glu Val Thr Cys Val Val Val Asp Val Gly Gln Asp Asp Pro Glu Val
 165 170 175

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Arg Thr
 180 185 190

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Ala
 195 200 205

Leu Arg Ile Gln His Gln Asp Trp Leu Gln Gly Lys Glu Phe Lys Cys
 210 215 220

Lys Val Asn Asn Lys Gly Leu Pro Ala Pro Ile Val Arg Thr Ile Ser
 225 230 235 240

Arg Thr Lys Gly Gln Ala Arg Glu Pro Gln Val Tyr Val Leu Ala Pro
 245 250 255

Pro Arg Glu Glu Leu Ser Lys Ser Thr Leu Ser Leu Thr Cys Leu Ile
 260 265 270

Thr Gly Phe Tyr Pro Glu Glu Ile Asp Val Glu Trp Gln Arg Asn Gly
 275 280 285

Gln Pro Glu Ser Glu Asp Lys Tyr His Thr Thr Ala Pro Gln Leu Asp
 290 295 300

Ala Asp Gly Ser Tyr Phe Leu Tyr Ser Arg Leu Arg Val Asn Lys Ser
 305 310 315 320

Ser Trp Gln Glu Gly Asp His Tyr Thr Cys Ala Val Met His Glu Ala
 325 330 335

Leu Arg Asn His Tyr Lys Glu Lys Ser Ile Ser Arg Ser Pro Gly Lys
 340 345 350

<210> 92

<211> 990

<212> DNA

<213> Bos taurus

<400> 92

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tggaactcgg gtgccctgaa gageggcgctg cacaccttcc cggtgtctct teagtcctcc 180

gggtgtact ctctcagcag catggtgacc gtgcccgga gcacctcagg acagaccttc 240

acctgcaacg tagccacccc ggccagcagc accaaggtgg acaaggtgt tgatcccaca 300

tgcaaaccat caccctgtga ctgttgccca cccctgagc tccccggagg accctctgtc 360

ttcatcttcc caccgaaacc caaggacacc ctcaaatct cgggaacgcc cgaggtcacg 420

tgtgtggtgg tggacgtggg ccacgatgac cccgaggtga agttctcctg gttcgtggac 480

gacgtggagg taaacacagc cagcaggaag ccgagagagg agcagttcaa cagcacctac 540

cgcgtggtca ggcacctgcg catccagcac caggactgga ctggaggaaa ggagttcaag 600

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<210> 93

<211> 990

<212> DNA

<213> Bos taurus

<400> 93

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 tggaaactcg gtgccctgaa gagcggcgtg cacaccttc cgccgtctct tcagtcctcc 180
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 aagtcacct ctaagtctgc gggtaaata 990

<210> 94
 <211> 990
 <212> DNA
 <213> Bos taurus

<400> 94
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<210> 95
 <211> 981
 <212> DNA
 <213> Bos taurus

<400> 95
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 tctaagtctg cgggtaaatg a 981

<210> 96

<211> 981

<212> DNA

<213> Bos taurus

<400> 96

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 ccaccgaaac ccaaagacac cctgatgac acaggaacgc ccgaggtcac gtgtgtggtg 420
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cgggagccgc aggtgtatgt cctggacceca cccaaggaag agctcagcaa aagcacggtc 720
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 cgctctact tctgtacag caagctcagg gtggacagga acagctggca gagaggagac 900
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<210> 97

<211> 984

<212> DNA

<213> Bos taurus

<400> 97

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<210> 98
 <211> 1059
 <212> DNA
 <213> Bos taurus

<400> 98
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 tacaagaga agtccatctc gaggtctccg ggtaaatga 1059

<210> 99
 <211> 1059
 <212> DNA
 <213> Bos taurus

<400> 99
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 ctgtctgtct tcatttccc accgaaacce aaggacacce tcacaatctc gggaacgccc 480
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 cccagctgg atgtgacgg ctctacttc ctgtacagca ggctcagggt gaacaagagc 960
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 taaaaagaga agtccatctc gaggtctccg ggtaaata 1059

<210> 100

<211> 105

<212> PRT

<213> Bos taurus

<400> 100

Gln Pro Lys Ser Pro Pro Ser Val Thr Leu Phe Pro Pro Ser Thr Glu
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Glu Leu Asn Gly Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 20 25 30

Tyr Pro Gly Ser Val Thr Val Val Trp Lys Ala Asp Gly Ser Thr Ile
 35 40 45

Thr Arg Asn Val Glu Thr Thr Arg Ala Ser Lys Gln Ser Asn Ser Lys
 50 55 60

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Ser Ser Asp Trp Lys Ser

65 70 75 80

Lys Gly Ser Tyr Ser Cys Glu Val Thr His Glu Gly Ser Thr Val Thr

85 90 95

Lys Thr Val Lys Pro Ser Glu Cys Ser
100 105

<210> 101
<211> 318
<212> DNA
<213> Bos taurus

<400> 101
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tggaaggcag acggcagcac catcacccgc aacgtggaga ccaccgggc ctccaaacag 180
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ccctcagagt gttcttag 318

<210>	102
<211>	328
<212>	PRT
<213>	Bos taurus

<400> 102

Ala Ser Thr Thr Ala Pro Lys Val Tyr Pro Leu Ser Ser Cys Cys Gly
1 5 10 15

Asp Lys Ser Ser Ser Thr Val Thr Leu Gly Cys Leu Val Ser Ser Tyr
20 25 30

Met Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Lys Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Met Val Thr Val Pro Gly Ser Thr Ser Gly Gln Thr Phe
65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Ala
85 90 95

Val Asp Pro Thr Cys Lys Pro Ser Pro Cys Asp Cys Cys Pro Pro Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Thr Ile Ser Gly Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Gly His Asp Asp Pro Glu Val Lys Phe Ser Trp Phe Val Asp Asp
145 150 155 160

Val Glu Val Asn Thr Ala Thr Thr Lys Pro Arg Glu Glu Gln Phe Asn
165 170 175

Ser Thr Tyr Arg Val Val Ser Ala Leu Arg Ile Gln His Gln Asp Trp
180 185 190

Thr Gly Gly Lys Glu Phe Lys Cys Lys Val His Asn Glu Gly Leu Pro
195 200 205

Ser Ser Ile Val Arg Thr Ile Ser Arg Thr Lys Gly Pro Ala Arg Glu
210 215 220

Pro Gln Val Tyr Val Leu Ala Pro Pro Gln Glu Glu Leu Ser Lys Ser
225 230 235 240

Thr Val Ser Leu Thr Cys Met Val Thr Ser Phe Tyr Pro Asp Tyr Ile
245 250 255

Ala Val Glu Trp Gln Arg Asn Gly Gln Pro Glu Ser Glu Asp Lys Tyr
260 265 270

Gly Thr Thr Pro Pro Gln Leu Asp Ala Asp Ser Ser Tyr Phe Leu Tyr
275 280 285

Ser Lys Leu Arg Val Asp Arg Asn Ser Trp Gln Glu Gly Asp Thr Tyr

290 295 300

Thr Cys Val Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
305 310 315 320

Ser Thr Ser Lys Ser Ala Gly Lys
325

<210> 103

<211> 987

<212> DNA

<213> Bos taurus

<400> 103

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tggaattctg gtgcccttaa gtccggcgtc cataccttcc ctgctgtgct gcagtcctct 180

ggcctgtaca gtttgtcttc tatggtgaca gtaccgggtt ccacctccgg acagaccttt 240

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tgtaaacca gtccatgcga ctgctgtccc cccctccag ttgccggacc ctcagtcttt 360

attttccac ccaaaccac aaacacctg acaatctctg gaacaccaga agtcacctgc 420

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gtggaagtga atacagctac tacaaaacct cgcgaagage agtttaactc tacctatcga 540

gtggtttctg ctttgcggat tcagcatcag gattggacag gcggcaaaga gtttaaatgt 600

aaagtcata acgagggact tccttctagt atcgtgcgca ctatcagtag aactaaaggg 660

cctgctcggg aacctcaggt gtacgtcctg gcacctccac aggaagagct gagtaagtct 720

acagtttctc tgacttgat ggtaacatct ttttatccag attacatgc agttgaatgg 780

cagaggaacg ggcagccaga gaggaggat aagtacggga ctactccacc acagctggac 840

gcagactcaa gttacttct gtactcaaag ctgagggttg acagaaactc atggcaggag 900

ggggacactt acacttgcgt agttatgcac gaggcacttc acaaccacta cactcagaag 960

agtacttcaa agagtgcagg gaagtaa 987

<210> 104

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> codon-optimized sequence

<400> 104

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tggaaagctg atgggtccac cattactcgg aatgtggaaa ccaccgggc ttctaagcag    180
tccaacteta aatacgcagc atcctctat ttgagtetta ctagtagtga ctggaagtca    240
aagggtagtt acagttgcga agtcacacat gaaggttcaa cagtgacaaa gacagtcaag    300
ccctcagagt gtcctag                                     318
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<210> 105

<211> 238

<212> PRT

<213> Artificial Sequence

<220>

<223> chimeric L chain

<400> 105

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```

```
Gly Thr Tyr Gly Asp Ile Ala Ile Thr Gln Ser Pro Ser Ser Val Ala
      20        25        30
```

```
Val Ser Val Gly Glu Thr Val Thr Leu Ser Cys Lys Ser Ser Gln Ser
      35        40        45
```

```
Leu Leu Tyr Ser Glu Asn Gln Lys Asp Tyr Leu Gly Trp Tyr Gln Gln
      50        55        60
```

```
Lys Pro Gly Gln Thr Pro Lys Pro Leu Ile Tyr Trp Ala Thr Asn Arg
      65        70        75        80
```

```
His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
      85        90        95
```

```
Phe Thr Leu Ile Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr
      100       105       110
```

Tyr Cys Gly Gln Tyr Leu Val Tyr Pro Phe Thr Phe Gly Pro Gly Thr
 115 120 125

Lys Leu Glu Leu Lys Gln Pro Lys Ser Pro Pro Ser Val Thr Leu Phe
 130 135 140

Pro Pro Ser Thr Glu Glu Leu Asn Gly Asn Lys Ala Thr Leu Val Cys
 145 150 155 160

Leu Ile Ser Asp Phe Tyr Pro Gly Ser Val Thr Val Val Trp Lys Ala
 165 170 175

Asp Gly Ser Thr Ile Thr Arg Asn Val Glu Thr Thr Arg Ala Ser Lys
 180 185 190

Gln Ser Asn Ser Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Ser
 195 200 205

Ser Asp Trp Lys Ser Lys Gly Ser Tyr Ser Cys Glu Val Thr His Glu
 210 215 220

Gly Ser Thr Val Thr Lys Thr Val Lys Pro Ser Glu Cys Ser
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Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 40 45

Thr Ser Asn Phe Met His Trp Val Lys Gln Gln Pro Gly Asn Gly Leu
 50 55 60

Glu Trp Ile Gly Trp Ile Tyr Pro Glu Tyr Gly Asn Thr Lys Tyr Asn
 65 70 75 80

Gln Lys Phe Asp Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
 85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 105 110

Tyr Phe Cys Ala Ser Glu Glu Ala Val Ile Ser Leu Val Tyr Trp Gly
 115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Lys
 130 135 140

Val Tyr Pro Leu Ser Ser Cys Cys Gly Asp Lys Ser Ser Ser Thr Val
 145 150 155 160

Thr Leu Gly Cys Leu Val Ser Ser Tyr Met Pro Glu Pro Val Thr Val
 165 170 175

Thr Trp Asn Ser Gly Ala Leu Lys Ser Gly Val His Thr Phe Pro Ala
 180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val
 195 200 205

Pro Gly Ser Thr Ser Gly Gln Thr Phe Thr Cys Asn Val Ala His Pro
 210 215 220

Ala Ser Ser Thr Lys Val Asp Lys Ala Val Asp Pro Thr Cys Lys Pro
 225 230 235 240

Ser Pro Cys Asp Cys Cys Pro Pro Pro Pro Val Ala Gly Pro Ser Val
 245 250 255

Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu Thr Ile Ser Gly Thr
 260 265 270

Pro Glu Val Thr Cys Val Val Val Asp Val Gly His Asp Asp Pro Glu
 275 280 285

Val Lys Phe Ser Trp Phe Val Asp Asp Val Glu Val Asn Thr Ala Thr
 290 295 300

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 305 310 315 320

Ala Leu Arg Ile Gln His Gln Asp Trp Thr Gly Gly Lys Glu Phe Lys
 325 330 335

Cys Lys Val His Asn Glu Gly Leu Pro Ser Ser Ile Val Arg Thr Ile
 340 345 350

Ser Arg Thr Lys Gly Pro Ala Arg Glu Pro Gln Val Tyr Val Leu Ala
 355 360 365

Pro Pro Gln Glu Glu Leu Ser Lys Ser Thr Val Ser Leu Thr Cys Met
 370 375 380

Val Thr Ser Phe Tyr Pro Asp Tyr Ile Ala Val Glu Trp Gln Arg Asn
 385 390 395 400

Gly Gln Pro Glu Ser Glu Asp Lys Tyr Gly Thr Thr Pro Pro Gln Leu
 405 410 415

Asp Ala Asp Ser Ser Tyr Phe Leu Tyr Ser Lys Leu Arg Val Asp Arg
 420 425 430

Asn Ser Trp Gln Glu Gly Asp Thr Tyr Thr Cys Val Val Met His Glu
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Lys
 465

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 ctgtctgca agtcagtcga gtctcttctc tactccgaga atcaaaagga ctacctgggc 180
 tggtagcaac agaagcccg ccagacccca aagccactga tatactgggc aaccaacagg 240
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 attactcgga atgtggaaac caccgggct tctaagcagt ccaactctaa atacgcagca 600
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 ggaaatggct tggagtggat tggctggatc tatccgaat atggtaacac caagtataat 240
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 cagctcagca gctgaccag cgaggattcc gctgtgtact tctgtgccag cgaagaggct 360
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 agttacttcc tgtactcaa gctgagggtt gacagaaact catggcagga gggggacact 1320
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26

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ccgctcgaga tgaggatatg tagtatctt

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<400> 124

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<210> 125

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<223> primer

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28

<210> 126

<211> 28

<212> DNA

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<210> 127

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29

<210> 138

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26

CLAIMS

1. An anti-PD-L1 antibody comprising (a) a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat; and (b) a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.
2. The antibody of claim 1, wherein the light chain variable region and the heavy chain variable region are derived from rat.
3. The antibody of claim 2, wherein the light chain variable region is the light chain variable region of a rat anti-bovine PD-L1 antibody and the heavy chain variable region is the heavy chain variable region of a rat anti-bovine PD-L1 antibody.
4. The antibody of claim 3, wherein the light chain variable region has the amino acid sequence as shown in SEQ ID NO. 1 and the heavy chain variable region has the amino acid sequence as shown in SEQ ID NO: 2.
5. The antibody of any one of claims 1 to 4, wherein the light chain constant region of an antibody of an animal other than rat has the amino acid sequence of the constant region of lambda chain or kappa chain.
6. The antibody of any one of claims 1 to 5, wherein the heavy chain constant region of an antibody of an animal other than rat has the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4.
7. The antibody of any one of claims 1 to 5, wherein the animal other than rat is bovine and the heavy chain constant region of the bovine antibody has mutations introduced therinto that reduce ADCC activity and/or CDC activity.
8. The antibody of claim 6, wherein the animal other than rat is canine; the light chain constant region of the canine antibody has the amino acid sequence of the constant region of lambda chain; and the heavy chain constant region of the canine antibody has the amino acid sequence of the constant region of an immunoglobulin equivalent to human IgG4.
9. The antibody of claim 7, wherein the light chain constant region of the bovine antibody

has the amino acid sequence of the constant region of lambda chain and the heavy chain constant region of the bovine antibody has mutations introduced therein that reduces ADCC activity and/or CDC activity.

10. The antibody of claim 8, wherein the light chain constant region of the canine antibody has the amino acid sequence as shown in SEQ ID NO: 3 and the heavy chain constant region of the canine antibody has the amino acid sequence as shown in SEQ ID NO: 4.
11. The antibody of claim 9, wherein the light chain constant region of the bovine antibody has the amino acid sequence as shown in SEQ ID NO: 100 and the heavy chain constant region of the bovine antibody has the amino acid sequence as shown in SEQ ID NO: 102.
12. The antibody of any one of claims 1 to 11 which has a four-chain structure comprising two light chains and two heavy chains.
13. A pharmaceutical composition comprising the antibody of any one of claims 1 to 12 as an active ingredient.
14. The composition of claim 13 for prevention and/or treatment of cancers and/or inflammations.
15. The composition of claim 14, wherein the cancers and/or inflammations are selected from the group consisting of neoplastic diseases, leukemia, Johne's disease, anaplasmosis, bacterial mastitis, mycotic mastitis, mycoplasma infections (such as mycoplasma mastitis, mycoplasma pneumonia or the like), tuberculosis, *Theileria orientalis* infection, cryptosporidiosis, coccidiosis, trypanosomiasis and leishmaniasis.
16. An artificial genetic DNA comprising (a') a DNA encoding a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat and (b') a DNA encoding a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.
17. A vector comprising the artificial genetic DNA of claim 16.
18. A host cell transformed with the vector of claim 17.
19. A method of preparing an antibody, comprising culturing the host cell of claim 18 and

collecting an anti-PD-L1 antibody from the resultant culture.

20. A DNA encoding a light chain comprising a light chain variable region containing CDR1 having the amino acid sequence of QSLLYSENQKDY (SEQ ID NO: 37), CDR2 having the amino acid sequence of WAT and CDR3 having the amino acid sequence of GQYLVYPFT (SEQ ID NO: 38) and the light chain constant region of an antibody of an animal other than rat.
21. A DNA encoding a heavy chain comprising a heavy chain variable region containing CDR1 having the amino acid sequence of GYTFTSNF (SEQ ID NO: 39), CDR2 having the amino acid sequence of IYPEYGNT (SEQ ID NO: 40) and CDR3 having the amino acid sequence of ASEEAVISLVY (SEQ ID NO: 41) and the heavy chain constant region of an antibody of an animal other than rat.