

DESCRIPTION

ANTI-PD-L1 ANTIBODY FOR DETECTING PD-L1

TECHNICAL FIELD

The present invention relates to an anti-PD-L1 antibody for detecting PD-L1.

BACKGROUND ART

Malignant melanoma originating from melanocytes is one of the most commonly observed malignant tumors in the canine oral cavity (Non-Patent Document No. 1: Todoroff et al., J Am Vet Med Assoc. 1979 Sep 15; 175(6):567-71). Since this type of melanoma generally tends to be highly invasive and metastatic, early diagnosis and treatment are desired. On the other hand, malignant melanoma has a wide tissue variation, presenting various morphologies such as epithelial-like, round cell-like or fibrosarcoma-like morphology. Thus, malignant melanoma is one of those tumors which involve difficulty in tissue diagnosis. Although confirmation of melanin pigment is important for their diagnosis, a large number of malignant melanomas do not have melanin pigment and, sometimes, diagnosis cannot be made with histological observations alone. This has led to searches for diagnostic markers that can be used in immunohistochemical techniques. Among such markers, Melan A/MART-1, vimentin, S100, neuron-specific enolase and the like have been reported to be useful (Non-Patent Document No. 2: Ramos-Vara et al., Vet Pathol. 2000 Nov; 37(6):597-608). However, even Melan A/MART-1, the most widely used diagnostic marker, has a positive rate not higher than about 60% which varies among reports (Non-Patent Document No. 3: Koenig et al., Vet Pathol. 2001 Jul; 38(4):427-35). Because of this sensitivity problem, the utility of Melan A/MART-1 in actual diagnosis is still arguable. Further, Melan A/MART-1 is not stained in amelanotic melanoma (Non-Patent Document No. 3: Koenig et al., Vet Pathol. 2001 Jul; 38(4):427-35), so its application to diagnosis is limited. Under these circumstances, it is desired to develop highly sensitive, novel diagnostic markers to malignant melanoma.

PRIOR ART LITERATURE

Non-Patent Documents

Non-Patent Document No. 1: Todoroff et al., J Am Vet Med Assoc. 1979 Sep 15; 175(6):567-71

Non-Patent Document No. 2: Ramos-Vara et al., Vet Pathol. 2000 Nov; 37(6):597-608

Non-Patent Document No. 3: Koenig et al., Vet Pathol. 2001 Jul; 38(4):427-35

DISCLOSURE OF THE INVENTION

PROBLEM FOR SOLUTION BY THE INVENTION

It is an object of the present invention to provide a PD-L1 antibody capable of staining tumor cells such as melanoma cells.

MEANS TO SOLVE THE PROBLEM

The present inventors have established a number of monoclonal antibodies which react with the PD-L1 protein of various animals. It has been revealed that, among those monoclonal antibodies, a rat anti-bovine PD-L1 monoclonal antibody (6C11-3A11) is capable of staining melanoma tumor cells very strongly. Currently, this monoclonal antibody is used for selecting candidate dogs for therapy with chimeric antibodies. The subject PD-L1 antibody (6C11-3A11) is also capable of immunohistochemically staining ovine, porcine and bovine PD-L1 proteins. Further, the present inventors have determined the CDRs (complementarity-determining regions) of the variable regions of the subject PD-L1 antibody (6C11-3A11). 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 CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) and (b) a heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSGGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5).
- (2) The antibody of (1) above, which is derived from rat.
- (3) The antibody of (2) above, which is 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. 6 and the heavy chain variable region has the amino acid sequence as shown in SEQ ID NO: 7.
- (5) The antibody of any one of (1) to (4) above, wherein the light chain constant region has the amino acid sequence of the constant region of kappa chain.
- (6) The antibody of any one of (1) to (5) above, wherein the heavy chain constant region has the amino acid sequence of the constant region of IgG2a.

- (7) The antibody of (5) or (6) above, wherein the light chain constant region has the amino acid sequence as shown in any one of SEQ ID NOS: 8, 10 to 12 and the heavy chain constant region has the amino acid sequence as shown in SEQ ID NO: 9 or 13.
- (8) The antibody of any one of (1) to (7) above which has a four-chain structure comprising two light chains and two heavy chains.
- (9) A composition for detecting PD-L1, comprising the antibody of any one of (1) to (8) above as an active ingredient.
- (10) The composition of (9) above for use in diagnosis of cancers and/or inflammations.
- (11) The composition of (10) 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.
- (12) The composition of (9) above for use in selecting subject animals suitable for therapy with anti-PD-L1 antibodies.
- (13) A DNA encoding the anti-PD-L1 antibody of (1) above.
- (14) A vector comprising the DNA of (13) above.
- (15) A host cell transformed with the vector of (14) above.
- (16) A method of preparing an antibody, comprising culturing the host cell of (15) above and collecting an anti-PD-L1 antibody from the resultant culture.
- (17) A DNA encoding the light chain of an anti-PD-L1 antibody, said light chain comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2).
- (18) A DNA encoding the heavy chain of an anti-PD-L1 antibody, said heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSSGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKFD (SEQ ID NO: 5).

EFFECT OF THE INVENTION

According to the present invention, a novel anti-PD-L1 antibody capable of staining tumor cells, such as melanoma cells, has been obtained.

The present specification encompasses the contents disclosed in the specification and/or the drawings of Japanese Patent Application No. 2017-61389 based on which the

present patent application claims priority.

BRIEF DESCRIPTION OF THE DRAWINGS

[Fig. 1] Binding specificity of rat anti-bovine PD-L1 antibody 6C11-3A11. Rat anti-bovine PD-L1 antibody 6C11-3A11 did not bind to EGFP expressing cells, but specifically bound to canine PD-L1-EGFP expressing cells.

[Fig. 2] Predicted CDR regions of rat anti-bovine PD-L1 antibody 6C11-3A11. The regions of CDR1, CDR2 and CDR3 in the light chain variable region and the heavy chain variable region of rat anti-bovine PD-L1 antibody 6C11-3A11 are shown.

[Fig. 3] Comparative immunohistochemical staining images of canine melanoma. Left: stained with a commercial antibody (MelanA antibody). Tumor cells were stained very weakly. Right: stained with the PD-L1 antibody 6C11-3A11 established by the present inventors. Tumor cells were stained very strongly.

[Fig. 4] Immunohistochemical staining image of canine melanoma.

[Fig. 5-1] Immunohistochemical staining images of other tumors. Upper left: case of canine lymphoma. Upper right: case of canine osteosarcoma. Lower left: case 1 of canine renal cell carcinoma. Lower right: case 2 of canine renal cell carcinoma.

[Fig. 5-2] Immunohistochemical staining images of other tumors. Left: case of canine squamous cell carcinoma. Right: case of canine fibrosarcoma.

[Fig. 6] Immunohistochemical staining image of a case of ovine listeriosis. Left: PD-L1 staining image of a brain lesion of ovine listeriosis exhibiting neurologic symptoms. Right: enlarged photograph of the left image.

[Fig. 7] Immunohistochemical staining images of porcine infections. Left: case of porcine circovirus type 2 infection. Right: case of porcine mycoplasma pneumonia.

[Fig. 8] Alignment of amino acid sequences of the constant region of rat Ig kappa chain (light chain).

[Fig. 9] Alignment of amino acid sequences of the constant region of rat IgG2a chain (heavy chain).

[Fig. 10] Schematic drawing of pDC6 vector and a rat-human chimeric anti-PD-L1 antibody.

[Fig. 11] Binding of rat anti-bovine PD-L1 antibodies 6C11-3A11 and 6G7-E1 to canine PD-L1-EGFP expressing cells. 6C11-3A11 specifically bound to canine PD-L1-EGFP expressing cells.

[Fig. 12] Immunohistochemical staining images of skin squamous cell carcinoma,

nasal adenocarcinoma and transitional cell carcinoma in dogs. No specific signals were detected with 6G7-E1. Tumor cells were stained with 6C11-3A11.

[Fig. 13] Immunohistochemical staining images of anal sac gland carcinoma, soft tissue sarcoma and osteosarcoma in dogs. In anal sac gland carcinoma and soft tissue sarcoma, no specific signals were detected with 6G7-E1, but tumor cells were stained with 6C11-3A11. In osteosarcoma, both antibodies stained tumor cells, but stronger signals were obtained with 6C11-3A11.

[Fig. 14] Immunohistochemical staining images of oral malignant melanoma, mammary adenocarcinoma, histiocytic sarcoma, diffuse large B-cell lymphoma and transmissible venereal tumor in dogs using 6C11-3A11. In the tumor species other than transmissible venereal tumor, PD-L1 on tumor cells was stained.

[Fig. 15] Binding of rat anti-bovine PD-L1 antibody 6C11-3A11 to bovine PD-L1-EGFP expressing cells. 6C11-3A11 specifically bound to bovine PD-L1-EGFP expressing cells.

[Fig. 16] Immunohistochemical staining images of ileal lesions of cattle naturally and experimentally infected with *Mycobacterium avium* subsp. *paratuberculosis*, using (a) 6C11-3A11 and (b) Ziehl-Neelsen staining. 6C11-3A11 detected PD-L1 expression in cells infected with *M. avium* subsp. *paratuberculosis* (positive in Ziehl-Neelsen staining).

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 CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) and (b) a heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSSGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5).

CDR1, CDR2 and CDR3 in the light chain variable region (VL) of rat anti-bovine PD-L1 antibody 6C11-3A11 (monoclonal antibody) established by the present inventors are a region consisting of the amino acid sequence of KSISKY (SEQ ID NO: 1), a region consisting of the amino acid sequence of SGS and a region consisting of the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2), respectively (see Fig. 2).

Further, CDR1, CDR2 and CDR3 in the heavy chain variable region (VH) of rat anti-

bovine PD-L1 antibody 6C11-3A11 are a region consisting of the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), a region consisting of the amino acid sequence of INPDSSGN (SEQ ID NO: 4) and a region consisting of the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5), respectively (see Fig. 2).

In the amino acid sequences of KSISKY (SEQ ID NO: 1), SGS and QQHNEYPLT (SEQ ID NO: 2), as well as the amino acid sequences of GYTFTDYI (SEQ ID NO: 3), INPDSSGN (SEQ ID NO: 4) and ARGITMMVVISHWKDFD (SEQ ID NO: 5), one, two, three, four or five amino acids may be deleted, substituted or added. Even when such mutations have been introduced, the resulting amino acid sequences are capable of having the function as CDR of VL or CDR of VH of the PD-L1 antibody.

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.

The anti-PD-L1 antibody of the present invention may be derived from rat. For example, the anti-PD-L1 antibody may be a rat anti-bovine PD-L1 antibody.

The amino acid sequence of the VL and the amino acid sequence of the VH of rat anti-bovine PD-L1 antibody 6C11-3A11 (monoclonal antibody) are shown in SEQ ID NOS: 6 and 7, respectively. The amino acid sequences as shown in SEQ ID NOS: 6 and 7 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.

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) 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 and equine, and that of Kappa chain is higher in mouse, rat, human and porcine. Rat anti-bovine PD-L1 antibody 6C11-3A11 (monoclonal antibody) is a rat-derived IgG2a, and the CL thereof has the amino acid sequence of the constant region of Kappa chain.

The heavy chain constant region (CH) of the anti-PD-L1 antibody of the present invention may have the amino acid sequence of the constant region of rat IgG2a. 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 rat, sequences of IgG1, IgG2a, IgG2b and IgG2c have been identified as the heavy chain of IgG. Rat anti-bovine PD-L1 antibody 6C11-3A11 has the amino acid sequence of the CH of IgG2a.

In the antibody of the present invention, it is more preferable that the CL has the amino acid sequence of the constant region of Kappa chain and that the CH has the amino acid sequence of the constant region of IgG2a.

The amino acid sequence and the nucleotide sequence of the VL of rat anti-bovine

PD-L1 antibody 6C11-3A11 identified by the present inventors are shown in SEQ ID NOS: 6 and 14, respectively.

The amino acid sequence and the nucleotide sequence of the VH of rat anti-bovine PD-L1 antibody 6C11-3A11 identified by the present inventors are shown in SEQ ID NOS: 7 and 15, respectively.

The amino acid sequence and the nucleotide sequence of the CL (Kappa chain) of rat anti-bovine PD-L1 antibody 6C11-3A11 identified by the present inventors are shown in SEQ ID NOS: 8 and 16, respectively. These sequences are identical with the sequences registered at GenBank (a nucleotide sequence database provided by National Center for Biotechnology Information (NCBI)) under accession numbers #XM_008775358.2, #BC062802.1, #BC088255.1, #L22653.1, #L22655.1 and #M14434.1.

The amino acid sequence and the nucleotide sequence of the CH (IgG2a) of rat anti-bovine PD-L1 antibody 6C11-3A11 identified by the present inventors are shown in SEQ ID NOS: 9 and 17, respectively. These sequences are identical with the sequences registered at GenBank under accession numbers #BC088240.1, #BC091257.1, #BC091272.1, #BC088423.1, #L22652.1 and #L22654.1.

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

As an amino acid sequence and a nucleotide sequence of rat Ig Kappa chain, the sequence registered at GenBank under accession number #V01241.1 is shown in SEQ ID NOS: 10 and 18.

As an amino acid sequence and a nucleotide sequence of rat Ig Kappa chain, the sequence registered at GenBank under accession number #X16129.1 is shown in SEQ ID NOS: 11 and 19.

As an amino acid sequence and a nucleotide sequence of rat Ig Kappa chain, the sequence registered at GenBank under accession number #DQ402471.1 is shown in SEQ ID NOS: 12 and 20.

As the CH of rat IgG2a, the sequence registered at GenBank under accession number #DQ402472.1 is shown in SEQ ID NOS: 13 and 21.

The anti-PD-L1 antibody of the present invention may be an anti-PD-L1 antibody in which the CL has the amino acid sequence as shown in any one of SEQ ID NOS: 8 and 10 to 12 and the CH has the amino acid sequence as shown in SEQ ID NO: 9 or 13.

The amino acid sequences as shown in SEQ ID NOS: 8 to 13 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.

Alignments of amino acid sequences of the CL and the CH of a rat anti-PD-L1 antibody are shown in Fig. 8 and Fig. 9, respectively. The above-described mutations such as deletion, substitution or addition of amino acids may suitably have occurred at the mutation sites as shown in Figs. 8 and 9 or at the vicinity thereof.

The anti-PD-L1 antibody of the present invention may be a chimeric antibody. The VL and the VH of the antibody may be suitably derived from rat. For example, the VL may be the VL of a rat anti-PD-L1 antibody (e.g., 6C11-3A11); the VH may be the VH of a rat anti-PD-L1 antibody; and the CL and the CH may be derived from an animal other than rat. For example, when a rat antibody is chimerized using the constant regions of a mouse antibody, the resulting chimeric antibody will be useful for testing and diagnosis because various secondary antibodies to mouse antibodies are commercially available. Amino acid sequences and nucleotide sequences of the CLs and the CHs of antibodies of animals other than rat may be obtained from known databases for use in the present invention.

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

Table.

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference	
Human (Scientific Name: <i>Homo sapiens</i>)	Human Ig heavy chain constant region (CH1*CH3)	IgG4 variant 1	GAGTCCAAATATGGTCCCCCATGCCCATCATGCCA GCACCTGAGTTCCTGGGGGACCATCAGTCTCTCGT TTCCCCCAAAACCCAGGACACTTCATGATCTCC CGGACCCCTGAGGTGCAOGTGGTGGTGAGCGTG AGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGGGGGAGAGCAGATTCAACAGCAGCATACCGCTGTG GTACGGTCTCTGACGCTCTGCACAGGACACTGGCTG AACGGCAAGGAGTACAAAGTGCAAGGTGTCCAACAA GGCCTCCCGTCTCCATCGAGAAACCATCTCCAAA GCCAAAGGGCAGCCCGGAGAGCCACAGGTGTACACC CTGCCCCCATCCCAAGAGGAGATGACCAAGAACCCAG GTACGGCTGACCTGCCTGGTCAAAGGCTTCTACCCG AGCGACATCGCCGTGGAGTGGGAGGCAATGGCAG CCGGAGAACCACTACAAGACAGCGCCTCCCGTGCCTG GACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTA ACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTC TTTCTATGCTCGGTGATGCATGAGGCTCTGCACAA CACTACACGAGAGGAGCGCTTCCCTGTCTCTGGGT AAATGA (SEQ ID NO:31)	ESKYGPPPCSPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNATKPREEQFN TYRVSVLTVLHDDWLNKEYKCKVS NKGLPSSIEKTSKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGGPENNYKTPPVLDSDGSFPL YSRLTVDKSRWQEGNVFSCSVMEAL HNHYTKLSLSLGK* (SEQ ID NO:30)	K01316	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetabs&species=human&group=IGHC	Elison J. et al. DNA 1, 11-18 (1981). PMID: 6299662
		IgG4 variant 2	GAGTCCAAATATGGTCCCCCGTGCCCATCATGCCA GCACCTGAGTTCCTGGGGGACCATCAGTCTCTCGT TTCCCCCAAAACCCAGGACACTTCATGATCTCC CGGACCCCTGAGGTGCAOGTGGTGGTGAGCGTG AGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGGGGGAGAGCAGATTCAACAGCAGCATACCGCTGTG GTACGGTCTCTGACGCTCTGCACAGGACACTGGCTG AACGGCAAGGAGTACAAAGTGCAAGGTGTCCAACAA GGCCTCCCGTCTCCATCGAGAAACCATCTCCAAA GCCAAAGGGCAGCCCGGAGAGCCACAGGTGTACACC CTGCCCCCATCCCAAGAGGAGATGACCAAGAACCCAG GTACGGCTGACCTGCCTGGTCAAAGGCTTCTACCCG AGCGACATCGCCGTGGAGTGGGAGGCAATGGCAG CCGGAGAACCACTACAAGACAGCGCCTCCCGTGCCTG GACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTA ACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTC TTTCTATGCTCGGTGATGCATGAGGCTCTGCACAA CACTACACGAGAGGAGCGCTTCCCTGTCTCTGGGT AAATGA (SEQ ID NO:33)	ESKYGPPPCSPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNATKPREEQFN TYRVSVLTVVHDDWLNKEYKCKVS NKGLPSSIEKTSKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGGPENNYKTPPVLDSDGSFPL YSRLTVDKSRWQEGNVFSCSVMEAL HNHYTKLSLSLGK* (SEQ ID NO:32)	AJ001563		Brusco A. et al. Eur. J. Immunogenet. 25, 349-355 (1998). PMID: 9805657
		IgG4 variant 3	GCACCTGAGTTCCTGGGGGACCATCAGTCTTCTCGT TTCCCCCAAAACCCAGGACACTTCATGATCTCC CGGACCCCTGAGGTGCAOGTGGTGGTGAGCGTG AGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGATGGCGTGGAGGTGCATAATGCCAAGACAAG CCGGGGGAGAGCAGATTCAACAGCAGCATACCGCTGTG GTACGGTCTCTGACGCTCTGCACAGGACACTGGCTG AACGGCAAGGAGTACAAAGTGCAAGGTGTCCAACAA GGCCTCCCGTCTCCATCGAGAAACCATCTCCAAA GCCAAAGGGCAGCCCGGAGAGCCACAGGTGTACACC CTGCCCCCATCCCAAGAGGAGATGACCAAGAACCCAG GTACGGCTGACCTGCCTGGTCAAAGGCTTCTACCCG AGCGACATCGCCGTGGAGTGGGAGGCAATGGCAG CCGGAGAACCACTACAAGACAGCGCCTCCCGTGCCTG GACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTA ACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTC TTTCTATGCTCGGTGATGCATGAGGCTCTGCACAA CACTACACGAGAGGAGCGCTTCCCTGTCTCTGGGT AAATGA (SEQ ID NO:35)	APEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEV HNATKPREEQFNSTYRVSVLTVLHQ DNLNGKEYKCKVSNKGLPSSIEKTSKA KGQPREPQVYTLPPSQEEMTKNQVSL TCLVKGFYPSDIAVWEESNGGPENNYK TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMEALHNHYTKLSLSLG K* (SEQ ID NO:34)	AJ001564		
Human Ig light chain constant region	Ig kappa (CK)	ACTGTGGCTGCACCATCTGCTTCTATCTTCCGCGCA TCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTT GTGTGCTCTGTAATCTCTATCCGAGAGAGGCC AAAGTACAGTGGAGGTGGATAAGCGCCCTCCAAATG GGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCAGCTACGACCTCAGCAGACGCTGAGC CTGAGCAAAAGCAGCACTACGAGAAACACAAAGTTTAC GCCTGGCAAGTCAACCATCAGGGCCTGAGCTGCACC GTACAAAGAGCTTCAACAGGGGAGAGTGTATTAG (SEQ ID NO:29)	TVAAPSVFIFPPSDEQLKSGTASVVL LNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSYLSSTLTLSKADYEK HKVYACEVTHOGLSSPVTKSFNRGEC* (SEQ ID NO:28)	X96754	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetabs&species=human&group=IGKC	naL	

[illegible]

IgG2a variant 2	GCCCCAAACAGCCCCCATCGGTGTATCCACTGGCC CCTGTGTGTGGAGATACAACTGGCTCCTCGTGACTC TAGGATGGCTGGTCAAGGGTTATTTCCTCGAGGCAGT GACCTTGACCTGGAACCTCTGATGCCCTGTGCAGTGGT GTGCACACCTTCCCAGCTGTCTGCAGTCTGACCTCT ACACCCCTGAGCAGCTCAGTGACTGTAACCTCGAGCAC CTGGCCGAGCCAGTCCATCACTGCAATGTGGGCCA CCCGGCCAACACAGCAAGAGTGCACAGAAAAATTGA GCCACAGGGGCCCAATCAAGCCCTGTCTCCATG CAAAATGCCACGACCACTAACCTCTTGGGTGGACCTCC GTCTTCATCTTCCCTCCAAAGATCAAGGATGTACTCA TGATCTCCCTGAGTCCCATGGTGCATGTGTGGTGGT GGATGTGAGCGAGATGACCCAGTGTGTGCAGATCAG CTGGTTGCTGAACACGTGGAACTACTCACAGCTCAG ACACAAACCCATAGAGAGGATTACAACAGTACTCTCC GGGTGGTCACTGGCTCCCATCCAGCAGCAGGACT GGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACA ACAAAGCCCTGTCAAGCCCATCCAGAGAACCATCT CAAAACCCAAAGGGTCAGTAAGAGCTCCACAGGTATA TGTCTTGCCCTCCACCAAGAAAGAGATGACTAAGAAA CAGGTCACTCTGACCTGCATGGTACAGACTTCATGC CTGAAGACATTTAOGTGGAGTGGACCAACCAAGGGA AAACACAGCTTAAACTACAGAAACACTGAACCACTCT GGACTGTGATGGTTTCTTACTCATGTACAGCAAGCTG AGAGTGGAAAGAAAGCACTGGGTGGAAAGAAATAGC TACTCCTGTTCACTGGTCCACGAGGGTGTGCACAAATC ACCACACGACTAAGAGCTTCTCCCGGACTCCGGGTA AATGA (SEQ ID No: 51)	AKTTAPSVYPLAPVCGDTTGSSVTLGC LVKGYFPEPVLTWNSSLSSSVHTFP AVLQSDLYLTSSSVTVTSSWPSQST ONVAHPASSTKVDKKEPRGPTIKPCPP CKCPAPNLLGGPSVFIFPPKIKDVLMSL SPMVTCTVVVDVSEDDPDVQISWFVNN VEVLTAQTGTHREDYNSLRLVVSALPI QHGDWMSGKEFKCKVNMKALPAPIERT ISKPKGSVRAPQVYVLLPPEEEMTKKO VTLTCMVTDFMPEDIYVEWNNNGKTEL NYKNTEPVLDSGYSFYMSKLRVEKKN WVERNYSYSCSVHGLHNHHTTKSFSR TPGK (SEQ ID No: 50)	X16997	Morgado M.G. et al., EMBO J. 8, 3245- 3251 (1989). PMID: 2510996
IgG2b variant 1	GCCAAAAACACCCCCCATCAGTCTATCCACTGGCCC CTGGGTGTGGAGATACAACTGGTTCCCTCGTGACTCT GGGATGCCTGGTCAAGGGCTACTTCCCTGAGTCAGT GACTGTGACTTGGAACTCTGGATCCCTGTCCAGCAGT GTGCACACCTTCCAGCTCTCCTGCACTGTGCAGCTCT ACACTATGAGCAGCTCAGTGACTGTCCCTCCAGCAC TTGGCCAAAGTCAGACCTCAGCTGCACGGTGTGCTCAC CCAGCCAGCAGCACCGGTGGACAAAAAAGTTGAG CCCAGCGGGCCCATTTCAACAATAAACCCTGTCTCCT CTGCAAGAGGTGTCAAAGAGCAGCTCTCACTGACTCT CGAGGGTGGACCATCCCTGTCTCTTCCCTCCAAAT ATCAAGGATGTACTCATGATCTCCCTGACACCCAAGT TCACGTGTGTGGTGGTGGATGTGAGCGAGGATGACC CAGACGTCCAGATCAGCTGGTTTGTGAACAAGCTGGA AGTACACAGCTCAGACGACAAACCATAGAGAGGAT TACACAGCTACTTCCGGGTGGTGCAGACCCCTCCCA TCCAGCACCGAGCAGTGGATGAGTGGCAAGGAGTTCA AATGCAAGGTCAACAACAAGACCTCCCATACCCAT CGAGAGAACCATCTCAAAAAATTAAGGGCTAGTCAGA GCTCCCAAGTATACATCTTGGCGCCACAGCAGAGAGC AGTGTCTCAGGAAAGATGCACTGTCACTGTGCTGTGT CGTGGGCTTCAACCCTGGAGACATCAGTGTGAGAGTG GACCAGCAATGGGCATCAGAGGAGAACTACAAGGA CACCGCACCGATCCTAGACTCTGACGGTTCTTACTCTC ATATATAGCAAGCTCAATATGAAAAACAGCAAGTGGG AGAAAAAGATTCTTCTCATGCAACGTGAGACAGGA GGGTCTGAAAAATTACTACTGGAAGAACACATCTCC CGGTCTCCGGTAAATGA (SEQ ID No: 53)	AKTTPPSVYPLAPGCGDTTGSSVTLGC LVKGYFPESVTVTNSSLSSSVHTFP ALLQSLYTMSSSVTVPSSTWPSQTVT CSVAHPASSTTVDKKLEPSGPISTINP RPPCKECHKOPAPNLEGGPSVFIFPPNPK DVLMSLTPKVTCTVVVDVSEDDPDVQI SWFVNNVEVHTAGTQTHREDYNSTIRV VSTLPIQHGDWMSGKEFKCKVNMKDLPL SPIERTISKIKLVRAPQVYVLLPPEEQL SRKDVSLTCLVGFNPGDISVEWTSNG HTEENYKDTAPVLDSDGYSFYISKLN KTSKWEKTSFSCNVRHGLKNYLLK TISRSPGK (SEQ ID No: 52)	J00461 AH005309 V00801 D78344	Yamawaki-Kataoka Y. et al., Nature, 283, 786-789 (1980). PMID: 6766534 Olio R. and Rougeon F., Nature, 296, 761- 763 (1982). PMID: 6803173 Alahori Y. and Kurosawa Y., Genomics, 41, 100- 104 (1997). PMID: 9126488
IgG2b variant 2	GCCAAAAACACCCCCCATCAGTCTATCCACTGGCCC CTGGGTGTGGAGATACAACTGGTTCCCTCGTGACTCT TGGGTGCCTGGTCAAGGGGTACTTCCCTGAGCCAGT GACTGTGACTTGGAACTCTGATCCCTGTCCAGCAGT GTGCACACCTTCCCAGCTCTCCTGCAGTCTGCACTCT ACACTATGAGCAGCTCAGTGACTGTCCCTCCAGCAC CTGGCCAAAGTCAGACCTCAGCTGCACGGTGTGCTCA CCCAGCCAGCAGCACCGGTGGACAAAAAAGTTGA GCCACAGGGGCCCATTTCAACAATAAACCCTGTCTCCT CCATGCAAGGAGTGTCAAAATGCCAGCTCCTAACCC TCGAGGGGTGACCATCCGTCTCATCTTCCCTCCAAA TATCAAGGATGTACTCATGTCTCCCTGACACCCAAG GTACCTGTGTGTGGTGGTGGATGTGAGCGAGGATGAC CCAGACGTCCAGATCAGCTGGTTTGTGAACAACGTGG AAGTACACACAGCTCAGACACAACCCATAGAGAGG ATTACACAGTACTATCCGGGTGGTGCAGCACCTCCCT CATCCAGCACCGAGCTGGATGAGTGGCAAGGAGTT CAAAATGCAAGGTGAACAACAAGACCTCCCATGACCC ATCGAGAGAACCATCTCAAAAATTAAGGGCTAGTCA GAGTCCACAAGTATACACTTTGCCGCCACAGCAGAGA GCAAGTTTCCAGGAAAGATGTGAGTCTCACTTGGCCTG GTGCTGGGCTTCAACCTGGAGACATCAGTGTGGAGT GGACACCATGGGATACAGAGGAGAACTACAAGG ACACCGCAGCAGTTCTTGACTCTGACGGTCTTACTT CATATATAGCAAGCTCAATATGAAAAAGCAAGTGG GAGAAAAAGATTCTTCTCATGCAACGTGAGACACG AGGGTCTGAAAAATTACTACCTGAAGAACACCATCTC CGGTCTCCGGTAAATGA (SEQ ID No: 55)	AKTTPPSVYPLAPGCGDTTGSSVTSQ OLVKGYPPEPVTVTNSSLSSSVHTFP PALLQSLYTMSSSVTVPSSTWPSQTV TCSVAHPASSTTVDKKLEPSGPISTINP CPPCKECHKOPAPNLEGGPSVFIFPPN KDVLMSLTPKVTCTVVVDVSEDDPDVQ ISWFVNNVEVHTAGTQTHREDYNSTIRV VSTLPIQHGDWMSGKEFKCKVNMKDLPL SPIERTISKIKLVRAPQVYVLLPPEEQL SRKDVSLTCLVGFNPGDISVEWTSNG HTEENYKDTAPVLDSDGYSFYISKLN KTSKWEKTSFSCNVRHGLKNYLLK TISRSPGK (SEQ ID No: 54)	V00763	Tucker P.W. et al., Science, 206, 1303- 1308 (1979). PMID: 117549

IgG2c variant 1	GCCAAACAAACAGCCCCATCGGTCTATCCACTGGCC CCTGTGTGTGGAGGTACAACTGGCTCCTCGGTGACTC TAGGATGCCTGGTCAAGGGTATTTCCTCGAGCCAGT GACCTTGACCTGGAAGCTCTGGATCCCTGTCCAGTGGT GTGCACACCTTCCACAGCTCCTCGAGTCTGGCCCTCT ACACCCCTCAGCAGCTCAGTGACTGTAACTCGAAACAC CTGGCCAGCCAGCAGCCATCACCTGCAATGTGGCCCA CCCGGCAAGCAGCACCAGGTGGACAAAGAAATTGA GCCGAGAGTGCCCATTAACACAGACCCCTCTCCTCC ACTCAAAGAGTGTCCCCCATGGCCAGCTCCAGACCT CTTGGGTGGACCATCCGCTCTCATCTTCCCTCCAAAG ATCAAGGATGTACTCATGATCTCCCTGAGCCCATGG TCACATGTGTGGTGGTGGATGTGAGCGAGGATGACC CAGACCTCCAGATCAGCTGGTGTGTGAACACAGCTGGA AGTACACACAGCTCAGACACAAACCCATAGAGAGGAT TACAACAGTACTCTCCGGGTGGTCACTGCGCTCCCCA TCCAGCACCAGGACTGGATGAGTGGAAGGAGTTC AATGCAAGGTCAACACAGAGCCCTCCCATCCCCCAT CGAGAAAACCATCTCAAAACCCAGAGGGCCAGTAAG AGCTCCACAGGTATATGTCTTGCCTCCACAGCAGAA GAGATGACTAAGAAAGATTGAGTGTGACCTGCATGA TCACAGGCTTCTTACCTGCCGAAATTCGTGTGGACTG GACCGCAATGGGGTACAGAGCAAACTACAAGAA CACCGCAAGAGCTCTGGACTCTGATGGTTCTTACTTC ATGTACAGCAAGCTCAGAGTACAAAGAGCACTTGGG AAAGAGGAAGTCTTTTTCGCTGCTCAGTGGTCCACGA GGTGTGCACAATCACCTTACGACTAAGACCATCTCC CGGTCTCTGGGTAATGA (SEQ ID NO: 57)	AKTTAPSVYPLAPVCGGTTGSSVTLGC LVKGYFPEPVTLTWNSSLSSGVHTFP ALLQSGLYTLSSSVTVTSNTWPSQTIT CNVAHPASSTKVDKIEPRVITQNP PLKECPPCAAPDLLGGPSVFIFFPKIKD VLMISLSPMVTGVVVDVSEDDPDVQIS WVFNINVEVHTAQGTQTHREDYNSTLRV VSALPIQHQDWMWSGKEFKCKVNNRALP SPIEKTISKPRGPVRAPQVYVLPFAEE MTKKEFSLTCMITGFLPAEIAVDWTSNG RTEQNYKNTATVLDSDGSYFMYSKLRV OKSTWERSLFACSVVHEGLHNHLLTK TISRSLGK (SEQ ID NO: 56)	J00479	Ollio R. and Rougeon F. Cell. 32, 515-523 (1983). PMID: 6297797
IgG2c variant 2	GCCAAACAAACAGCCCCATCGGTCTATCCACTGGCC CCTGTGTGTGGAGGTACAACTGGCTCCTCGGTGACTC TAGGATGCCTGGTCAAGGGTATTTCCTCGAGCCAGT GACCTTGACCTGGAAGCTCTGGATCCCTGTCCAGTGGT GTGCACACCTTCCACAGCTCCTCGAGTCTGGCCCTCT ACACCCCTCAGCAGCTCAGTGACTGTAACTCGAAACAC CTGGCCAGCCAGCAGCATCAGCTGCAATGTGGCCCA CCCGGCAAGCAGCACCAGGTGGACAAAGAAATTGA ATCCAGAAAGCCCATACACCCCACTCCTGTCTCCCA TGCAAGAGGTGTTCCATTTCACAGCTCCTGACCTCT TGGGTGGACCATCCGCTCTTACCTTCCCTCCAAAGAT CAGAGTGTGACTGATGATCTCCCTGAGCCCATAGTCT ACATGTGTGGTGGTGGTGTGGAGGAGGATGACCA GATGTCCAGATCAGCTGGTGTGTGAACACGTGGAAG TACACACAGCTCAGACACAAACCCATAGAGAGGATTA CAACAGTACTCTCCGGGTGGTCACTGCGCTCCCCATC CAGCAGCAGCTCCTCGGGGTGGTCACTGCGCTCCCCATC TGCAGGTCAAGCAAGAGCCTCCCATCCCCCATG GAGAAACCATCTCAAAACCCAGAGGGCCAGTAAGA GCTCCACAGGTATATGTCTTGCCTCCACACAGAGAAG AGATGACTAAGAAAGAGTTCAGTCTGACCTGCATGAT CACAGACTTCTTACCTGCCGAAATTCGTGTGGACTGG ACGACGAATGGCATTAAGAGCTGAATACAGAGACA CCGACAGCTCTGGACATGATGGTCTTACTTTAT GTACAGCAAGCTCAGAGTGCAAAAGAGCACTTGGGA AAAAGGAAGTCTTTTCGCTGCTCAGTGGTCCACGAG GGTCTGCACAATCACCATACGACTAAGACCATCTCC GGTCTCTGGGTAATGA (SEQ ID NO: 59)	AKTTAPSVYPLAPVCGGTTGSSVTLGC LVKGYFPEPVTLTWNSSLSSGVHTFP ALLQSGLYTLSSSVTVTSNTWPSQTIT CNVAHPASSTKVDKIESRRIPPNSCP PKCECSIFAPDLLGGPSVFIFFPKIKDV LMISLSPVTCVVVDVSEDDPDVQISWF VNNVEVHTAQGTQTHREDYNSTLRVVS ALPIQHQDWMWSGKEFKCKVNNRALPSP IEKTSIKPRGPVRAPQVYVLPFAEEMT KKEFSLTCMITDFLPAEIAVDWTSNGHK ELNYKNTAPVLDTDGSYFMYSKLRVQK STWEKNSLFACSVVHEGLHNHLLTKT ISRSLGK (SEQ ID NO: 58)	X16998	Morgado M.G. et al., EMBO J. 8, 3245- 3251 (1989). PMID: 2510996
IgG2c variant 3	GCCAAACAAACAGCCCCATCGGTCTATCCACTGGCC CCTGTGTGTGGAGGTACAACTGGCTCCTCGGTGACTC TAGGATGCCTGGTCAAGGGTATTTCCTCGAGCCAGT GACCTTGACCTGGAAGCTCTGGATCCCTGTCCAGTGGT GTGCACACCTTCCACAGCTCCTCGAGTCTGGCCCTCT ACACCCCTCAGCAGCTCAGTGACTGTAACTCGAAACAC CTGGCCAGCCAGCAGCATCAGCTGCAATGTGGCCCA CCCGGCAAGCAGCACCAGGTGGACAAAGAAATTGA GCCGAGAGTGCCCATTAACACAGAACCCCTGTCTCC ACTCAAAGAGTGTCCCCCATGGCCAGCTCCAGACCT CTTGGGTGGACCATCCGCTCTCATCTTCCCTCCAAAG ATCAAGGATGTACTCATGATCTCCCTGAGCCCATGG TCACATGTGTGGTGGTGGATGTGAGCGAGGATGACC CAGACCTCCAGATCAGCTGGTGTGAACACGTGGA AGTACACACAGCTCAGACACAAACCCATAGAGAGGAT TACAACAGTACTCTCCGGGTGGTCACTGCGCTCCCCATC TCCAGCAGCAGACTGGATGAGTGGCAAGGAGTTC AATGCAAGGTCAACACAGAGCCCTCCCATCCCCCAT CGAGAAAACCATCTCAAAACCCAGAGGGCCAGTAAG AGCTCCACAGGTATATGTCTTGCCTCCACAGCAGAA GAGATGACTAAGAAAGAGTTCAGTCTGACCTGCATGA TCACAGGCTTCTTACCTGCCGAAATTCGTGTGGACTG GACCGCAATGGGGTACAGAGCAAACTACAAGAA CACCGCAAGCTCTGGACTCTGATGGTTCTTACTTC ATGTACAGCAAGCTCAGAGTACAAAGAGCACTTGGG AAAGAGGAAGTCTTTTTCGCTGCTCAGTGGTCCACGA GGGTCTGCACAATCACCTTACGACTAAGACCATCTCC CGGTCTCTGGGTAATGA (SEQ ID NO: 61)	AKTTAPSVYPLAPVCGGTTGSSVTLGC LVKGYFPEPVTLTWNSSLSSGVHTFP ALLQSGLYTLSSSVTVTSNTWPSQTIT CNVAHPASSTKVDKIEPRVITQNP PLKECPPCAAPDLLGGPSVFIFFPKIKD VLMISLSPMVTGVVVDVSEDDPDVQIS WVFNINVEVHTAQGTQTHREDYNSTLRV VSALPIQHQDWMWSGKEFKCKVNNRALP SPIEKTISKPRGPVRAPQVYVLPFAEE MTKKEFSLTCMITGFLPAEIAVDWTSNG RTEQNYKNTATVLDSDGSYFMYSKLRV OKSTWERSLFACSVVHEGLHNHLLTK TISRSLGK (SEQ ID NO: 60)	Y10606	Martin R.M. et al., Immunogenetics, 46, 167-168 (1997). PMID: 9162106

	IgG3	GCTACAACAAGCCGCACTGTGTCTATCCCTGGTGC CTGGCTGCACTGACACATCTGGATCCCTGGTGACACT GGGATGCCCTTGTCAAGGCTACTTCCCTGAGCGGTG ACTGTAAATGGAACTATGGAGCCGCTGTCCAGCGGTG TGCGACAGTGTCTATGTTCTGCGAGTCTGGGTCTTA TTCCCTCAGCAGCACTTGGTGACTGTACCTCCAGCAC TGGCCAGCCAGCACTGTCACTGCAACGTAGCCAC CCAGCCAGCAAGACTGAGTTGATCAAGAGAAATCGAG CCTAGAAATCCCAAGCCAGTACCCGCCAGGATCTT CATGCCACCTGTGAACATTTGGGTGAGCACTGGT CTTCATCTTCCGCCAAAGGCCAAGGATGCACTCATG ATCTCCCTAACCCCAAGGTTACGTGTGGTGGTGGT ATGTGAGCGAGGATGACCCAGATGTTCATGTGACGTG GTTTGTGGACACAAGAGATACACACAGCTGGGACA CAGCCCGCTGAACTCAGTACAACTACCTTCCGA GTGGTCACTGCCCTCCCACTCCAGACCACGAGACTGG ATGAGGGGCAAGGATTTCAAATGCAAGGTCAACAAC AAAGCCCTCCCAAGCCGCACTCGAGAGAACCATCTCA AAACCCAAAGGAAGAGCCAGACACCTCAAGTATAG ACCATACCCCGACCTGCTGAACAAATGTCCAAAGAGA AGGTTAGTCTGACCTGCCCTGGTCACCAACTTCTCTC TGAAGCCATCAGTGTGGAGTGGGAAAGGAACGGAGA ACTGGAGCAGGATTACAAGAACACTCCACCCCATCTGA GACTGATGGGACCTACTTCTCTACAGGAAGTCTCA CTGTGGATACACACAGTTGGTTCAGAGGAGAAATTT TACCTGCTCCGCTGGTGACTGAGGCTCTCCATAACCCAC CACACACAGAAGAACCTGTCTGCTGCCCTGGTGCTAAAT GA (SEQ ID NO: 63)	ATTAPSVYPLVPGCSDTSGSSVTLGC LVKGYPFVPLVKWNYGALSSGVRTVS SVLQSGFYLSLVLTPSSWPSQTVI DNVHAPSKTELKRIEPRPKSPTSPGS SOPGNILGOPSVFPPKPKDALMISL TPKVTCTVVVDSEDDPHVSVFVDN KEVHTAWTPREAQYNSTFRVSVLPI QHQDWMRGKEFKKQVNNKALPAPIERT ISKPKGRAQTPQVYTPPREQMSKK VSLTCLVTNPFSEASVWERNGELED YKNTPLILSDGTFLYSLKLTVDTDSWL QGEFTCSVVHEALHNHHTQKNLSRSP GK (SEQ ID NO: 62)	J00451 AH005309 X00915 D78343	Stanton L.W. and Marcu K.B., Nucleic Acids Res., 10, 5993- 6006 (1982). PMID: 6292864 Wels J.A. et al., EMBO J., 3, 2041- 2046 (1984). PMID: 6092053 Akahori Y. and Kurosawa Y., Genomics, 41, 100- 104 (1997). PMID: 9126488	
Mouse Ig light chain constant region	Ig kappa (CK)	GCTGATGCTGCACCACTGTATCCATCTTCCACCAT CCAGTGAAGCTTAAACATGGAGGTGCCTCAGTCTG GTGCTCTTGAGAACTTCTACCCCAAGACATGAAT GTCAAGTGGAGAGTTGATGGCAGTGAACGACAAATG CGCTCTGAAACAGTTGACTGATCAGGACAGCAAG ACAGCACCTACAGCATGAGCAGCACCCCTCAGCTTGA CCAAGGACGAGTATGAAGCAGATACAGAGCTATACCTG TGAGGCCACTCAACAGACATCAAGTTCAACCATTTGTG AAGAGCTTCAACAGGAATGAGTGTAG (SEQ ID NO: 37)	ADAAPTYSIFPPSSEQLTSGGASVVF LNKFYPKDNVKKWDGSRONGVNLN WTDQDSKSDTYSMSSTLTLTKDEYERH NSYTCEATHKTSPIPKFSNRNEC (SEQ ID NO: 36)	V00807 V00777 V01569 V00806 X67002 X67003 X67004 X67005 X67006 X67007 X67008 X67009 X67010 X67011 X67012	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGen&species=Mus_musculus&group=IGKC	Hieter P.A. et al., Cell, 22, 197-207 (1980). PMID: 6775818 Max E.E. et al., J. Biol. Chem., 256, 5116-5120 (1981). PMID: 6262318 Seidman J.G. et al., Nature, 280, 370-375 (1979). PMID: 111146 Solin M.L. and Kaartinen M., Immunogenetics, 37, 401-407 (1993). PMID: 8436414
	Ig lambda 1 (CL)	GGCGAGCCCAAGTCTTGGCGATCAGTACCCTGTTTC CACCTTCCCTCTGAAGAGCTCGAGACTAACAGGCCAC ACTGGTGTGTACGATCACTGATTTCACCCAGGTGTG GTGACAGTGGAGTGAAGGATAGATGGTACCCTGTCT ACTCAGGTTATGGAGAACCCAGCCTTCCAAAGAG AGCAACAACAAGTACATGGCTAGCAGCTACCTGACCC TGACAGCAAGAGCATGGGAAGGCATAGCAGTTTACA GCTGCCAGGTCACTCATGAAGGTCAACATGTGGAAGA AGAGTTTGTCCGCTGCTGACTGTCTCAG (SEQ ID NO: 39)	GOPKSSPSVTLFPPSSSELETNKATLV CTITDFYPGVVTVDWKVDGTPVTQGM TTOPSKOSNNKYMSSYLTLTARAWER HSSYSQVTHEGHTVEKLSRADCS (SEQ ID NO: 38)	J00587 AH005311 X58411 V00814	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGen&species=Mus_musculus&group=IGLC	Selsing E. et al., Proc. Natl. Acad. Sci. USA, 79, 4681-4685 (1982). PMID: 6812053 Weiss S. and Wu GE, EMBO J., 6, 927-937 (1987). PMID: 3109891 Bernard O. et al., Cell, 15, 1133-1144 (1978). PMID: 103630
	Ig lambda 2 (CL)	GGTCAGCCCAAGTCCACTCCCACTCTCACCGTGTTC CACCTTCCCTCTGAGGAGCTCAAGGAAACAAGCCAC ACTGGTGTGTCTGATTTCCAACTTTTCCCGAGTGGT GTGACAGTGGCCTGGAAGGCAATGGTACACCTATCA CCAGGGGTGTGGAGACTTGAATCCCAAGAGAG GCAACAAGTTCATGGCCAGCAGCTTCCATGATTGAC ATCGGACCAAGTGGAGATCTCACAACAGTTTACCTGT CAAGTTACACATGAAGGGGACACTGTGGAAGAGAGT CTGTCTCCTGAGAAATGTCTCTAA (SEQ ID NO: 41)	GOPKSTPTLTVFPSSSEELKENKATLV CLISNFPSPGVTVAWKANGTPTTGQVD TSNPTKEGNKFMASSFLHLTSDQWRSH NSFTCGVTHEGDTVEKLSPAECL (SEQ ID NO: 40)	J00595 AH001968 X00592 AH001967 X58414		Selsing E. et al., Proc. Natl. Acad. Sci. USA, 79, 4681-4685 (1982). PMID: 6812053 Wu G. et al., Cell, 33, 77-83 (1983). PMID: 6432336 Weiss S. and Wu GE, EMBO J., 6, 927-937 (1987). PMID: 3109891
	Ig lambda 3 (CL)	GGTCAGCCCAAGTCCACTCCCACTCACCATGTTTC CACCTTCCCTCTGAGGAGCTCCAGGAAACAAGCCA CACTCGTGTGTCTGATTTCGAATTTTCCCGAAGTGG TGTGACAGTGGCTGGAAGGCAATGGTACACCTATCA ACCGAGUGTGTGAGAGCTTGAATCCCAAGAGAG GACACAAGTACATGGCCAGCAGCTTCTTACATTTGA CATCGGACCAAGTGGAGATCTCACAACAGTTTACCTG CCAAGTTACACATGAAGGGGACACTGTGGAAGAGAG TCTGTCTCCTGAGAAATGTCTCTAA (SEQ ID NO: 43)	GOPKSTPTLTMFPSSPEELQENKATLV CLISNFPSPGVTVAWKANGTPTTGQVD TSNPTKEDNKYMSSFLHLTSDQWRSH NSFTCGVTHEGDTVEKLSPAECL (SEQ ID NO: 42)	J00585 AH005311 X58415 X58411		Selsing E. et al., Proc. Natl. Acad. Sci. USA, 79, 4681-4685 (1982). PMID: 6812053 Weiss S. and Wu GE, EMBO J., 6, 927-937 (1987). PMID: 3109891

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Bovine (Scientific Name: Bos taurus)	Bovine Ig heavy chain constant region (CH1-CH3)	IgG1 variant 1 GCCTCCACACAGCCCGGAAAGTCTACCCCTCTGAAGTTC TTGCTGCGGGGACAAGTCCAGCTCCACCGTGACCCCTGG GCTGCCCTGGTCTCCAGCTACATGCCGAGCCGGTGACC GTGACCTGGAAGTCTGGTGCCTGAAGAGCGCGCTGCA CACCTTCCCGGCTGCTCTCAGTCTCCGGGCTGTACTCT CTCTCAGCAGCATGGTGACCGTGCCCGGACGACGCTCA GGACAGACCTTCACTGCCAAGTACGCCACCCCGCCAG CAGCAGCAAGGIGGACAAGGCTGIGGAGCAGCAGCAGC AAGCATCACCGCTGACCTGTGGCCACCCCGCTGAGCTC CCCGGAGGACCTGTGTTGATCTTCCACCGCAAGC CAAGGACACCCCTCAAAATCTCGGGAACGCCCGAGGTCA CGTGTGGTGGTGACGCTGGGCCACGATGACCCCGAG GTGAAGTTCTCCTGTTCTGTGGACGACGTGGAGGTAAA CACAGCCACGACGAAGCGGAGAGGAGGAGTTCGAACA GCACCTACCGCTGGTGAGCGCCCTGCGCATCCAGCAG CAGGACTGGACTGGAAGAGGAGTTCAAGTGCAAGGT CCACAACGAAGGCTCCCGGCCCTCATGTGAGGACCA TCTCCAGGACCAAAAGGCCGCCGCCGGGAGCGCCAGGT GTATGCTCTGGCCCAACCCAGGAAGAGCTCAGCAAAA GACCGGTGACGCTGACCTGTGATGGTGAGCAAGTTGTAC CCAGACTACATCGCGCTGGAGTGGCAGAGAAAGCGGCA GCCTGAGTCGGAAGGACAAAGTACGGCAGCAGCCCGCCC CAGCTGGACGCGCGACAGCTCCTACTTCTCTGTACAGCAA GCTCAGGGTGGACAGGAACAGCTGGCAGGAAGGAGAC ACCTACACGCTGTGGTGTGATGCAAGGAGCCCTGCACAA TGACTACAGCGAAGTCCACCTCTAAGTCTGGGGGTAA AATGA (SEQ ID NO: 67)	ASTTAPKVVPLSSCCGDKSSSTVTLGC LVSSYMPEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSMMVTPGTSVGTFT CNVAHPASSTKVDKAVDPTCKPSPDC COPPELPGGPSVFPPPKDPTLTISG TPEVTCVVVDVGHDDPEVKFSWFDD VEVNTATTKPREEQFNSTYRVVSALRI QHQUWIIGKEFKCKVHNEGLPAPIVRI ISRTKGPAREPQVYVLAPOEELSKST VSLTCMVTFSFYPDYIAVEWQRNGQPE EDKYGTTPQLDADSSYFLSKLRVDR NSWQEGDITYTCVMHEALHNHYTQKS TSKSAGK* (SEQ ID NO: 66)	X62916	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGen&repertoire=gen&species=bovine&group=IGHC	Symons D.B. et al., J. Immunogenet., 14, 273-283 (1987). PMID: 3141517 Symons D.B. et al., Mol. Immunol., 26, 841-850 (1989). PMID: 2513487 Kacskovics I. and Butler J.E., Mol. Immunol., 33, 189-195 (1996). PMID: 8649440 Rabbani H. et al., Immunogenetics, 46, 326-331 (1997). PMID: 9218535 Saini S.S. et al., Scand. J. Immunol., 65, 32-8 (2007). PMID: 17212764
	IgG1 variant 2	GCCTCCACACAGCCCGGAAAGTCTACCCCTCTGAAGTTC TTGCTGCGGGGACAAGTCCAGCTCCACCGTGACCCCTGG GCTGCCCTGGTCTCCAGCTACATGCCGAGCCGGTGACC GTGACCTGGAAGTCTGGTGCCTGAAGAGCGCGCTGCA CACCTTCCCGGCTGCTCTCAGTCTCCGGGCTGTACTCT CTCTCAGCAGCATGGTGACCGTGCCCGGACGACGCTCA GGACAGACCTTCACTGCCAAGTACGCCACCCCGCCAG CAGCACCAGGTTGACAGGCTGTTGATCCACATGCA AAGCATCACCTGTGACTGTTGCCACCCCGCTGAGCTC CCCGGAGGACCTGTGCTTCTCATCTTCCACCGCAAGC CAGGACACCCCTGCAAAATCTCGGGAACGCCCGAGGTCA CGTGTGGTGGTGACGCTGGGCCACGATGACCCCGAG GTGAAGTTCTCCTGTTCTGTGGACGACGTGGAGGTAAA CACAGCCACGACGAAGCGGAGAGGAGGAGTTCGAACA GCACCTACCGCTGGTGAGCGCCCTGCGCATCCAGCAG CAGGACTGGACTGGAAGAGGAGTTCAAGTGCAAGGT CCACAACGAAGGCTCCCGGCCCTCATGTGAGGACCA TCTCCAGGACCAAAAGGCCGCCGCCGGGAGCGCCAGGT GTATGCTCTGGCCCAACCCAGGAAGAGCTCAGCAAAA GACCGGTGACGCTGACCTGTGATGGTGAGCAAGTTGTAC CCAGACTACATCGCGCTGGAGTGGCAGAGAAAGCGGCA GCCTGAGTCGGAAGGACAAAGTACGGCAGCAGCCCGCCC CAGCTGGACGCGCGACAGCTCCTACTTCTCTGTACAGCAA GCTCAGGGTGGACAGGAACAGCTGGCAGGAAGGAGAC ACCTACACGCTGTGGTGTGATGCAAGGAGCCCTGCACAA TGACTACAGCGAAGTCCACCTCTAAGTCTGGGGGTAA AATGA (SEQ ID NO: 69)	ASTTAPKVVPLSSCCGDKSSSTVTLGC LVSSYMPEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSMMVTPGTSVGTFT CNVAHPASSTKVDKAVDPTCKPSPDC COPPELPGGPSVFPPPKDPTLTISG TPEVTCVVVDVGHDDPEVKFSWFDD VEVNTATTKPREEQFNSTYRVVSALRI QHQUWIIGKEFKCKVHNEGLPAPIVRI ISRTKGPAREPQVYVLAPOEELSKST VSLTCMVTFSFYPDYIAVEWQRNGQPE EDKYGTTPQLDADSSYFLSKLRVDR NSWQEGDITYTCVMHEALHNHYTQKS TSKSAGK* (SEQ ID NO: 68)	X16701 (M25278)		
	IgG1 variant 3	GCCTCCACACAGCCCGGAAAGTCTACCCCTCTGAAGTTC TTGCTGCGGGGACAAGTCCAGCTCCACCGTGACCCCTGG GCTGCCCTGGTCTCCAGCTACATGCCGAGCCGGTGACC GTGACCTGGAAGTCTGGTGCCTGAAGAGCGCGCTGCA CACCTTCCCGGCTGCTCTCAGTCTCCGGGCTGTACTCT CTCTCAGCAGCATGGTGACCGTGCCCGGACGACGCTCA GGACAGACCTTCACTGCCAAGTACGCCACCCCGG CAGCAGGACCAAGTGGACAAGGCTGTTGATCCAGAT GCAAAACACCTGTGACTGTTGCCACCGCCTGAGCTC CCTGGAGGACCTGTGCTTCTCATCTTCCACCGCAAGC CAAGGACACCCCTCAAAATCTCGGGAACGCCCGAGGTCA CGTGTGGTGGTGACGCTGGGCCACGATGACCCCGAG GTGAAGTTCTCCTGTTCTGTGGACGACGTGGAGGTAAA CACAGCCACGACGAAGCGGAGAGGAGGAGTTCGAACA GCACCTACCGCTGGTGAGCGCCCTGCGCATCCAGCAG CAGGACTGGACTGGAAGAGGAGTTCAAGTGCAAGGT CCACAACGAAGGCTCCAGCCCGCTCATGTGAGGACCA TCTCCAGGACCAAAAGGCCGCCGCCGGGAGCGCCAGGT GTATGCTCTGGCCCAACCCAGGAAGAGCTCAGCAAAA GACCGGTGACGCTGACCTGTGATGGTGAGCAAGTTGTAC CCAGACTACATCGCGCTGGAGTGGCAGAGAAATGGCA GCCTGAGTCAGAGGACAAAGTACGGCAGCAGCCCTCCCG AGCTGGACGCGGACGCGCTCTACTTCTCTGTACAGCAGG CTCAGGGTGGACAGGAACAGCTGGCAGGAAGGAGACA CCTACAGCTGTGTGGTGTGATGCAAGGAGCCCTGCACAA CACTACACGCAAGGTCCACCTCTAAGTCTGCGGGGTAA ATGA (SEQ ID NO: 71)	ASTTAPKVVPLSSCCGDKSSSTVTLGC LVSSYMPEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSMMVTPGTSVGTFT CNVAHPASSTKVDKAVDPTCKPSPDC COPPELPGGPSVFPPPKDPTLTISG TPEVTCVVVDVGHDDPEVKFSWFDD VEVNTATTKPREEQFNSTYRVVSALRI QHQUWIIGKEFKCKVHNEGLPAPIVRI ISRTKGPAREPQVYVLAPOEELSKST VSLTCMVTFSFYPDYIAVEWQRNGQPE EDKYGTTPQLDADSSYFLSKLRVDR NSWQEGDITYTCVMHEALHNHYTQKS TSKSAGK* (SEQ ID NO: 70)	S82409		
	IgG2 variant 1	GCCTCCACACAGCCCGGAAAGTCTACCCCTCTGGGACTC CAGCTGGGGAGAGCAACTCAGCTGCCACCTGACCCCTGG GCTGCCCTGGTCTCCAGCTACATGCCGAGCCGGTGACC GTGACCTGGAAGTCTGGGTCGCTGAAGAGCGCGCTGCA CACCTTCCCGGCTGCTCTCAGTCTCCGGGCTGTACTCT CTCTCAGCAGCATGGTGACCGTGCCCGGACGAGCTCA GGACAGACCTTCACTGGAACGTGCGCCCGACGAGCTCA GGACAGCAGCTTCACTGGAACGTGCGCCCGACCGCGCAG CAGCAGCAGAGTGGTGACGAGCTGTGGGCTGTCCATTG ACTGCTCCAGGAGTCAATCAAGCAGCTTGGCTGAAGGAAA CCATCTGTCTTCACTTCTCCACCGCAAAACCAAGACAC CTCGATGATCAGCAGGAAGCCCGGAGGTCAGCTGTGTGG TGGTGAACCTGGGCCACGATTAACCCCGAGGTGTCAGGTTG TCTCGCTGTGTGGATGACGTGGAGCTGTGGACGAGCTCA GTGCAAGCGCAAGAGAGGACGTTCAACAGCAGCTACCC GGGTGGTCAAGCGCCTGCCATCCAGACACGAGACTGG ACTGGAGAAAGAGGATTCAAGTGCAAGGTCAACAACAAA AGGCGCTTCGGGCCCCCATCGTGAGGATATCTCTCAGAGA GCAAAAGCGCCCGGACGAGCGGACAGGTGATGTGCTG GGACCCACCCAGGAAGAGCTCAAGCAAAAGCAGCGTCA GGTCACTGCTGATGGTCAACCGGCTTCTACCCAGAAGAT GTAGCGCTGGAGTGGCGAGAGAACCGCGCAGCTGAGCTG GGAGGAGCAAGTACCGCAGACCCCGGCCAGCTGGAC ACCGACCGCTGCTACTTCTGTGACAGCAGCTCAGGCT GGACAGGAACAGCTGCGAGGAAGGACGCGCTACAGC TGTGTGGTATCAGCAGGAGCCCTGCACAACTCACTACAT CGAGAAGTCCACCTCTAAGTCTGCGGGTAAATGA (SEQ ID NO: 73)	ASTTAPKVVPLASSCGDTSSTVTLGC LVSSYMPEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSMMVTPASSSGTFT CNVAHPASSTKVDKAVGVSDCSKCHN QPCVREPSVFIFPPPKDPTLMTGTPEV TCVVNVGHNDPEVGFWSFVDDVEVH TARSKPREEQFNSTYRVVSALPIQHD WTGGKEFKCKVHNEGLPAPIVRI GPAREPQVYVLDPEELSKSTLSVTC MVTGYPEDVAVEWQRNRTSEDEKY RTTPQLDTRSYFLSKLRVDRNSWQ EQDATTCCVMHEALHNHYMOKSTSKS AGK* (SEQ ID NO: 72)	S82407		

	IgG2 variant 2	GCCTCCACCACAGCGCCGAAAGTTACCCCTCTGAGTTC TTGCTGGGGGACAGTCCAGCTCCACCGTGACCCCTGG GCTGCTGTGTCTCAGACTACATGCCCGAGCCGGTGACG GTGACCTGGAACTGGGTGCCGTGAAGAGCGGGTGCA CACCCTCCCGCGCTCCTTCAGTCTCCCGGGCTCTACT CTCTCAGCAGCATGGTGACCGTGCCCGGAGCACCTCA GGACAGACCTCTCAGCTGCAACGTAGCCACCCCGGCGAG CAGCAGCAAGAGTGGACAAGGCTGTTGGGTCTCCAGTG ACTGCTCCAGAGCTTAACAGAGATTGGTGAGGAGAA CCATCTGTCTTCATCTTCCACCCGAAACCCAAAGACAC CCTGATGATCACAGGAACGCCGAGGTCAAGTGTGTGG TGGTGAACGTGGGCGCAGATAACCCCGAGGTGCAGTGT TCCTGTTCTGTGAGCAGCTGGAGTGCACAGCGCCAG GACGAAGCCGAGAGAGGAGCAGTTCAACAGCACGTACG CGCTGGTTCAGCGCCCTGCCATCCAGCACAGGACTGG ACTGGAGGAAGGAGTTCAAGTGCAAGGTCAACATCAA AGGCCTCTCGGCTCCATCGTGAAGATCATCTCCAGGA GCAAAAGCCCGCCCGCGAGGCCAGCTGTATGTCCT GGACCCACCCAAAGGAAGCTCAGCAAAAGCACCGTCA GCCTCACCTGCATGGTCACTGGCTTCTACCCAGAAGAT GTAGAGCTGGAGTGGCAGAGAGACCGGACGACTGAGTC GAGAGCAAGTACCTGACACGCTGCTGCTGAGCTTAC GCCGACCGCTGCTACTTCCCTGACAGCAAGCTCAGGCT GGACAGGAACAGCTGGCAGAGAGGAGACACTACACGT GTGTGGTGTGACGAGGCGCTGCACATCACTACATG CAGAAGTCCACCTTAAGTCTCGGGGTAATGA (SEQ ID NO: 75)	ASTTAPKVYPLSSCCGDKSSSTVTLGC LVSSYMEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSLSMVTVPASSSGTQTF TCNVHAPASSTKVDAKVGVSSDCKSP NNQHCVRPSVFIFPPKDTLMTGTP VTCVNVNVDHNPVQFSWFVDDVEV HTARTKPREQFNSTYRVVSALPIQH DNTGGKEFKKYNKGLSASIVRISRS GPAREPOVYVLDPPKEELSKSTVSLT CMVIGFYPEDVDVEWRDRQTESEDKYR TTPQLDADRSFYLSKLRVDRNSWQR GDTYTCVMHEALHNHYMKSTSKSA GK* (SEQ ID NO: 74)	M36946 (X06703)		
	IgG2 variant 3	GCCTCCACCACAGCGCCGAAAGTTACCCCTCTGAGTTC TTGCTGGGGGACAGTCCAGCTCGGGGCTGACCCCTGG GCTGCTGTGTCTCAGACTACATGCCCGAGCCGGTGACG GTGACCTGGAACTGGGTGCCGTGAAGAGCGGGTGCA CACCCTCCCGCGCTCCTTCAGTCTCCCGGGCTCTACT CTCTCAGCAGCATGGTGACCGTGCCCGGAGCACCTCA GGAACCCAGACCTTCACCTGCAACGTAGCCACCCCGGCG CAGCAGCAACAGTGGGACAAGGCTGTTGGGTCTCCGA GTGACTGTGCTCAGAGTAAAGAGCAATTGGGTGACGA GAACCATCTGTCTTCATCTTCCACCCGAAACCCAAAGA CACCCCTGATGATCACAGGAACGCCGAGGTCAAGTGTG TGGTGGTGAACGTGGGCGCAGATAACCCCGAGGTGCAG TTCTGCTGGTGGTGGAGCAGCTGGAGGTGCACACAGCG GAGGACAACCGCGCGCGCGGAGCGGAGGTGCACACAGCG ACCCGCTGGTCAAGCGCCCTGCCATCCAGCACAGGAC TGGACTGGAGGAAGGAGTTCAAGTGCAAGGTCAACAT CAAAGGCTCTCGGCTCCATCGTGAAGATCATCTCCGA GGAGCAAAAGGCGCGCGCGGAGCGGCGAGGTGTATGT CCTGGACCCAGCCAGAGAGAGCTGAGCAAAAGCAGCG TCAGCCTCACCTGCATGGTCACTGGCTTCTACCCAGAA GATGTAGAGCTGGAGTGGCAGAGAGACCGGACAGCTGA GTGGAGGACAAGTACCGCAGACACCCCGCGCGAGGTG GACGCGGACCGCTCCTACTGCTGTACAGGAAGCTCAG GGTGGACAAGACAAGCTGGCAGAGAGCAGAGCTAC AGTGTGTGGTATGCACGAGGCGCTGCACAACTCACTA CATGAGAAGTCCACCTTAAGTCTCGGGGTAATGA (SEQ ID NO: 77)	ASTTAPKVYPLSSCCGDKSSSGVTLGC LVSSYMEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSLSMVTVPASSSGTQTF TCNVHAPASSTKVDAKVGVSSDCKSP NNQHCVRPSVFIFPPKDTLMTGTP EVTCCVNVNVDHNPVQFSWFVDDVE VHTARTKPREQFNSTYRVVSALPIQH QDWTGGKEFKKYNKGLSASIVRISRS GPAREPOVYVLDPPKEELSKSTVSLT CMVIGFYPEDVDVEWRDRQTESEDKY RTTPQLDADRSFYLSKLRVDRNSWQ RGDTYTCVMHEALHNHYMKSTSKS AGK* (SEQ ID NO: 76)	X16702 (M25279)		
	IgG3 variant 1	GCCTCCACCACAGCGCCGAAAGTTACCCCTCTGGCATC CAGCTGCGGAGACACATCCAGCTCCACCGTGACCCCTGG GCTGCTGTGTCTCAGACTACATGCCCGAGCCGGTGACG GTGACCTGGAACCTGGGTGCCCTGAAGAGCGGGTGCA CAGCTTCCCGCGCTCCTTCAGTCTCCCGGGCTCTACT CTCTCAGCAGCATGGTGACTGTGCCCGCAGCAGCTCA GAAACCCAGACCTTCACCTGCAACGTAGCCACCCCGGCG CAGCAGCACCAAGGTGGACAAGGCTGTCACTGCAAGGG GTCCAGTCCCGAGCAGCCCAAGACCAACTATCCCTCTC GGAACCCACACAGCAGCTGTGAAGTTGAAAGAGC ACCTGCCAGTGTCCAAATGCCAGAACCTCTGGGAG GACTGTGTCTTCATCTTCCACCCGAAACCCAAAGAC ACCTCACAATCTGGGGAACGCCGAGGTCAAGTGTGT GCTGGTGACCTGGGCGCAGATGACCCGAGGTGCAG TTCTGCTGGTGTGAGCAGCTGGAGTGCACAGCGCG CAGGACGAAGCCGAGAGAGGACAGTTCAACAGCACCT ACCGGCTGGTCAAGCGCCCTGCGCATCCAGCACCAAGGA CTGGCTGCAAGGAAGGAGTTCAAGTGCAAGGTCAACA ACAAAGGCTCCCGCGCCCGCAATTGTGAGGACCATCTCC AGGACCAAAAGGCAAGCTCCCGGAGCGCGAGGTGTATG TCCTGGCCCGCCCGGGAAGAGCTCAGCAAAAGCAGCG CTCAGCCTCACCTGCCCTGATCACCGGTTCTACCCAGA AGAGATAGAGCTGGAGTGGCAGAGAAATGGGCAAGCTG AGTGGAGGACAGTACACACAGCAGCCACCCAGAGTG GATGCTGAGCGCTCTACTCTCTGTACAGAACGCTGAG GGTGAACAGAGCAGCTGGCAGGAAGAGAACCACTACA CGTGTGCAATGATGCACGAAGCTTACGGAATCACTAC AAAGAGAAGTCCATCTCGAGGCTCCGGGTAAATGA (SEQ ID NO: 79)	ASTTAPKVYPLSSCGDTSSTVTLGC LVSSYMEPVTVTWNSGALKSGVHTFP AVRQSSGLYLSLSMVTVPASSSETQTF TCNVHAPASSTKVDAKAVTARRPVPTTP KTTPPPKPTFPPKEVETPCQCKSP EPLGLSVFIFPPKPDILTISTGPEVT CVVVDVGDDPEVQFSWFVDDVEVHT ARTKPREQFNSTYRVVSALRIQHODW LQGEKFKKYNKGLPAPVIRTSRTKG QAREPOVYVLDPPKEELSKSTVSLT TGIFYPEEDVEWRNGQPESEDKYHT APQLDADGSFYLSKLRVKNKSSWQEG DHYTCVMHEALRNHYKESIRSPPGK * (SEQ ID NO: 78)	U83638		
	IgG3 variant 2	GCCTCCACCACAGCGCCGAAAGTTACCCCTCTGGCATC CCGCTGCGGAGACACATCCAGCTCCACCGTGACCCCTGG GCTGCTGTGTCTCAGACTACATGCCCGAGCCGGTGACG GTGACCTGGAACCTGGGTGCCCTGAAGAGTGGCGTGCA CAGCTTCCCGCGCTCCTTCAGTCTCCCGGGCTCTACT CTCTCAGCAGCATGGTGACTGTGCCCGCAGCAGCTCA GAAACCCAGACCTTCACCTGCAACGTAGCCACCCCGGCG CAGCAGCACCAAGGTGGACAAGGCTGTCACTGCAAGGG GTCCAGTCCCGAGCAGCCCAAGACCAACTATCCCTCTC GGAACCCACACAGCAGCTGTGAAGTTGAAAGAGC ACCTGCCAGTGTCCAAATGCCAGAACCTCTGGGAG GACTGTGTCTTCATCTTCCACCCGAAACCCAAAGAC ACCTCACAATCTGGGGAACGCCGAGGTCAAGTGTGT GCTGGTGACCTGGGCGCAGATGACCCGAGGTGCAG TTCTGCTGGTGTGAGCAGCTGGAGTGCACAGCGCG CAGGACGAAGCCGAGAGAGGACAGTTCAACAGCACCT ACCGGCTGGTCAAGCGCCCTGCGCATCCAGCACCAAGGA CTGGCTGCAAGGAAGGAGTTCAAGTGCAAGGTCAACA ACAAAGGCTCCCGCGCCCGCAATTGTGAGGACCATCTCC AGGACCAAAAGGCAAGCTCCCGGAGCGCGAGGTGTATG TCCTGGCCCGCCCGGGAAGAGCTCAGCAAAAGCAGCG CTCAGCCTCACCTGCCCTGATCACCGGTTCTACCCAGA AGAGATAGAGCTGGAGTGGCAGAGAAATGGGCAAGCTG AGTGGAGGACAGTACACACAGCAGCCACCCAGAGTG GATGCTGAGCGCTCTACTCTCTGTACAGAACGCTGAG GGTGAACAGAGCAGCTGGCAGGAAGAGAACCACTACA CGTGTGCAATGATGCACGAAGCTTACGGAATCACTAC AAAGAGAAGTCCATCTCGAGGCTCCGGGTAAATGA (SEQ ID NO: 81)	ASTTAPKVYPLSRCGDTSSSTVTLGC LVSSYMEPVTVTWNSGALKSGVHTFP AVLQSSGLYLSLSMVTVPASTSETQTF TCNVHAPASSTKVDAKAVTARRPVPTTP KTTPPPKPTFQSEVEKTPCQCKSP EPLGLSVFIFPPKPDILTISTGPEVT CVVVDVGDDPEVQFSWFVDDVEVHT ARTKPREQFNSTYRVVSALRIQHODW LQGEKFKKYNKGLPAPVIRTSRTKG QAREPOVYVLDPPKEELSKSTVSLT TGIFYPEEDVEWRNGQPESEDKYHT APQLDADGSFYLSRLVKNKSSWQEG DHYTCVMHEALRNHYKESIRSPPGK * (SEQ ID NO: 80)	U83639		
Bovine Ig light chain constant region (CL)	Ig lambda	CAGCCCAAGTCCCAACCTCGGTCAACCTGTTCCCGCC CTCCACGGAGGAGCTCAACGGCAACAGGCTCAACCTG GTGTGTCTCATCAGCGACTTCAACCGGTTAGCGTGAC CGTGGTCTGGAAGGACAGCGGAGCAGCATCAACCCGCG AGCTGGAGACACCGCGGCTCCGAAAGAGGACAGCAAG CAAGTACCGCGGACGAGCTACCTGAGCTGACAGGACA GCGACTGGAAATCGAAAGGACGTTACAGCTGCGAGGTC ACGCAAGGGGAGGACCGTGACGAAAGACAGTGGAAGC CCTCAGAGTGTCTTAG (SEQ ID NO: 65)	QPKSPSPVTLFPPSTEELNGNKATLVC IISDFYPSVTVVWKAIGSTITRNVLT RASKQSNKYAASSYLSLSDSWKSGK SYSQEVTHEGSTVTKTVKPSKC* (SEQ ID NO: 64)	X82917	Not registered	Chen L. et al., Vet. Immunol. Immunopathol., 124, 284-294 (2008). PMID: 18538661

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	GCCTCCACGACGGCCCCCTCGGTTTTCCGACTGGCC CCCAGCTGGGGTCCACTTCCGGCTCCACGGTGGCC CTGGCCTGGCTGGTGTACAGGCTACTTCCCGAGCCT GTAACCTGTGCTGGAATTCGGGCTCCTTGACCAGC GGTGTGCACACCTTCCCGTCCGTCCGTGGAGTCCCTCA GGGCTGTACTCGCTCAGGAGCAGCGTGACAGTGGCC TCCAGCAGGTGGCCAGCCAGACCTTCACTGTCAAC GTGGTCCACCGCCGACCAACACTAAAGTAGACAAG CCAGTGGCCAAAGAGTCCACCTGCAAGTGTATATCC CCATGCCAGTCCCTGAATCACTGGGAGGGCCTTCG GTCTTGAATTTTCCCGGAAACCAAGGACATCCTC AGGATTACCCGAACACCCGAGATCACCTGTGTGGTG TTAGATTGGGCGGTGAGGACCTGAGGTGCAGATC AGCTGGTTGGTGGATGTAAGGAGGTGCACACAGCC AAGCGGAGCCTGCTGAGCAGGAGTTCAACAGCAGC TACCGTGTGTGACGCTGCTCCCGATTGAGCAGCAG GACTGGCTCAGCCGAAAGGAGTTCAAAGTGCAGAGTC AACACATAGGCTCCGCTCCCGATCGAGAGGACT ATCTCCAAAGCCAGAGGGGAAAGCCATCAGCCAGT GTGTATGTGCTGCCACCATCCGAAAGGAGTTGTGA TCCAGTGACAGGTGACCTGACCTGCTGTATCAAA GACTTCTTCCACCTGAGATTGATGTGGAGTGGCAG AGCAATGGACAGCCGGAGCCGAGAGCAAGTACCAC ACGACTGGCCCCAGCTGGACGAGGACGGTCTAC TTCTGTACAGCAAGCTCTCTGTGGACAAGAGCGCG TGGCAGCAGGGAGACCTTCACATGTGCGGTGATG CATGAAGCTCTACAGAACCACTACACAGATCTATCCC TCTCCATTCTCCGGGTAATGA (SEQ ID NO: 85)	ASTTAPSVFPLAPSCGSGTSGTVALAC LVSGYFPEPVTVSWSGLTSGVHTFP SVLGSSGLYLSSTVTVPSSRWPSETF TCNVVHPASNTKVDKVPKESTCKCIS PCPVPESLGGPSVFIFPPKPKDILRTRT PEITGVLDLGRDEPVGQSWFVDGKEV HTAKTOPREQQFNSTYRVVSVLPIEHQ DWLTGKEFKORVNHIGLPSPIERTISKA RQGAHQPSVYVLPSPKELSSSDTVTL TGLKDFPPEDVWQSNQGPPEPSKY HTTAPOLDEDSYFLYKLSVOKSRWQ QGDFTFTCAVMHEALQNHYDLSLSHS PGK* (SEQ ID NO: 84)	AF354267	http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetab&species=dog&group=IGHG	Tang L. et al., Vet. Immunol. Immunopathol. 80 (3-4), 259-270 (2001). PMID: 11457479
	Canine Ig light chain constant region	Ig lambda (CL)	CAGCCCAAGGCTCCCCCTGGGTACACTOTTTCCCG CCCTCCTCTGAGAGCTCGGCGCAACAAGGCCAAC CTGGTGTGCCTCATCAGGAGCTTCTACCCAGCGCG GTGACGGTGGCTGGAAGGCAAGCGCAGCCCGT CACCAGGGCGTGAGACCAACCAAGCCCTCCAGCA GAGCAACAACAAGTACGGGGCCAGAGTACCTGAG CCTGACGCTGACAAAGTGGAAATCTCAGAGCAGCTT GAGTGGCTGCTGACGACGAGGGGAGACCCGTGG AGAAGAAGGTGGCCCCCGAGAGTGTCTTAG (SEQ ID NO: 83)	QPKASPSVTLFPPSSEELGANKATLVG LISDFYPSGVTVANKASQSPVTGQVET TKPSKGSNNKYAASSYLSLTPDKWKSH SFSCLVTHEGSTVEKKVPAECS* (SEQ ID NO: 82)	E02824	Not registered	None

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Ovine (Scientific Name: <i>Ovis aries</i>)	Ovine Ig heavy chain constant region (CH1*CH3)	GGCTCAACAAACACCCCGAAAGTCTACCGTCTGACTTCTTGGCTGGGGGACAGCTCCAGCTCCATGCTGACCTGGGGCTGGCTGGTCTCCAGCTATATGCCCGAGCCGGTGACCGGTGACCTGGAACCTCGTGGTGGCTGACACGGGGGTGGACACCTTCCCGGCCATCCTGGAGTCTCTCCGGGCTCTACTCTCTCAGACGCGTGGTGACCGTGCCGGCCAGCACCTGAGAGCCAGACCTTCACTGTGCCAACGTAGGCCACCCGGCCAGCAGCAACAGGTGGACAAGCGTGTGGAGCCGGATGCCCGACCCATGCAAAACATGGCCGATGCCACCCCTGAGCTCCCGGAGGACCGGTCTGTCTTCACTTCCACCGAAACCCGAAAGGACACCTTACAATCTCTGGAACGCCGAGGTACAGTGTGTGGTGGTGAGCTGGGCCAGCTGACCCGAGGTGCGACAGTGTCTCTGAGCAACAGTGGAGGTGGCGCAGGACAAAGCCGAGAGGAGCAGTTCAACAGCACCTTCGGGTGGTCAAGCCCTGCCCATCCAGCCACCAAGACTGGACTGGAGGAAAGGAGTTCAAGTGCAAGGTCCACAAACGAGCCCTCCCGGCCCCATCGTGAAGACCATCTCCAGGACAAAGGGAGGGCCGGAGCCGACAGGTGACGTCTGGCCACCCAGGAGAGCTCAGCAAAAGCAGCGTCAAGGTGACGTGCTGGTACCGGCTTACCCAGACTACATGCCGTGGAGTGGCAGAAAAATGGGACGCTGAGTGGAGGACAAAGTACGGACGACACATCCGAGCTGGAGCCGACGGGCTCTACTTCTGTACAGCAGGCTCAGGTTGGACAAGAACAGCTGGCAAGGAGACACCTACGGTGTGTGGTGATGCACGAGGCTCTGCACAACCACTACACACAGAAGTCGATCTCTAAGCCTCCGGGTAATGA (SEQ ID NO: 91)	ASTTPPKVYPLTSCCGDTSSSIVTLGCLVSSYMPEPVTVWNSGALTSGVHTFPAILQSSGLYLSVVTVPASTSGAQTFCINVAHPASSTKVDKRVEPGCPDPCKHCRPPPELPGPSVFIFPPKPDLTISGTPEVTGVVVDVGGDDPEVQFSWFVDNVEVRTARTKPREEQNSTFRVYSALPIQHODWTGGEKFKCVHNEALPAPIVRTISRTKGQAREPQVYVLAPPQELSKSTLSVTCLVTGYPDYIAVEWQKNGPESDEKYGTITTSQLDADGSFVLYSRLRVDKNSWQEGDTYACVVMHEALHNHYTKSKISKPPGK* (SEQ ID NO: 90)	X69797	http://www.imgt.org/IMGT/Trasptoire/index.php?section=LocusGenes&repertoire=genetab&species=sheep&group=IGHC	Dufour V. et al., J. Immunol., 156: 2163-2170 (1996). PMID: 8690905
	IgG2	GGCTCACCACAGCCCGAAAGTCTACCGTCTGACTTCTTGGCTGGGGGACAGCTCCAGCTCCATGCTGACCTGGGGCTGGCTGGTCTCCAGCTATATGCCCGAGCCGGTGACCGTGGACCTTCCCGGCCATCCTGGAGTCTCTCCGGGCTCTACTGTCTCAGACGCGTGGTGACCGGGCCAGCACCTCAGGAGGCCAGACCTTCACTGCGAAGCTAGCCACCCGGCCAGGAGCGTGGACAAGCGTGTGGGATCTCCAGTGACTTCCAAAGTGTCTAAACCGCCTGGCTGAGCCGACCGCTGTCTTTCATCTTCCCGCGAAACCAAGGACGCGCTCATGATCACAGGAACGCCGAGGTGACGTGTGTGGTGGTGACGTGGGCCAGGGTGACCCGAGGTGGAGTTCTCTGGTTCGTGGACAACCTGAGGTGGCCACGCGCAGGACAAAGCCGAGAGAGCAGTTCACACGACCTTCGGGTGTCAAGCCCTGCCCATCCAGCAGCAGCTGGACTGGAGGAAAGGAGTTCAAGTGCAAGGTCCACAGCAAGGCTCCCGGCCCCATCGTGAGGACCATGTCCAGGGCCAAAGGAGGCGCCGAGGCGCAGGTGTACGTCTGGCCCAACCCAGGAAGAGCTCAGCAAAGCACGCTCAGCGTCACTGCTGGTGGTGGCTTCTACCCAGACTACATCGCCGTGGAGTGGCAGAGAGCGCGCAGCCTGAGTGGAGGACAAGTACGGCACGACACATCCGAGCTGGAGCGCCGACGGCTCTAATTGCTGTACACGAGCTCAGGGTGAGCAAGAGAGACTGGCAAGAGGAGACACTACCGCTGTGTGGTGTGACGAGGGCTCTGTCACACAGCAAGTGTGATCTTAAGCCTCCGGGTAATGA (SEQ ID NO: 93)	ASTTAPKVYPLTSCCGDTSSSIVTLGCLVSSYMPEPVTVWNSGALTSGVHTFPAILQSSGLYLSVVTVPASTSGAQTFCINVAHPASSAKVDKRVGISSDYSKSKPPCVSRPSVFIFPPKPDLSMITGTPEVTGVVVDVGGDDPEVQFSWFVDNVEVRTARTKPREEQNSTFRVYSALPIQHODHWTGGEKFKCVHNEALPAPIVRSRAKQAREPQVYVLAPPQELSKSTLSVTCLVTGYPDYIAVEWQKNGPESDEKYGTITTSQLDADGSFVLYSRLRVDKSSWQEGDTYACVVMHEALHNHYTKSISKPPGK* (SEQ ID NO: 92)	X70983		Clarkson C.A. et al., Mol. Immunol., 30: 1195-1204 (1993). PMID: 8413324
	Ovine Ig light chain constant region	CCATCCGCTCTTCTCTTCAAAACCATCTGAGGAACAGCTGAGGAGCGGAAGTGTCTGTCTGTGTGTGGTGAAATGATTTCTACCCCAAGATATCAATGTCAAGGTGAAGTGGATGGGGTTACCCAGACAAGCAACTTCCAGACAGCTTACAGACCCAGGACAGCAAGAAAGCACCTACAGGCTCAGGAGCACCTGACACTGTCCAGCTCAGAGTACCAAGAGGATTAACGCTATGCGTGTGAGGTCAGCCACAAAGAGCTGCCACCGCCCTGGTCAAGAGAGTCAATAAGATGAATGTTAG (SEQ ID NO: 87)	PSVFLFKPSEEQLRTGTVSVOLVNDIFYPKDINKVKVDVITQNSNFONSFDTQDSKSTYSLSSTLSSSEYQSHNAYACEVSHKSLPTALVKSFNKNEC* (SEQ ID NO: 86)	X54110	Not registered	Jenne C.N. et al., Dev. Comp. Immunol., 30 (1-2), 165-174 (2006). PMID: 16083958
	Ig lambda (CL)	GGTCAGCCCAAGTCCGACCCCTGGGTACCCCTGTTCGCCCTTCCACGGAGGAGCTCAGTACCAACAAGGCCACCGTGTGTCTCATCAACGACTGTACCCGGGTAGCGTGAACGTGTCTGGAAGGCAGATGGCAGCACATCAATCAGAACGTGAAGACACCCAGGCCCTCCAAAAGAGCAACGCAAGTACGCGGCCAGCAGCTACCTGACCTGACGGGACGAGGTGGAAGTCTAAGAGCAGTACACCTGGAGGTACAGCACAGGGGAGCAGCGTGAAGAGAGCTGAAGCCCTCAGAGTGTCTTAG (SEQ ID NO: 89)	GQPKSAPSVTLFPPSTEELSTNKATVCLINDFYPGSVNWNKADGSTINGNKTTQASKGSNSKYAASSYLTLTGSEWKS KSSYTCEVTHEGSTYTKVTKPSECS* (SEQ ID NO: 88)	AY734681		

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Porcine (Scientific Name: Sus scrofa)	Porcine Ig heavy chain constant region (CH1-CH3)	lgG1* GCCGCCAAGACGGCCCATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AAGGCTATAGGCGAGACCGGAGCCGAGGAGTGTACACCTGCCCCACCGCCGCGGAG AGCTGTCCAGGAGCAAGATCACGTAACCTGGCTGGTCATTTGGCTTATACCCAGCTGAC ATCATGTTGAGTGCAGAGCAACGACCGGAGCGAGGAGGAGGGAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCCATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 95)	AKPTAPSVLPALPGDSRVSIGNVALG GLASSYFPEPVITWNISGLTSVHT PSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 94)	U03781 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331 6130: 239-230 (2009) PMID: 19405248	Butler J.E. et al., Immunogenetics 1995; 35:73-79 PMID: 7930579	
		lgG1* GCCGCCAAGACGGCCCATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AAGGCTATAGGCGAGACCGGAGCGGAGGAGTGTACACCTGCCCCACCGCCGCGGAG AGCTGTCCAGGAGCAAGATCACGTAACCTGGCTGGTCATTTGGCTTATACCCAGCTGAC ATCATGTTGAGTGCAGAGCAACGACCGGAGCGAGGAGGGAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCCATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 97)	AKPTAPSVLPALPGDSRVSIGNVALG GLASSYFPEPVITWNISGLTSVHT PSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 96)	U03778 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331 6130: 239-230 (2009) PMID: 19405248		
		lgG2* GCCGCCAAGACGGCCCATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCAACAAGACGCTCCAGCCGCCATCACAGGATCATCTG AAGGCAAGAAGGAGCAGCGGAGCGGAGGCTGTACACAGTGTGGTGTGATGAGCAGCG AGCTGTCTCCAGGAGCAAGTCAAGATACGCTGGCTGGTGTATACCGCTGACG ATCGATGTGAGTGCAGAAAGAACGACGAGCGGAGCGAGGACCAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCTATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 99)	AKPTAPSVLPALPGDSRVSIGNVALG GLASSYFPEPVITWNISGLTSVHT PSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 98)	U03779 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331 6130: 239-230 (2009) PMID: 19405248		
		lgG2* GCCGCCAAGACGGCCCATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCAACAAGACGCTCCAGCCGCCATCACAGGATCATCTG AAGGCAAGAAGGAGCAGCGGAGCGGAGGCTGTACACAGTGTGGTGTGATGAGCAGCG AGCTGTCTCCAGGAGCAAGTCAAGATACGCTGGCTGGTGTATACCGCTGACG ATCGATGTGAGTGCAGAAAGAACGACGAGCGGAGCGAGGACCAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCTATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 101)	AKPTAPSVLPALPGDSRVSIGNVALG GLASSYFPEPVITWNISGLTSVHT PSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 100)	U03780 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331 6130: 239-230 (2009) PMID: 19405248		
		lgG3 GGCTACACACAGAGTCGATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG TCATCAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC CTGTGAAGCTGGGTCGCTTGTGACAGATGTTGATGACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCAACAAGACGCTCCAGCCGCCATCACAGGATCATCTG AAGGCAAGAAGGAGCAGCGGAGCGGAGGCTGTACACAGTGTGGTGTGATGAGCAGCG AGCTGTCTCCAGGAGCAAGTCAAGATACGCTGGCTGGTGTATACCGCTGACG ATCGATGTGAGTGCAGAAAGAACGACGAGCGGAGCGAGGACCAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCTATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 103)	AYNTAPSVLPALPGDRVSDHNVALG GLVSSYFPEPVITWNISGLSRVHT PSVLPSQSLYSLSSMTVPASSLS PTCNVYHPATNTYDKRDPDITLY GPEPCSPCAEVLGAPSVFLPPEKKD ILMSIRTPKTVKDNVDEAVSFGVSV VYDVQVQLTATITRMEELNSTYRV VSVLIQHGDWLKKEFKKVNNDLPAPF AGITTRTSKATGSRPVQVITLPAAE ELSKSVSYCTLVGTDFVIDEVRQ GDQPEEYNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH NHYTKTSIKSTGQ* (SEQ ID NO: 102)	EU372658 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331		
		lgG4* ACCTTCCCATCGGCTGTGGAGCGGCTGAGGGCTGTACTCGTCCAGCAAGATGTGATGACGCT GCCGCCAAGACGAGTCGATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGTCAAGATACGCTGGCTGGTCACTCGGCT TCCAGCGCTGATGATCGATGTGGTGTGGAGCAGACGAGGACCAAGAAGGAGGAGGAG AATTAAGCCACCGCCAGCAGCAGGAGCTGTGGAGCTTCTCTGTCACGAGCA GCTGCCGGCTGGACAAGGTCAGGTGGCAGCGTGAAGACATTTCCAGTGTGGCGTGTGAC AGAGGAGCTGTGCAACCAACATCACACCAGAGTCCATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 105)	TFPSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 104)	U03782 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331 6130: 239-230 (2009) PMID: 19405248		
		lgG4* GCCGCCAAGACGGCCCATCGGTTACACCTCTGGCCDCTTGGCGGAGGACAGCGTTGTG GCCCTTAACGTGGCCTTGGGCTGGCTGGCCTAAGCTACTTCCCGGACGAGTCAGCTGATC ACCTGGACATTCGGGCGCCCTGACCACTGGGTGCATACCTTCCGATCGCTCTGCAGCG TGCAGGGCTCTACTCCCTCAGCAGCATGTTGACGCTGCCGGCAGCAGAGCTGTCCAGCA AGAGTCACACTGGAATGTCAACCAACCGGCCACACACCAAGGTGGAACAAGCGTTGT GGAATACACACGGCCAAACATGTCCCATATGCCAGGCTGTGAAGTGGCGGGCCGCTC GGTTCTCATCTTCCGTCAAAACCCAGCAGACCGTTATGATGTCCGTCAGCCAGCGGAG TCAAGTGGTGGTGGTGAAGCTCAGAAGAAGCAGCGGAGGTCGAACTTCTCTGGTATG GTGACGGGCTAGAGTGCACACCGCCGAGACGAGACCAAGAAGGAGGAGTTCAACAG CAGCTTCAAGTGTGGTGAAGCTCTGCCCATCAGACAGCAGAGCTGGTAGAAGGAGAG AAGTTCAAGTGCAGAGTGTGGAGCAACAAGACGCTCCAGCCGCCATCACAGGATCATCTG AAGGCAAGAAGGAGCAGCGGAGCGGAGGCTGTACACAGTGTGGTGTGATGAGCAGCG AGCTGTCTCCAGGAGCAAGTCAAGATACGCTGGCTGGTGTATACCGCTGACG ATCGATGTGAGTGCAGAAAGAACGACGAGCGGAGCGAGGACCAATACCGCAACAG CCGCCCGGACGAGAGCTGGAGCGGAGCTTCTTCCGTACAGCAAGCTGGGTGGAGCA AGGCAAGTAGGACATGGAGACAAMTTTGAAGTGTGGGTGATGACGAGGCGTGTGCAC AACCACTACACCAAGAGTCTATCTCCAGAGTCAGGGTAAATGA (SEQ ID NO: 107)	AKPTAPSVLPALPGDRVSDHNVALG GLVSSYFPEPVITWNISGLTSVHT PSVLPSQSLYSLSSMTVPASSLS KSYTNNVNHATTTKVDRVGHQHP TOPICPGCEVAGSVFFPKPKMTLMI SDTEVHTADTRKPEEFNSTYRVSV LIQHGDWLKKEFKKVNNDLPAPF LRITSKAGQSGREPQVYTPPAAEELS NRYSTVCTLGVYFPDDHVEVNSNGQ PEPEGNYRTTPPGQDVDTFLYSKL AVDKARWHDGKFEACVAMEALHNH TKGSIKSTGQ* (SEQ ID NO: 106)	U0372654 http://www.ncbi.nlm.nih.gov/Trac/Transtool/seqmatch/101331		

		IgG5⁺ GCCTCCAAAGACGGCCCATCGGCTACCCCTCTGGCCCTCGAGCAGGACAGCTGTG GCCTTAACGTGGCCTTGGGCTGGCTGGCTCAAGCTACTTCCCAGGACGAGTGAACGTG ACCTGGAACCTCGGGCCCTGACCACTGGCTGGCTGACACCTTCCCATCCCTCGACAGC GTGAGGGCTTACTTCCCTGACGACATGGTGAAGCTGGCCGCGCAGAGCTTGTCCAGCA AGCGGTATACGTGCAATGTCAACACCCAGCCACCAAAACCAAGGTGAAGCTGTGTGTT GGACGACATGTCCATATGCCAGAGCTGTGAAGTGGCCGGCCCTCGGCTTTCATCTT CCCTCCAAACCCAGGACATCTCATGTATCTCCGACCCGACAGTCAAGTGGCTGGTGG TGGTGGAGCTGACGAAAGACGACCCGAGTCCAGTTCCTCGTACGTGGACGCGGAA GAGGTGACAGCGCCGAGACGAGGCCAAGGAGGAGGAGTTCACAGCACCTACCGCTG GGTCAAGCTGTCTGCCATCCAGCAGGAGCTGGCTGAAGGGAGAGGATTCAGATGCA AGGTCAACAGCAAGAGCTCCAGGCGCATCAAGGAGGACATTCGAAAGGCAAAAGG GTGGTACGAGGCGCGGAGGTGTACACCTGCCCCACCCGCGGAGAGCTGTCCAAAG GCAATGTCAGCTTAACCTGGCTGGTCAAAAGCATTTCCGCTTTCATCCATGTTGAGT GGAAATCAACGAAACAGAGCAGGACGAAACCATATCCAGCACCCCGGCTGAGGAG GAGGAGGACAGGAGCTACTTCTGTACAGAGCTCCGCGTGGCAAGGACAGATGGGA CCATGGAGAAACATTTGAGTGTGGGCTGATGACAGGCTGTGCACAAACCACTACACCC AGAAGTCCATCTCCAAAGCTCAGGGTAAATGA (SEQ ID NO: 109)	APKTAPSVYPLAPCRDTSQPNVALG CLVSSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYLSMMVTPAHSLS KRYTCNVNHPATTKVLDVGRPCPI CPGCEVAGPSVFPPPKDILMSRTP EVTGVVDVDSKEHAEVQFSWYVDGEE VHTAETRPKEQFNSTYRVSVLPQH EDWLKQKEFECKVNNEDLPQPTRTIS KAKGVVRSPEVYTLPPAEELSKSVT TCLVKSPFPFTHVEWKNGKPEPENA RTRTPQDEDRITFLYSLKLVAKAR WDHGTETECAMHEALHNHYTKSIS KTQK* (SEQ ID NO: 108)	EU372857	
		IgG5⁺ GCCTACACACAGCTCCATCGGCTACCCCTCTGGCCCTGTGGCAGGAGCTGTCTGA TCATTAACGTGGCCTTGGGCTGGCTGGCTCAAGCTACTTCCCAGGACGAGTGAACGTGA CCTGGAACCTGGGGGCGCGAGAGAGTGGGCTGACAGCTTCCCATGTGTGTGGAGCGC TCAGGGCTTACTTCCCTCGAGCAGCGGTGACCTGCCCGGCCACAGCTTGTCCAGCA GTGGCTTCAAGTGCATGTCAACACCCGCGCCACGACCAAGGTGGAGCTGTGTGTTG GAAAAAGACGACAGCTCGATGTCCATATGCCAGGGCTGTGAAGTGGCGGGCCGCTCG GTCTTCTATCTTCCCTCCAAAGCCCAAGACATCTCATGATGTCCGAGCCCGGAGGT CAGCTGGCTGGTGGAGCTGACGAAAGGAGCAGCGGAGTTCAGTTCCTCGTGGTACG TGGAGCGGCAAGAGGTGCACACGCGCGCAGACGACCAAGAGGAGGAGCTTCAACAGC ACTTACCGCGTGGTGAAGCTCTCCCATCCAGCAGGAGGAGTGGCTGAGCGGGAAGGA GTGTGAGTGCAGGTCAACACGAAAGCTCCAGGCGCCATCAGGAGGACCATCTCCA AGGCCAAGGGGTGGTACGAGCGCGGAGGTGTACACCTGCCCGCACCCGCGGAGGA GCTGTTCAGAGGACATAGTCAAGCTTAACCTGGCTGGTCAAAAGCTTGTTCGCGCTTTCAT CGATGTTGAAGTGAATAATCAAGCAAAACAGAGCCAGAAAGGACCATCCGACCCACCC CGCCCCAGGAGCAGGAGCGGACCTACTTCTGTACAGCAAGTTCGCTGGAGAAAG TTCAAGTGGCAGAGTGGAGGATCCATGTGGGCTGATGACAGGAGCTGTGCACAAACCA CTACACCC (SEQ ID NO: 111)	AYNTAPSVYPLAPCRDVSQHNVALG CLVSSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYLSSTYTPPAHLSBK CFTCNVNHATTTKVDLCVQKTKPR CPICPGCEVAGPSVFPPPKDILMS RTRPEVTCVVDVDSKEHAEVQFSWYVD GEEVHTAETRPKEQFNSTYRVSVL PIQHEWLKQKEFECKVNNEDLPQPT RTISKAKGVVRSPEVYTLPPAEELSK SVITLTCLVKSPFPFTHVEWKNGKPE PENAYRTRTPQDEDRITFLYSLKSV KFRWHSQGHCAVMHEALHNHYT (SEQ ID NO: 110)	EU372856	
		IgG6⁺ GCCTCCAAAGACGGCCCATCGGCTACCCCTCTGGCCCTCGGGGAGGAGACGCTGTG GCCTTAACGTGGCCTTGGGCTGGCTGGCTCAAGCTACTTCCCAGGACGAGTGAACGTG ACCTGGAACCTCGGGCCCTGACCACTGGCTGGCTGACATCTTCCCATCCCTCGACAGC GTGAGGGCTTACTTCCCTCAGCAGCAGTGTGACCTGGCGGCGCAGAGCTGTCCAGCA AGAGCTTACAGCTGCATGTGACACCGCGGCGACGACGAGTGCAGTGTGTGTGTT GGACGACATGTCCCATATGCCAGGCTGTGAAGGGCGCGGCGCTCGGTCTTCATCTT CCCTCCAAACCCAGGACACCTCATGATCTCCCGACACCCAGGTCAGCTGGCTGG TGGTATGTGAGTGAGCAAAATCAAGCAAAACAGAGCCAGAAAGGACCATCCGACCCAC GAGGTGACAGCGCCAGCAGGCGGCAAGGAGGCGGAGTTCACAGCACCTACCGTGT GGTCAAGCTGTCTGCCATCCAGCAGGAGCTGGCTGAAGGGGAAGGAGTTCGAGTGCA AGGTCAACCAACAAAGACCTCCGACGCCCATCAACAGGATCATCTTCAAGGCCAAAGGG CCGAGCGCGGAGCGGAGGTATACAGCTGTGCCATCCGCGGAGAGGCTGTCCAGGA GCAAAAGTCAGCATAACCTGCCTGGTCACTGGCTTCAACCCAGCTGACATCGATGTCGAG TGGAGAGCAACGAGCAGCGCGGAGCGGAGGCGCAATTACCGCACCCCGCGCCAGC AGGAGCTGGACGGGACCTACTTCTGTACAGCAAGCTCGCGGTGGACAAAGGCCAGCTGG CAGCGTGGAGACCATTCAGTGTGGGCTGATGACAGGAGCTGTGCACAGCAGCTACAG CC (SEQ ID NO: 113)	APKTAPSVYPLAPCRDTSQPNVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYLSSTVTPARSSSRK FTCNVNHATTTKVDLCVGRPCPI CPACEGNGPSVFPPPKDILMSRTP PQVTCVVDVDSQENPEVQFSWYVDG VEVHTAETRPKEQFNSTYRVSVLPI QHEWLKQKEFECKVNNEDLPQPT SKAKGPSREPVYTLSPSAELSRKSV SITCLVTGFPYDIDVEKNSGQPEPE GNYRTRTPQGDVDGTYFLYSLKLVAK ASWGRDGFCAVMHEALHNHYT (SEQ ID NO: 112)	EU372855	
		IgG6⁺ GCCTCCAAAGACGGCCCATCGGCTACCCCTCTGGCCCTCGGGGAGGAGACGCTGTG GCCTTAACGTGGCCTTGGGCTGGCTGGCTCAAGCTACTTCCCAGGACGAGTGAACGTG ACCTGGAACCTCGGGCCCTGACCACTGGCTGGCTGACATCTTCCCATCCCTCGACAGC GTGAGGGCTTACTTCCCTCAGCAGCAGTGTGACCTGGCGGCGCAGAGCTGTCCAGAA AGTGTTCAGGTGCATGTGACACCGCGGCGACGACGAGTGCAGTGTGTGTGTT GGACGACATGTCCCATATGCCAGGCTGTGAAGGGAGCAGGCGCTCGGTCTTCATCTT CCCTCCAAACCCAGGACACCTCATGATCTCCCGACACCCAGGTCAGCTGGCTGG TGGTATGTGAGTGAGCAAAATCAAGCAAAACAGAGCCAGAAAGGACCATCCGACCCAC GAGGTGACAGCGGAGCTTCCATGATGACAGCAAGCTCGCGGTGGACAAAGGCCAGCTGG CAGCGTGGAGACCATTCAGTGTGGGCTGATGACAGGAGCTGTGCACAGCAGCTACAG CC (SEQ ID NO: 115)	APKTAPSVYPLAPCRDTSQPNVALG CLASSYFPEPVTVTWNSGALTSQVHT FPSVLQPSGLYLSSTVTPARSSSRK FTCNVNHATTTKVDLCVGRPCPI CPACEGNGPSVFPPPKDILMSRTP EVTGVVDVDSQENPEVQFSWYVDGEE VHTAETRPKEQFNSTYRVSVLPQH QDWLKKQKEFECKVNNEDLPQPT AKGPSREPVYTLSPSAELSRKSVI TCLVTGFPYDIDVEKNSGQPEPEG NYRSTRPQDEDRITFLYSLKLVAKA RLQSGGHCAVMHEALHNHYTKSISK T (SEQ ID NO: 114)	EU372853	
Porcine Ig light chain constant region	Ig kappa (CK) variant 1		FP312998	http://www.imgt.org/IMGTrepertoire/index.php?action=LocusGenes&repertoire=genetab&species=Porc&group=IGLC	Schwartz J.C. et al. Immunogenetics, 64, 303-311 (2012). PMID: 22109540
	Ig kappa (CK) variant 2		CU694848		
	Ig lambda (CL) variant 1		CU467669	http://www.imgt.org/IMGTrepertoire/index.php?action=LocusGenes&repertoire=genetab&species=Porc&group=IGLC	
	Ig lambda (CK) variant 2		CU467599		

Species	Ig Domain	Nucleotide Sequence	Amino Acid Sequence	GenBank Accession No.	IMGT Database	Reference
Water buffalo (Scientific Name: <i>Bubalus bubalis</i>)	Water buffalo Ig heavy chain constant region (CH1'CH3)	IgG1? GAGCGGGCTGCACACCTTCGCGGCGCTCTCAGTCC TCCGGGCTGTACTCTCTCAGCAGCAGCGTGACCGCGC CGCGCAGCGGCCACAAAAGCAGACCTTCAACCTGCAA CGTAGCGCCACCGCGCCAGCAGCACCAAGGTGGACAAG GCTGTTGTTGCCCCCTGCAGACGCCGAAACCCCTGTGATTG CTCGCCACCCCGCTGAGCTCCGCGGAGAGCGCTGTGTC TTCTATCTTCCGCAAAACCCAGGACACCTCACAAT CTCTGGAACCTCTGAGGTCAAGTGTGTGGTGGTGGAC GTGGGCGACGATGACCCCGAGGTGAAGTTCTCTCTGGT TGGTGGAACGATGTGGAGGTAAACAGCGCCAGGACGAA GCCAAGAGAGAGGAGCGATTCAACAGCAGCTACCGCGTG GTGACGCGCCTGGCCATCCAGCACACGAGCTGGAGT GAGGAAAGGAGTTCAGTGTCAAGGTCTACAATGAAGGC CTCCAGCGCCCATCGTGAGGACCATCTCCAGGACCA AAGGGCAGCGCGGAGCGCGCAGGTGTACGCTCTGGC CCGACCCGAGGACGAGGTGAGCAAAAGAGCGTGCAGC ATCACTTGGATGTTCACTGGCTTCTACCGCAGACTACAT CGCCGTAGAGTGGCAGAAAGATGGGCAGCGCTGAGTCA GAGGACAAATATGGCAGCAGCCCGCGCCAGCTGGACA GGGATGGCTCTCACTTCTCTGACAGCAGGCTCAGGCT GAACAAGAACAGCTGGGAAAGAGGAGGCGCTACAGC TGTGTAGTGATGCGATGAGGC (SEQ ID NO: 119)	SGVHTFPAVLQSSGLYSLSSTVTAPAS ATKSQTFCTNVAHPASSTKVDKAVVP PCRPKPCDCPPPELPGGPSVFIFPPK PKDRLTISGTPVTVVVDVGHDDPEV KFSWFDVDEVTARTKPREEDFNSTY RVVSLALPIQHNDWTGKREKFKAVYNEG LPAPIVRTISRTKGAREPQVYVLAAPP QDELKSTVSTVMTVMGTGFYPDYIAVEW QKDGQPESEDKYGTTPQLDSDGSYF LYSRLRVNKNWGEAGGAYTCVVMHE (SEQ ID NO: 118)	NW_00569090 3	Not registered	None
	IgG2?	GCCTCCATCACAGCCCGGAAAGTCTACCGTCTGACTTC TTCCGCGGGGAAACCTCCAGCTTCAGCGTGCAGCGT GGCTGCTGCTGCTCCAGCTACATGCCGAGCGCGGTGA CCGTGACCTGGAACCTGGGTCGCCCTGAAGAGCGCGGT GCACACCTTCCGCGCGCTCTCTCACTCTCTGGGCTC TACTCTCTGAGCAGCAGGTGACCGCGCGCGCAGCG CCACAAAAGCGCAGCCTTCACCTGGAACGTAGCGCAC CCGCGCAGCAGCAGCAAGGTGGACACGCGTGTGGGT TCTCCAGTGACTGCTGCAAGTTTCTCAAGCCTTGTGTG AGGGGACCATCTGCTTCTATCTTCCGCGCAAAACCCAA AGACACCGCTGATGATCACAGGAAATCCGAGGTGCACAT GTGTGGTGGTGAGCTGGGCGGGGATAACCCGAGGT GCAGTTCTCTGCTGCTGCTGCTGCTGCTGCTGCTGCT ACGGGCGAGTCSAAGCGCGAGAGGAGGAGCATTCACCA GCACCTACCGCGTGGTCAGCACCGCTGCCATCCAGCA CAATGACTGGACTGGAGGAAAGGAGTTCAAGTGGCAAG GTCAACAAAGGAGGCTCCAGCGCCCATCGTGAGGA CCATCTCCAGGAGCAGAAAGGCGCGCGGAGCGCGCA GGTGTAGCTCTCTGCGCCACCGCCAGGAAGAGCTCAGC AAAAGCAGCGTGCAGCTCACTTGCATGGTCACTGGCTT CTACCCAGACTACATCGCGGTAGAGTGGCATAGAGACG GGCAGGCTGAGTGGAGGACAGATACCGGACGAGCCCG GCGCGAGGCTGGAGAGCGAAGGCGCGCGCGCGCGCG GGTGTAGCTCTCTGCGCCACCGCCAGGAAGAGCTCAGC AAAAGCAGCGTGCAGCTCACTTGCATGGTCACTGGCTT CTACCCAGACTACATCGCGGTAGAGTGGCATAGAGACG GGCAGGCTGAGTGGAGGACAGATACCGGACGAGCCCG GCGCGAGGCTGGAGAGCGAAGGCGCGCGCGCGCGCG AGCAGGCTCAAGGTGAACAGAACAGCTGGCAAGAAAG GAGGCGCCTACACGTGTGTAGTGATGCATGAGGC (SEQ ID NO: 121)	ASITAPKVPLYTSRGETSSSTVTLGQ LVSSYMPPEVTVVWNSGALKNSQVHTF PAVLQSSGLYSLSSTVTAPASATKSGT FTCNVAHPASSTKVDVAVGFSDDCK FPKPVGRPSVFIFPPKPKDLMITGNP EVTCTVVDVGRDNPEVQFSWVGDE VHTGRSKPREQFNSTYRVVSTLPIQH NDWTGKREKFKCKVNNKGLPAPIVRTIS RTKGQAREPQVYVLAAPPPEELSKSTVS YTCMVTGFYPDYIAVEWHDRQAESE KYRTTPQLDSDGSYFLYSRLKNKNS WGEAGYATCVMHSE (SEQ ID NO: 120)	NW_00576614 3		
	IgG3?	GCCTCCACACAGCCCGGAAAGTCTACCGTCTGGCAT CCAGCTGCGGGGACAGCTCCAGCTCCACCGTGACCGT GGGCTGCTGCTGCTCCAGCTACATGCCGAGCGCGGTG ACCGTGACCTGGAACCTGGGTCGCTGGAAGAACGGGG TGACACACCTTCCGCGCGCTCGCGAGTCTCTCGGCT CTACTCTCTCAGCAGCATGTGACCATGCCACAGCAGCA CCGCGAGGAACCCAGACCTTCACCTGCAACGTAGCCCA CCCGCGCAGCAGCAACCAAGTGGACAGCGAGCTGTCACT GCAAGGCTATCCGGTCCGAGACAGCAGGACGACGCTA TCCATCTGTAAAACCCCAACCGAGGAGCCAGAGAT GAAAAGACACCGCTGCCAGTGTCCCAAATGCCCGAAAC CTTGGAGGAGCTGTGCTGTTCTATCTTCCACCGCAAAC CCAGGAGACACCTCACAACTCTCTGGAACGCCCGAGGT CACGTGTGTGTGGTGGTGGAGCTGGGCAGGATGACGCC GAGTGTGCACTTCTGCTGCTGCTGCTGCTGCTGCTGCT TGACACACAGCCAGGATGAAGCGCAAGAGAGGAGCAGTT CAACAGCACCTACCGCGTGTGCTGAGCGCCTGCCCATC CAGCAGCAGGAGCTGCGTGGGGGAAAGGAGTTCAAGT GCAAGGTTCAGCAACAAAGGCTTCGCGGCGCCCATCTG GAGGACCATCTCCAGCAGCAAGGCGAGGCGCGCGGAG CCACAGGTGTATGCTCTGGCCCAACCCCGGGAAGAGC TCAGCAAAAGCAGCGCTCAGCCTCACTGCTAATCACCC GGCTTCTACCCAGAGAGGATGAGCGTGGAGTGGCAGA GAAATGGGACAGCGTGAATCAGAGGACAAAGTACGACAC GACCGCACCGCAGCTGCGAGCGTGAAGGCGCGCGCTCT CTGTACAGCAGGCTCAGGCTGAACAGGAGCAGCTGGC AGGAAGGAGACCACTACAGCTGTGCAGTGATGCATGAA GCTTTACGGAATCACTACAAAGAGAAAGCCCATCTCGAG TGTCTCGGGTAAATGA (SEQ ID NO: 123)	ASTTAPKVPLYLASSCGDTSSSTVTLGC LVSSYMPPEVTVVWNSGALKNVHTF PAVRSSGLYSLSMVMTPTSTAGTQ TFTCNVAHPASSTKVDVAVTARHPVP KTPEPIHPKPTQEPREKTPCGCP KCEPLGLSVFIFPPKPKDRLTISGTP EVTCTVVDVGGDDPEVQFSWVVDVE VHTARMKPREEQFNSTYRVVSLALPIQH QDWLREKFKCKVNNKGLPAPIVRTISR TKGQAREPQVYVLAAPPREELSKSTLSL TCLITGFYPEVDVWQNRGQPESEDK YHTTPQLDADGSYFLYSRLRVNRSSW QEGDHYTCAMVHEALRNHYKEKPIRS PKK* (SEQ ID NO: 122)	NW_00578420 6		
Water buffalo Ig light chain constant region (CL)	Ig lambda?	CAGCCCAAGTCCGACACCTCAGTCACCTGTTCCAC CCTCCAGGAGGAGCTCAGCGGCAACAGGCGCACCT GGTGTGTCTCATCAGCGACTTCTACCCGGGTAGCATGA CCGTGGCCAGGAAGGAGCAGCGGACCATCAACCG GAACGTGGAGACCAACCGCGGCTCCAAACAGAGCAAC AGCAAGTACCGCGGCGCAGCAGTACCTGAGGCTGAGCG GCGAGGAGTGAATCGAAAGGAGGATTACAGCTGGCA GGTCAACGACAGGAGGAGGAGCAGCGTGACAAAGACAGTG AAGCCCTCAGAGTGTGTTTAG (SEQ ID NO: 117)	QPKSPASVTLFPSTELSANKATLVC LISDFYPSMTVARADGSTITRNVETT RASKGNSKYAASSYLSLTGSEWKS SYSCVEHTGSTVTKVPSECS* (SEQ ID NO: 116)	NW_00569078 6	Not registered	None

The amino acid sequences as shown in SEQ ID NOS: 8 to13, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120 and 122 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.

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 the light chain sequence (variable region sequence and constant region sequence) and the heavy chain sequence (variable region sequence and constant region sequence) of the anti-PD-L1 antibody of the present invention. 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. In the synthesis of the artificial gene, codons of the nucleotide sequence may be optimized.

The present invention provides a DNA encoding an anti-PD-L1 antibody comprising (a) a light chain comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) and (b) a heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSGGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5). The present invention also provides a DNA encoding a light chain of an anti-PD-L1 antibody comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) (the DNA of (a')). Further, the present invention provides a DNA encoding a heavy chain of an anti-PD-L1 antibody comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSGGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5) (the DNA of (b')).

For (a) a light chain comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) and (b) a heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSGGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5), reference should be had to the foregoing description. A 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 this DNA.

The present invention also provides a vector comprising the above-mentioned DNA encoding an anti-PD-L1 antibody.

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) is 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 a 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).

It is also possible to prepare the anti-PD-L1 antibody of the present invention by culturing a hybridoma which may be prepared by the method disclosed in the literature (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K, Immunology. 2014 Aug;142(4):551-61). A hybridoma producing anti-PD-L1 antibody 6C11-3A11 is stored at the laboratory of the present inventors (Laboratory of Infectious Diseases, Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University).

The PD-L1 antibody of the present invention may be used for detecting PD-L1. Therefore, the present invention provides a composition for detecting PD-L1, comprising the PD-L1 antibody as an active ingredient.

Detection of PD-L1 may be performed by such methods including, but are not limited

to, immunohistochemical staining, immunocytochemical staining, flow cytometry, enzyme linked immunosorbent assay (ELISA) and Western blotting.

Analytes for detection may be exemplified by samples such as tissues or body fluids taken from organisms (e.g., blood (whole blood, plasma, serum, or specific cell such as erythrocyte, leukocyte or lymphocyte), urine, saliva, etc.); cell culture; and cultured cells (established cell lines, primary cultured cells, subcultured cells, etc.). The source of such analytes is not particularly limited. Examples include rat, canine, ovine, goat, porcine, feline, human, equine, bovine, water buffalo, yak, rabbit, mouse, hamster, and guinea pig.

The PD-L1 antibody of the present invention may be labeled with radioisotopes, enzymes, luminescent substances, fluorescent substances, biotin, or the like. If reaction with a primary antibody (the anti-PD-L1 antibody of the present invention) which specifically binds to a target molecule (PD-L1) is followed by reaction with a secondary antibody which binds to the primary antibody so as to detect the target molecule, it is suitable to label the secondary antibody.

Since PD-L1 is strongly expressed in cancer cells and virus-infected cells, the composition of the present invention may be used for diagnosis of cancers and/or infections. Usually, the amount (concentration) of PD-L1 in an analyte is determined based on the amount (concentration) of the complex of PD-L1 and anti-PD-L1 antibody. When the amount (concentration) of PD-L1 in the analyte is high compared to negative control (e.g., healthy surrounding tissue (connecting tissue, blood vessels, etc.)), the analyte may be diagnosed as suffering cancer and/or infection. Alternatively, if PD-L1 is detected in the analyte, the analyte may be diagnosed as suffering cancer and/or infection.

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, John'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 composition of the present invention can be used to select subject animals suitable for therapy using an anti-PD-L1 antibody. For example, animals satisfying the following two points may be considered as candidate animals.

1. A case diagnosed as suffering cancer (such as melanoma) or infection in pathological examination
2. A case found positive for anti-PD-L1 antibody

Negative control may be healthy surrounding tissue (connecting tissue, blood vessels, etc.), and positive control may be a case of cancer (such as melanoma) or infection. Basically, animals with a tumor which is positive in immunohistochemical staining of almost all regions may be subjected to clinical trial.

Subject animals are not particularly limited and may include rat, canine, ovine, goat, porcine, feline, human, equine, bovine, water buffalo, yak, rabbit, mouse, hamster, and guinea pig.

The composition of the present invention may further comprise reagents for detecting labels, diluents, lavage fluids, written instructions describing criteria for diagnosis/selection, and so on.

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]

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 infections and tumors in various animals. In the subject Example, an anti-bovine PD-L1 monoclonal antibody was prepared by immunizing rats, and then a clone (6C11-3A11) capable of detecting canine PD-L1 was selected. Further, the present inventors performed immunohistochemical staining to examine whether or not this anti-bovine PD-L1 antibody 6C11-3A11 would be useful for detecting PD-L1 in canine malignant tumors (such as melanoma) and porcine/ovine infections.

2. Materials and Methods

2.1 Rat Anti-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 in the footpad with this recombinant protein, and hybridomas were established by the iliac lymph node method. As a result, a plurality of hybridomas producing rat anti-bovine PD-L1

monoclonal antibodies were obtained (Ikebuchi R, Konnai S, Okagawa T, Yokoyama K, Nakajima C, Suzuki Y, Murata S, Ohashi K. Immunology 2014 Aug.; 142(4):551-561). Rat anti-bovine PD-L1 antibody 6C11-3A11 is one of the monoclonal antibodies established from the above-described immunized rat.

2.2 Identification of Full-Length Canine PD-L1 Gene

To determine the full length of canine PD-L1 cDNA, PCR primers were first designed based on the putative nucleotide sequence of canine PD-L1 already registered at The National Center for Biotechnology Information (NCBI) (GenBank accession number; XM_541302). Briefly, primers to amplify the inner sequence of the open reading frame (ORF) of this gene were designed (cPD-1 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 sequence of full-length PD-L1 cDNA, primers (cPD-L1 5' GSP and 3'GSP) were designed based on the canine PD-L1 cDNA sequences determined above. 5'-RACE and 3'-RACE were then performed using, respectively, the 5'-RACE system for rapid amplification of cDNA ends and 3'-RACE system for rapid amplification of cDNA ends (Invitrogen). The resultant gene fragments of interest were sequenced as described above (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-L1 inner F): ATGAGAATGTTTAGTGTCTT (SEQ ID NO: 22)

Primer (cPD-L1 inner R): TTATGTCTCTTCAAATTGTATATC (SEQ ID NO: 23)

Primer (cPD-L1 5'GSP): TTTTAGACAGAAAGTGA (SEQ ID NO: 24)

Primer (cPD-L1 3'GSP): GACCAGCTCTTCTTGGGGAA (SEQ ID NO: 25)

2.3 Preparation of Canine PD-L1 Expressing COS-7 Cells

For preparing a canine PD-L1-EGFP expression plasmid, PCR was performed using a synthesized beagle PBMC-derived cDNA as a template and primers designed by adding *Bgl*II and *Eco*RI recognition sites on the 5' side (cPD-L1-EGFP F and R). The resultant PCR products were digested with *Bgl*II (New England Biolabs) and *Eco*RI (Takara), and then purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics), followed by cloning into pEGFP-N2 vector (Clontech) similarly treated with restriction enzymes. 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 pEGFP-N2-cPD-L1.

Primer (cPD-L1-EGFP F): GAAGATCTATGAGAATGTTTAGTGTC (SEQ ID NO: 26)

Primer (cPD-L1-EGFP R): GGAATTCTGTCTCTTCAAATTGTATATC (SEQ ID NO: 27)

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-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 (canine cPD-L1-EGFP expressing cell and EGFP expressing cell). In order to confirm the expression of 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 Cross-Reactivity of Rat Anti-Bovine PD-L1 Antibody 6C11-3A11 with Canine PD-L1

In order to confirm that rat anti-bovine PD-L1 antibody 6C11-3A11 specifically binds to canine PD-L1, flow cytometry was performed using the canine cPD-L1-EGFP expressing cell or the EGFP expressing cell prepared in 2.3 above. To 2×10^5 - 1×10^6 cells, 10 µg/ml of anti-bovine PD-L1 antibody 6C11-3A11 was added and reacted for 30 min at room temperature. After washing, the antibody binding to cell surfaces was detected with Allophycocyanine-labeled goat anti-rat Ig antibody (Beckman Coulter). For the analysis, FACS Verse (Becton, Dickinson and Company) was used. As a negative control antibody, rat IgG2a (κ) isotype control (BD Bioscience) was used. For every washing operation and dilution of antibodies, 10% inactivated goat serum-supplemented PBS was used. The results are shown in Fig. 1.

2.5 CDR Analysis of Rat Anti-Bovine PD-L1 Antibody 6C11-3A11

The heavy chain and the light chain genes of rat anti-bovine PD-L1 antibody 6C11-3A11 were identified from a hybridoma producing the antibody by RACE method. The complementarity-determining regions (CDRs) of rat anti-bovine PD-L1 antibody 6C11-3A11 were determined using NCBI IGBLAST (<http://www.ncbi.nlm.nih.gov/igblast/>). The results are shown in Fig. 2.

2.6 Immunohistochemical Staining of Canine Tumor Tissues and Ovine/Porcine Infected

Tissues

In order to confirm that rat anti-bovine PD-L1 antibody 6C11-3A11 is applicable to PD-L1 immunohistochemical staining of canine tumors, formalin-fixed and paraffin-embedded canine tumor samples were immunohistochemically stained. According to conventional methods, the resultant samples were deparaffinized and then subjected to microwave treatment (5 min, twice) in citrate buffer. Subsequently, the samples were reacted with PD-L1 antibody 6C11-3A11 (400-fold dilution) for 30 min and then with Simple Stain Mouse MAX-PO (Rat) (Nichirei Bioscience) for 30 min. For coloring, diaminobenzidine (DAB) was reacted for 10 min.

The results are shown in Figs. 3, 4, 5-1, 5-2, 6 and 7.

Anti-MelanA antibody, the only commercially available antibody specific to melanoma, stained tumor cells very weakly (Fig. 3, left). On the other hand, the PD-L1 antibody (6C11-3A11) established by the present inventors stained tumor cells very strongly (Fig. 3, Right). The PD-L1 antibody (6C11-3A11) was capable of staining almost all cases of melanoma.

In canine melanoma, tumor cells were found diffusely positive for the PD-L1 antibody (6C11-3A11). (Positive number/tested number = 12/12; positive rate 100%)

In canine lymphoma, tumor cells were found diffusely positive for the PD-L1 antibody (6C11-3A11). In canine osteosarcoma, some tumor cells were stained intracellularly. In canine renal cell carcinoma, tumor cells were found diffusely positive in various tissue types.

In a case of ovine listeriosis, a PD-L1 staining image of a brain lesion of ovine listeriosis showing neurologic symptoms is shown in Fig. 6, left panel. In an enlarged photograph of this image, expression of PD-L1 was observed in macrophages infiltrating into brain lesions (Fig. 6, Right).

In a case of porcine circovirus type 2 infection, PD-L1 was stained with lymphoid follicles, and virus was stained in these cells (Fig. 7, Left).

In a case of porcine mycoplasma pneumonia, a great number of macrophages infiltrated pulmonary lesions, and PD-L1 was stained in these infiltrating cells (Fig. 7, Right).

As described so far, anti-bovine PD-L1 antibody 6C11-3A11 may be used for detecting PD-L1 in various canine tumors (such as malignant melanoma) and ovine/porcine infections by immunohistochemical staining. This suggests the possibility of using anti-bovine PD-L1 antibody 6C11-3A11 for diagnosis in a multiple-animal and a multiple-disease manner.

[Example 2]

1. Introduction

Monoclonal antibodies may be produced by culturing hybridomas and purifying antibodies from the resultant culture supernatants. Alternatively, when the nucleotide sequence of an antibody of interest has been identified, a cell expressing the antibody may be prepared by transfecting cultured cells with a vector for expressing the nucleotide sequence; the thus prepared antibody expressing cell may be used as a substitute for hybridoma. In the subject Example, a method will be illustrated below in which an antibody is produced by a protein expression system using an expression vector and a mammalian cell.

2. Materials and Methods

2.1 Preparation of Rat Anti-Bovine PD-L1 Antibody 6C11-3A11 Expression Vector

Based on the nucleotide sequence of rat anti-bovine PD-L1 antibody 6C11-3A11 identified in 2.5 of Example 1 above, gene synthesis is performed so that *NotI* restriction enzyme recognition site, KOZAK sequence, antibody's light chain sequence, poly-A addition signal sequence (PABGH), promoter sequence (PCMV), *SacI* restriction enzyme recognition site, intron sequence (INRBG), KOZAK sequence, antibody's heavy chain sequence and *XbaI* restriction enzyme recognition site will be located in this order. In this case, codons of the antibody gene may have been optimized in advance depending on the type of the cell that is to express the gene. The synthesized gene strand is incorporated into an expression vector pDC6 (kindly provided by Prof. S. Suzuki, Research Center for Zoonosis Control, Hokkaido University) at the cloning site (*NotI* and *XbaI* restriction enzyme recognition sequences located downstream of PCMV and between INRBG and PABGH) using restriction enzyme recognition sequences so that the above-listed sequences will be located in the above-mentioned order to thereby construct a rat anti-bovine PD-L1 antibody expressing vector pDC6.

2.2 Expression of Rat Anti-bovine PD-L1 Antibody 6C11-3A11

The rat anti-bovine PD-L1 antibody expressing vector pDC6 as prepared in 2.1 above is transfected into CHO-DG44 cells (CHO-DG44(dfhr⁻/)) which are dihydrofolate reductase deficient cells, and high expression clones are selected by dot blotting. For increased expression, gene amplification treatment may be performed by adding load on cells in a medium containing 60 nM, 250 nM or 1000 nM methotrexate (Mtx). The thus prepared cells

stably expressing rat anti-bovine PD-L1 antibody 6C11-3A11 are transferred to Mtx-free Opti-CHO medium. By culturing those cells under shaking for 14 days (125 rpm, 37°C, 5% CO₂), a culture supernatant containing the antibody of interest can be obtained. The antibody in the culture supernatant may be purified by known methods such as affinity chromatography or ion exchange chromatography for use in various experiments.

[Example 3]

1. Introduction

For the purpose of establishing a novel diagnosis method for tumor diseases, a rat-human chimeric anti-PD-L1 antibody is obtained in the subject Example by culturing Chinese hamster ovary cells (CHO cells) that will express a chimeric antibody gene in which the variable region gene of rat anti-bovine PD-L1 antibody 6C11-3A11 is combined with the constant region gene of human immunoglobulin (IgG4) .

2. Materials and Methods

2.1 Preparation of Rat-Human Chimeric Anti-PD-L1 Expression Vector (Fig. 10)

Hereinbelow, a rat-human chimeric anti-PD-L1 antibody is established using rat anti-bovine PD-L1 monoclonal antibody 6C11-3A11 as its variable region.

Briefly, heavy chain and light chain variable region genes were identified from a hybridoma producing the rat anti-bovine PD-L1 antibody 6C11-3A11. Further, a nucleotide sequence was prepared by linking the heavy chain and light chain variable region genes of the above rat antibody to the constant region of heavy chain IgG4 and the constant region of light chain Kappa of a known human antibody, respectively. After codon optimization, gene synthesis is 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 will be located in this order. The synthesized gene strand is incorporated into the expression vector pDC6 (kindly provided by Prof. S. Suzuki, Research Center for Zoonosis Control, Hokkaido University) at the cloning site (*NotI* and *XbaI* restriction enzyme recognition sequences located downstream of PCMV and between INRBG and PABGH) using restriction enzyme recognition sequences so that the above-listed sequences will be located in the above-mentioned order (Fig. 10). Thus, a rat-human chimeric anti-PD-L1 antibody expressing vector is constructed. This expression vector is

transfected into CHO-DG44 cells (CHO-DG44(dfhr^{-/-})) which are dihydrofolate reductase deficient cells, and high expression clones are selected by dot blotting. For increased expression, gene amplification treatment may be performed by adding load on cells in a medium containing 60 nM, 250 nM or 1000 nM methotrexate (Mtx). The thus prepared cells stably expressing rat-human chimeric anti-PD-L1 antibody 6C11-3A11 are transferred to Mtx-free Opti-CHO medium. By culturing those cells under shaking for 14 days (125 rpm, 37°C, 5% CO₂), a culture supernatant containing the antibody of interest can be obtained. The antibody in the culture supernatant may be purified by known methods such as affinity chromatography or ion exchange chromatography for use in various experiments.

[Example 4]

1. Introduction

With respect to PD-L1 in canine tumors, a detection method by immunohistochemical staining with rat anti-bovine PD-L1 antibody 6G7-E1 was previously established, and the expression profiles in various tumors have been reported (Maekawa N, Konnai S, Okagawa T, Ikebuchi R, Izumi Y, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Kato Y, Murata S, Ohashi K. PLoS One. 2016 Jun 11(6): e0157176). In the subject Example, in order to examine whether rat anti-bovine PD-L1 antibody 6C11-3A11 is more useful than existing anti-PD-L1 antibody 6G7-E1 in expression analysis of PD-L1 in canine tumors, immunohistochemical staining of various canine tumors was performed to thereby directly compare the PD-L1 detection sensitivities of 6G7-E1 and 6C11-3A11.

2. Materials and Methods

2.1 Comparison by Flow Cytometry Using Canine PD-L1-EGFP Stably Expressing CHO-DG44 Cells (Fig. 11)

First, in order to prepare canine PD-L1 membrane expressing cells, 2.5 µg of canine PD-L1-EGFP expression plasmid (pEGFP-N2-cPD-L1) prepared in 2.3 of Example 1 or pEGFP-N2 (negative control) was introduced into 4x10⁶ 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 µg/ml, GlutaMAX supplement (Life Technologies) 20 ml/L, and 10% Pluronic F-68 (Life Technologies) 18 ml/L, followed by selection of stably expressing cells and cloning by limiting dilution. The thus prepared canine PD-L1 membrane expressing cell or EGFP expressing cell was reacted with rat anti-bovine PD-L1 antibody 6C11-3A11 or 6G7-E1 at

room temperature for 30 min. After washing, antibodies binding to cell surfaces were detected with Allophycocyanine-labeled goat anti-rat Ig antibody (Beckman Coulter). For analysis, FACS Verse (Becton, Dickinson and Company) was used. As a negative control, rat IgG2a (κ) or IgM (κ) isotype control (BD Bioscience) was used. For every washing operation and dilution of antibodies, 10% inactivated goat serum-supplemented PBS was used.

The results are shown in Fig. 11. Rat anti-bovine PD-L1 antibodies 6C11-3A11 and 6G7-E1 bound specifically to canine PD-L1 membrane expressing cells. The resultant fluorescence intensity was higher with 6C11-3A11 than with 6G7-E1, suggesting that 6C11-3A11 is an antibody with higher affinity.

2.2 Comparison of the Detection Sensitivities of Both Antibodies in PD-L1 Expression Analysis of Various Canine Tumors (Immunohistochemical Staining)

Using samples of canine skin squamous cell carcinoma (n=5), nasal adenocarcinoma (n=5), transitional cell carcinoma (n=5), anal sac gland carcinoma (n=5), soft tissue sarcoma (n=5) and osteosarcoma (n=5), immunohistochemical staining with rat anti-bovine PD-L1 antibody 6C11-3A11 was performed according to the method described in 2.6 of Example 1. With rat anti-bovine PD-L1 antibody 6G7-E1, immunohistochemical staining was performed in the same manner using sections derived from the same analytes. The final concentration of 6G7-E1 used on this occasion was 10 μ g/ml, and biotin-labeled goat anti-rat IgM antibody (Jackson ImmunoResearch Laboratories) was used as a secondary antibody.

The results are shown in Figs. 12 and 13. While specific signals were not observed in squamous cell carcinoma, nasal adenocarcinoma, transitional cell carcinoma, anal sac gland carcinoma and soft tissue sarcoma upon staining with 6G7-E1, satisfactory positive reactions were obtained upon staining with 6C11-3A11. On the other hand, specific signals were also obtained with 6G7-E1 in osteosarcoma but staining with 6C11-3A11 provided higher signal intensities. The PD-L1 positive rate of these tumors obtained by 6C11-3A11 staining was 100% (5 out of 5 cases) in all of the above-listed tumor species excepting soft tissue sarcoma which turned out to be PD-L1 positive at a rate of 80% (4 out of 5 cases).

Subsequently, samples of oral malignant melanoma (n=17), mammary adenocarcinoma (n=10), histiocytic sarcoma (n=10), diffuse large B-cell lymphoma (n=10) and transmissible venereal tumor (n=4) were immunohistochemically stained with 6C11-3A11 to analyze PD-L1 expression therein.

The results are shown in Fig. 14. The PD-L1 positive rate was 100% in oral

malignant melanoma (17 out of 17 cases), 100% in mammary adenocarcinoma (10 out of 10 cases), 20% in histiocytic sarcoma (2 out of 10 cases), 20% in diffuse large B-cell lymphoma (2 out of 10 cases) and 0% in transmissible venereal tumor (0 out of 4 cases).

The above-described results revealed that 6C11-3A11 is superior to the existing anti-PD-L1 antibody 6G7-E1 in the detection of canine PD-L1.

[Example 5]

1. Introduction

Johne's disease is a bovine chronic infection caused by *Mycobacterium avium* subsp. *paratuberculosis*. In cattle affected with Johne's disease, PD-L1 expression has been confirmed in *M. avium* subsp. *paratuberculosis*-infected cells in ileal lesions which are a localized site of infection with this bacterium (Okagawa T, Konnai S, Nishimori A, Ikebuchi R, Mizorogi S, Nagata R, Kawaji S, Tanaka S, Kagawa Y, Murata S, Mori Y and Ohashi K. Infect Immun, 84:77-89, 2016). In the subject Example, immunohistochemical staining of ileal lesions of cattle with Johne's disease was performed in order to examine whether rat anti-bovine PD-L1 antibody 6C11-3A11 could be used for detecting bovine PD-L1 or not.

2. Materials and Methods

2.1. Construction of Bovine PD-L1 Expressing Cells

The nucleotide sequence of the full-length cDNA of 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) was determined. Based on the resultant nucleotide sequence, bovine PD-L1 membrane expressing cells were prepared. First, for preparing a bovine PD-L1 expressing plasmid, PCR was performed using a synthesized bovine PBMC-derived cDNA as a template and primers having *NheI* and *XhoI* recognition sites added on the 5' side (boPD-L1-EGFP F and R). The PCR products were digested with *NheI* (Takara) and *XhoI* (Takara), purified with FastGene Gel/PCR Extraction Kit (NIPPON Genetics) and cloned into pEGFP-N2 vector (Clontech) that had been subjected to similar restriction enzyme treatments. 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 pEGFP-N2-boPD-L1.

Primer (boPD-L1-EGFP F): CTAGCTAGCACCATGAGGATATATAGTGTCTTAAC (SEQ ID NO: 124)

Primer (boPD-L1-EGFP R): CAATCTCGAGTTACAGACAGAAGATGACTGC (SEQ ID

NO: 125)

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 4x10⁶ 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 µg/ml, GlutaMAX supplement (Life Technologies) 20 ml/L, and 10% Pluronic F-68 (Life Technologies) 18 ml/L; thereafter, selection was performed simultaneously with cloning by limiting dilution (bovine PD-L1 expressing cell and EGFP expressing cell). In order to confirm the expression of bovine PD-L1 in the thus prepared bovine PD-L1 expressing cell, intracellular localization of EGFP was visualized with an inverted confocal laser microscope LSM700 (ZEISS).

2.2. Binding Specificity of Rat Anti-Bovine PD-L1 Antibody 6C11-3A11 to Bovine PD-L1

It was confirmed by flow cytometry that rat anti-bovine PD-L1 antibody 6C11-3A11 specifically binds to the bovine PD-L1 expressing cell (described above). First, rat anti-bovine PD-L1 antibody 6C11-3A11 or rat IgG2a (κ) isotype control (BD Biosciences) as a negative control was reacted with the bovine PD-L1 expressing cell or the EGFP expressing cell (negative control) at room temperature for 30 min. After washing, APC-labeled anti-rat Ig goat antibody (Southern Biotech) was reacted at room temperature for 30 min. After washing, antibodies bound to cell surfaces were 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 results are shown in Fig. 15. It was revealed that rat anti-bovine PD-L1 antibody 6C11-3A11 binds specifically to the bovine PD-L1 expressing cell.

2.3. Immunohistochemical Staining Using Tissue Samples from Infected Cattle

In order to confirm that rat anti-bovine PD-L1 antibody 6C11-3A11 is applicable to PD-L1 immunohistochemical staining of bovine tissues, immunohistochemical staining was performed with formalin-fixed, paraffin-embedded bovine tissue samples. Briefly, ilium tissue blocks from cattle which naturally developed Johne's disease (#1, presenting clinical symptoms of Johne's disease such as diarrhea and severe emaciation), cattle experimentally infected with *M. avium* subsp. *paratuberculosis* (#65, clinical symptoms such as shedding of *M. avium* subsp. *paratuberculosis* and diarrhea were observed; Okagawa T, Konnai S, Nishimori A, Ikebuchi R, Mizorogi S, Nagata R, Kawaji S, Tanaka S, Kagawa Y, Murata S,

Mori Y and Ohashi K. Infect Immun, 84:77-89, 2016) and uninfected control cattle (C#6) (the blocks kindly provided by Dr. Yasuyuki Mori, National Institute of Animal Health, National Agriculture and Food Research Organization) were used for staining. According to conventional methods, the stained samples were deparaffinized and then subjected to microwave treatment (5 min, twice) in citrate buffer. Subsequently, the samples were reacted with rat anti-bovine PD-L1 antibody 6C11-3A11 (400-fold dilution) for 30 min and then with Simple Stain Mouse MAX-PO (Rat) (Nichirei Bioscience) for 30 min. Finally, the samples were reacted with diaminobenzidine (DAB) for 10 min for coloring, followed by observation with an optical microscope.

The results are shown in Fig. 16. Rat anti-bovine PD-L1 antibody 6C11-3A11 detected expression of PD-L1 in *M. avium* subsp. *paratuberculosis*-infected cells (confirmed by Ziehl-Neelsen staining) in ileal lesions of cattle #1 that naturally developed Johne's disease and experimentally infected cattle #65 (Fig. 16a, b). On the other hand, PD-L1 was not expressed in the ileum of uninfected cattle (C#6), so reaction of rat anti-bovine PD-L1 antibody 6C11-3A11 (non-specific reaction) was not recognized (Fig. 16a).

As described above, it was shown that rat anti-bovine PD-L1 antibody 6C11-3A11 can be used for detecting PD-L1 in bovine tissues by immunohistochemical staining.

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 diagnosis of cancers and/or infections. Further, the anti-PD-L1 antibody of the present invention is also applicable to selection of subject animals suitable for therapy with anti-PD-L1 antibodies.

SEQUENCE LISTING FREE TEXT

<SEQ ID NO: 1>

SEQ ID NO: 1 shows the amino acid sequence of CDR1 of the light chain variable region (VL) of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

KSISKY

<SEQ ID NO: 2>

SEQ ID NO: 2 shows the amino acid sequence of CDR3 of the VL of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

QQHNEYPLT

<SEQ ID NO: 3>

SEQ ID NO: 3 shows the amino acid sequence of CDR1 of the heavy chain variable region (VH) of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

GYTFTDYI

<SEQ ID NO: 4>

SEQ ID NO: 4 shows the amino acid sequence of CDR2 of the VH of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

INPDSSGN

<SEQ ID NO: 5>

SEQ ID NO: 5 shows the amino acid sequence of CDR3 of the VH of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

ARGITMMVVISHWKDFD

<SEQ ID NO: 6>

SEQ ID NO: 6 shows the amino acid sequence of the VL of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

MRVQIQFWGLLLLWTSGIQCDVQMTQSPSNLAASPGESVSINCKASKSISKYLAWYQ
QKPGKANKLLIYSGSTLQSGTPSRFSGSGSGTDFTLTIRNLEPEDFGLYYCQQHNEYPL
TFGSGTKLEIK

<SEQ ID NO: 7>

SEQ ID NO: 7 shows the amino acid sequence of the VH of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

MGWICHIFLVAIATGAHSQVKLLQSGAALVKPGDSVKMSCKASGYTFTDYIHHWVKQS
HGKSLEWIGYINPDSSGNNYNEKFKSKATLTVDKSSSTAYMEFSRLTSEDSAIYYCAR
GITMMVVISHWKDFDWGPGTMVTVSS

<SEQ ID NO: 8>

SEQ ID NO: 8 shows the amino acid sequence of the light chain (kappa chain) constant region of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

RADAAPTVSIFPPSTEQLATGGASVVCLMNNFYPRDISVKWKIDGTERRDGVLD SVT
DQDSKDSTYSMSSTLSLTKADYESHNLTYCEVVHKTSSSPVVKSFNRNEC*

<SEQ ID NO: 9>

SEQ ID NO: 9 shows the amino acid sequence of the heavy chain constant region (CH) of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

AETTAPSVYPLAPGTALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVL
QSGLYTLTSSVTVPSSWSSQAVTCNVAHPASSTKVDKKIVPRECNPCGCTGSEVSSVF
IFPPKTKDVLITLTPKVTCVVVDISQNDPEVRFSWFIDDVEVHTAQTHAPEKQSNSTL
RSVSELPIVHRDWLNGKTFKCKVNSGAFFAPIEKSISKPEGTPRGPQVYTMAPPKEEM
TQSQVSITCMVKGFFYPDIYTEWKMNQGPQENYKNTPTMDTDGSYFLYSKLNVKK
ETWQQGNTFTCSVLHEGLHNHHTEKSLSHSPGK*

<SEQ ID NO: 10>

SEQ ID NO: 10 shows the amino acid sequence (GenBank: #V01241.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

ADAAPTVSIFPPSTEQLATGGASVVCLMNNFYPRDISVKWKIDGTERRDGVLD SVTD
QDSKDSTYSMSSTLSLTKADYESHNLTYCEVVHKTSSSPVVKSFNRNEC*

<SEQ ID NO: 11>

SEQ ID NO: 11 shows the amino acid sequence (GenBank: #X16129.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

RADAAPTVSIFPPSTEQLATGGASVVCLMNNFYPRDISVKWKIDGTERRDGVLD SVT
DQDSKDSTYSMSSTLSLSKADYESHNLTYCEVVHKTSSSPVVKSFNRNEC

<SEQ ID NO: 12>

SEQ ID NO: 12 shows the amino acid sequence (GenBank: #DQ402471.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

AAPTVSIFPPSMEQLTSGGATVVCVNNFYPRDISVKWKIDGSEQRDGVLD SVTDQDS
KDSTYSMSSTLSLTKVEYERHNLYTCEVVHKTSSSPVVKSFNRNEC*

<SEQ ID NO: 13>

SEQ ID NO: 13 shows the amino acid sequence (GenBank: #DQ402472.1) of the CH of a rat antibody (IgG2a).

APSVYPLAPGTALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGL
 YTLTSSVTVPSSTWSSQAVTCNVAHPASSTKVDKKIVPRECNPCGCTGSEVSSVFIFPP
 KTKDVLTLTPKVTVCVVVDISQNDPEVRFSWFIDDVEVHTAQTHAPEKQSNSTLRSL
 SELPIVHRDWLNGKTFKCKVNSGAFFAPIEKSISKPEGTPRGPQVYTMAPPKEEMTQS
 QVSITCMVKGFYPPDIYTEWKMNQGPQENYKNTPTMDTDGSYFLYSKLNKVKETW
 QQGNTFTCSVLHEGLHNHHTKSLSHSPGK*

<SEQ ID NO: 14>

SEQ ID NO: 14 shows the nucleotide sequence of the VL of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

ATGAGGGTCCAGATTCAGTTTTGGGGGCTTCTTCTGCTCTGGACATCAGGTATACA
 GTGTGATGTCCAGATGACCCAGTCTCCATCTAATCTTGCTGCCTCTCCTGGAGAAA
 GTGTTTCCATCAATTGCAAGGCAAGTAAGAGCATTAGCAAGTATTTAGCCTGGTAT
 CAACAGAAACCTGGGAAAGCAAATAAGCTTCTTATCTACTCTGGGTCAACTTTGC
 AATCTGGAACCTCCATCGAGGTTTCAAGTGGCAGTGGATCTGGTACAGATTTCACTCTC
 ACCATCAGAAACCTGGAGCCTGAAGATTTTGGACTCTATTACTGTCAACAGCATAA
 TGAATACCCGCTCACGTTTCGGTTCTGGGACCAAGCTGGAGATCAAA

<SEQ ID NO: 15>

SEQ ID NO: 15 shows the nucleotide sequence of the VH of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

ATGGGATGGATCTGTATCATCTTTCTTGTGGCAATAGCTACAGGTGCCCACTCCCAG
 GTCAAGCTGCTGCAGTCTGGGGCTGCACTGGTGAAGCCTGGGGACTCTGTGAAG
 ATGTCTTGCAAAGCTTCTGGTTATACATTTCACTGACTACATTATACTGGGTGAAG
 CAGAGTCATGGAAAAAGCCTTGAGTGGATTGGTTATATTAATCCTGACAGTGGTGG
 TAATAACTACAATGAAAAGTTCAAGAGCAAGGCCACATTGACTGTAGACAAATCC
 AGCAGCACAGCCTATATGGAGTTTAGCAGATTGACATCTGAGGATTCTGCAATCTA
 CTACTGTGCAAGAGGGATTACCATGATGGTAGTTATTAGCCACTGGAAGTTTGACT
 TCTGGGGCCCAGGAACCATGGTCACCGTGTCTCA

<SEQ ID NO: 16>

SEQ ID NO: 16 shows the nucleotide sequence of the light chain (kappa chain) constant region of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

CGGGCTGATGCTGCACCAACTGTATCTATCTTCCCACCATCCACGGAACAGTTAGC

AACTGGAGGTGCCTCAGTCGTGTGCCTCATGAACAACCTTCTATCCCAGAGACATC
 AGTGTCAAGTGGAAGATTGATGGCACTGAACGACGAGATGGTGTCTGACAGT
 GTTACTGATCAGGACAGCAAAGACAGCACGTACAGCATGAGCAGCACCTCTCGT
 TGACCAAGGCTGACTATGAAAGTCATAACCTCTATACCTGTGAGGTTGTTTCATAAG
 ACATCATCCTCACCCGTCGTCAAGAGCTTCAACAGGAATGAGTGTTAG

<SEQ ID NO: 17>

SEQ ID NO: 17 shows the nucleotide sequence of the CH of anti-PD-L1 antibody 6C11-3A11 (IgG2a).

GCTGAAACAACAGCCCCATCTGTCTATCCACTGGCTCCTGGAACCTGCTCTCAAAA
 GTAACCTCCATGGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTC
 ACCGTGACCTGGAACCTCTGGAGCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTG
 TCCTGCAGTCTGGACTCTACACTCTCACCAGCTCAGTGACTGTACCCTCCAGCACC
 TGGTCCAGCCAGGCCGTCACCTGCAACGTAGCCCACCCGGCCAGCAGCACCAG
 GTGGACAAGAAAATTGTGCCAAGGGAATGCAATCCTTGTGGATGTACAGGCTCAG
 AAGTATCATCTGTCTTCATCTTCCCCCAAAGACCAAAGATGTGCTCACCATCACT
 CTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATTAGCCAGAATGATCCCGAGGT
 CCGGTTTCAGCTGGTTTATAGATGACGTGGAAGTCCACACAGCTCAGACTCATGCC
 CCGGAGAAGCAGTCCAACAGCACTTTACGCTCAGTCAGTGAACCTCCCCATCGTGC
 ACCGGGACTGGCTCAATGGCAAGACGTTCAAATGCAAAGTCAACAGTGGAGCAT
 TCCCTGCCCCCATCGAGAAAAGCATCTCCAAACCCGAAGGCACACCACGAGGTCC
 ACAGGTATACACCATGGCGCCTCCCAAGGAAGAGATGACCCAGAGTCAAGTCAGT
 ATCACCTGCATGGTAAAAGGCTTCTATCCCCCAGACATTTATACGGAGTGGAAGAT
 GAACGGGCAGCCACAGGAAACTACAAGAACTCCACCTACGATGGACACAGA
 TGGGAGTTACTTCCTCTACAGCAAGCTCAATGTAAAGAAAGAAACATGGCAGCAG
 GGAAACACTTTCACGTGTTCTGTGCTGCATGAGGGCCTGCACAACCACCATACTG
 AGAAGAGTCTCTCCCACTCTCCTGGTAAATGA

<SEQ ID NO: 18>

SEQ ID NO: 18 shows the nucleotide sequence (GenBank: #V01241.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

GGGCTGATGCTGCACCAACTGTATCTATCTTCCCACCATCCACGGAACAGTTAGCA
 ACTGGAGGTGCCTCAGTCGTGTGCCTCATGAACAACCTTCTATCCCAGAGACATCA
 GTGTCAAGTGGAAGATTGATGGCACTGAACGACGAGATGGTGTCTGACAGTGT

TACTGATCAGGACAGCAAAGACAGCACGTACAGCATGAGCAGCACCCCTCTCGTTG
 ACCAAGGCTGACTATGAAAGTCATAACCTCTATACCTGTGAGGTTGTTTCATAAGAC
 ATCATCCTCACCCGTCGTCAAGAGCTTCAACAGGAATGAGTGTTAG

<SEQ ID NO: 19>

SEQ ID NO: 19 shows the nucleotide sequence (GenBank: #X16129.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

CGGGCTGATGCTGCACCAACTGTATCTATCTTCCCACCATCCACGGAACAGTTAGC
 AACTGGAGGTGCCTCAGTCGTGTGCCTCATGAACAACCTTCTATCCCAGAGACATC
 AGTGTCAAGTGGAAGATTGATGGCACTGAACGACGAGATGGTGTCTTGGACAGT
 GTTACTGATCAGGACAGCAAAGACAGCACGTACAGCATGAGCAGCACCCCTCTCGT
 TGTCCAAGGCTGACTATGAAAGTCATAACCTCTATACCTGTGAGGTTGTTTCATAAG
 ACATCATCCTCACCCGTCGTCAAGAGCTTCAACAGGAATGAGTGTTAG

<SEQ ID NO: 20>

SEQ ID NO: 20 shows the nucleotide sequence (GenBank: #DQ402471.1) of the light chain (kappa chain) constant region of a rat antibody (IgG2a).

GCCGCACCAACTGTATCCATCTTCCCACCATCCATGGAACAGTTAACATCTGGAGG
 TGCCACAGTCGTGTGCTTCGTGAACAACCTTCTATCCCAGAGACATCAGTGTCAAG
 TGGAAGATTGATGGCAGTGAACAACGAGATGGTGTCTTGGACAGTGTTACTGATC
 AGGACAGCAAAGACAGCACGTACAGCATGAGCAGCACCCCTCTCGTTGACCAAGG
 TTGAATATGAAAGGCATAACCTCTATACCTGTGAGGTTGTTTCATAAGACATCATCCT
 CACCCGTCGTCAAGAGCTTCAACAGGAATGAGTGTTAG

<SEQ ID NO: 21>

SEQ ID NO: 21 shows the nucleotide sequence (GenBank: #DQ402472.1) of the CH of a rat antibody (IgG2a).

CAGCCCCCTCTGTCTATCCACTGGCTCCTGGAAGTCTCTCAAAAGTAACTCCATG
 GTGACCCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTCACCGTGACCT
 GGAAGTCTGGAGCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTCTTGCAGTC
 TGGACTCTACACTCTCACCAGCTCAGTGACTGTACCCTCCAGCACCTGGTCCAGC
 CAGGCCGTACCTGCAACGTAGCCACCCGGCCAGCAGCACCAAGGTGGACAAG
 AAAATTGTGCCAAGGGAATGCAATCCTTGTGGATGTACAGGCTCAGAAGTATCATC
 TGTCTTCATCTTCCCCCAAAGACCAAAGATGTGCTCACCATCACTCTGACTCCTA

AGGTCACGTGTGTTGTGGTAGACATTAGCCAGAATGATCCCGAGGTCCGGTTCAG
 CTGGTTTATAGATGACGTGGAAGTCCACACAGCTCAGACTCATGCCCCGGAGAAG
 CAGTCCAACAGCACTTTACGCTCAGTCAGTGAAGTCCCCATCGTGCAACGGGACT
 GGCTCAATGGCAAGACGTTCAAATGCAAAGTCAACAGTGGAGCATTCCCTGCCCC
 CATCGAGAAAAGCATCTCCAAACCCGAAGGCACACCACGAGGTCCACAGGTATAC
 ACCATGGCGCCTCCCAAGGAAGAGATGACCCAGAGTCAAGTCAGTATCACCTGCA
 TGGTAAAAGGCTTCTATCCCCCAGACATTTATACGGAGTGGAAGATGAACGGGCA
 GCCACAGGAAACTACAAGAAGACTCCACCTACGATGGACACAGATGGGAGTTA
 CTTCTCTACAGCAAGCTCAATGTAAAGAAAGAAACATGGCAGCAGGGAAACAC
 TTTCACGTGTTCTGTGCTGCATGAGGGCCTGCACAACCACCATACTGAGAAGAGT
 CTCTCCCACTCTCCTGGTAAATGA

<SEQ ID NOS: 22 to 27>

SEQ ID NOS: 22 to 27 show the nucleotide sequences of primers cPD-L1 inner F, cPD-L1 inner R, cPD-L1 5'GSP, cPD-L1 3'GSP, cPD-L1-EGFP F and cPD-L1-EGFP R, in this order.

<SEQ ID NO: 28>

SEQ ID NO: 28 shows the amino acid sequence of the light chain (kappa chain) constant region of a human antibody.

<SEQ ID NO: 29>

SEQ ID NO: 29 shows the nucleotide sequence of the light chain (kappa chain) constant region of a human antibody.

<SEQ ID NO: 30>

SEQ ID NO: 30 shows the amino acid sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 1).

<SEQ ID NO: 31>

SEQ ID NO: 31 shows the nucleotide sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 1).

<SEQ ID NO: 32>

SEQ ID NO: 32 shows the amino acid sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 2).

<SEQ ID NO: 33>

SEQ ID NO: 33 shows the nucleotide sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 2).

<SEQ ID NO: 34>

SEQ ID NO: 34 shows the amino acid sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 3).

<SEQ ID NO: 35>

SEQ ID NO: 35 shows the nucleotide sequence of the CH (CH1-CH3) of a human antibody (IgG4 variant 3).

<SEQ ID NO: 36>

SEQ ID NO: 36 shows the amino acid sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 37>

SEQ ID NO: 37 shows the nucleotide sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 38>

SEQ ID NO: 38 shows the amino acid sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 39>

SEQ ID NO: 39 shows the nucleotide sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 40>

SEQ ID NO: 40 shows the amino acid sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 41>

SEQ ID NO: 41 shows the nucleotide sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 42>

SEQ ID NO: 42 shows the amino acid sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 43>

SEQ ID NO: 43 shows the nucleotide sequence of the light chain (kappa chain) constant region of a mouse antibody.

<SEQ ID NO: 44>

SEQ ID NO: 44 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG1 variant 1).

<SEQ ID NO: 45>

SEQ ID NO: 45 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG1 variant 1).

<SEQ ID NO: 46>

SEQ ID NO: 46 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG1 variant 2).

<SEQ ID NO: 47>

SEQ ID NO: 47 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG1 variant 2).

<SEQ ID NO: 48>

SEQ ID NO: 48 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2a variant 1).

<SEQ ID NO: 49>

SEQ ID NO: 49 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2a variant 1).

<SEQ ID NO: 50>

SEQ ID NO: 50 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2a variant 2).

<SEQ ID NO: 51>

SEQ ID NO: 51 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2a variant 2).

<SEQ ID NO: 52>

SEQ ID NO: 52 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2b variant 1).

<SEQ ID NO: 53>

SEQ ID NO: 53 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2b variant 1).

<SEQ ID NO: 54>

SEQ ID NO: 54 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2b variant 2).

<SEQ ID NO: 55>

SEQ ID NO: 55 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2b variant 2).

<SEQ ID NO: 56>

SEQ ID NO: 56 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody

(IgG2c variant 1).

<SEQ ID NO: 57>

SEQ ID NO: 57 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2c variant 1).

<SEQ ID NO: 58>

SEQ ID NO: 58 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2c variant 2).

<SEQ ID NO: 59>

SEQ ID NO: 59 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2c variant 2).

<SEQ ID NO: 60>

SEQ ID NO: 60 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG2c variant 3).

<SEQ ID NO: 61>

SEQ ID NO: 61 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG2c variant 3).

<SEQ ID NO: 62>

SEQ ID NO: 62 shows the amino acid sequence of the CH (CH1-CH3) of a mouse antibody (IgG3).

<SEQ ID NO: 63>

SEQ ID NO: 63 shows the nucleotide sequence of the CH (CH1-CH3) of a mouse antibody (IgG3).

<SEQ ID NO: 64>

SEQ ID NO: 64 shows the amino acid sequence of the light chain (lambda chain) constant region of a bovine antibody.

<SEQ ID NO: 65>

SEQ ID NO: 65 shows the nucleotide sequence of the light chain (lambda chain) constant region of a bovine antibody.

<SEQ ID NO: 66>

SEQ ID NO: 66 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 1).

<SEQ ID NO: 67>

SEQ ID NO: 67 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 1).

<SEQ ID NO: 68>

SEQ ID NO: 68 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 2).

<SEQ ID NO: 69>

SEQ ID NO: 69 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 2).

<SEQ ID NO: 70>

SEQ ID NO: 70 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 3).

<SEQ ID NO: 71>

SEQ ID NO: 71 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG1 variant 3).

<SEQ ID NO: 72>

SEQ ID NO: 72 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 1).

<SEQ ID NO: 73>

SEQ ID NO: 73 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 1).

<SEQ ID NO: 74>

SEQ ID NO: 74 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 2).

<SEQ ID NO: 75>

SEQ ID NO: 75 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 2).

<SEQ ID NO: 76>

SEQ ID NO: 76 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 3).

<SEQ ID NO: 77>

SEQ ID NO: 77 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG2 variant 3).

<SEQ ID NO: 78>

SEQ ID NO: 78 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG3 variant 1).

<SEQ ID NO: 79>

SEQ ID NO: 79 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG3 variant 1).

<SEQ ID NO: 80>

SEQ ID NO: 80 shows the amino acid sequence of the CH (CH1-CH3) of a bovine antibody (IgG3 variant 2).

<SEQ ID NO: 81>

SEQ ID NO: 81 shows the nucleotide sequence of the CH (CH1-CH3) of a bovine antibody (IgG3 variant 2).

<SEQ ID NO: 82>

SEQ ID NO: 82 shows the amino acid sequence of the light chain (lambda chain) constant region of a canine antibody.

<SEQ ID NO: 83>

SEQ ID NO: 83 shows the nucleotide sequence of the light chain (lambda chain) constant region of a canine antibody.

<SEQ ID NO: 84>

SEQ ID NO: 84 shows the amino acid sequence of the CH (CH1-CH3) of a canine antibody (IgG-D).

<SEQ ID NO: 85>

SEQ ID NO: 85 shows the nucleotide sequence of the CH (CH1-CH3) of a canine antibody (IgG-D).

<SEQ ID NO: 86>

SEQ ID NO: 86 shows the amino acid sequence of the light chain (kappa chain) constant region of an ovine antibody.

<SEQ ID NO: 87>

SEQ ID NO: 87 shows the nucleotide sequence of the light chain (kappa chain) constant region of an ovine antibody.

<SEQ ID NO: 88>

SEQ ID NO: 88 shows the amino acid sequence of the light chain (lambda chain) constant region of an ovine antibody.

<SEQ ID NO: 89>

SEQ ID NO: 89 shows the nucleotide sequence of the light chain (lambda chain) constant region of an ovine antibody.

<SEQ ID NO: 90>

SEQ ID NO: 90 shows the amino acid sequence of the CH (CH1-CH3) of an ovine antibody

(IgG1).

<SEQ ID NO: 91>

SEQ ID NO: 91 shows the nucleotide sequence of the CH (CH1-CH3) of an ovine antibody (IgG1).

<SEQ ID NO: 92>

SEQ ID NO: 92 shows the amino acid sequence of the CH (CH1-CH3) of an ovine antibody (IgG2).

<SEQ ID NO: 93>

SEQ ID NO: 93 shows the nucleotide sequence of the CH (CH1-CH3) of an ovine antibody (IgG2).

<SEQ ID NO: 94>

SEQ ID NO: 94 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG1^a).

<SEQ ID NO: 95>

SEQ ID NO: 95 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG1^a).

<SEQ ID NO: 96>

SEQ ID NO: 96 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG1^b).

<SEQ ID NO: 97>

SEQ ID NO: 97 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG1^b).

<SEQ ID NO: 98>

SEQ ID NO: 98 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG2^a).

<SEQ ID NO: 99>

SEQ ID NO: 99 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG2^a).

<SEQ ID NO: 100>

SEQ ID NO: 100 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG2^b).

<SEQ ID NO: 101>

SEQ ID NO: 101 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG2^b).

<SEQ ID NO: 102>

SEQ ID NO: 102 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG3).

<SEQ ID NO: 103>

SEQ ID NO: 103 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG3).

<SEQ ID NO: 104>

SEQ ID NO: 104 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG4^a).

<SEQ ID NO: 105>

SEQ ID NO: 105 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG4^a).

<SEQ ID NO: 106>

SEQ ID NO: 106 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG4^b).

<SEQ ID NO: 107>

SEQ ID NO: 107 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG4^b).

<SEQ ID NO: 108>

SEQ ID NO: 108 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG5^a).

<SEQ ID NO: 109>

SEQ ID NO: 109 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG5^a).

<SEQ ID NO: 110>

SEQ ID NO: 110 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG5^b).

<SEQ ID NO: 111>

SEQ ID NO: 111 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG5^b).

<SEQ ID NO: 112>

SEQ ID NO: 112 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG6^a).

<SEQ ID NO: 113>

SEQ ID NO: 113 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG6^a).

<SEQ ID NO: 114>

SEQ ID NO: 114 shows the amino acid sequence of the CH (CH1-CH3) of a porcine antibody (IgG6^b).

<SEQ ID NO: 115>

SEQ ID NO: 115 shows the nucleotide sequence of the CH (CH1-CH3) of a porcine antibody (IgG6^b).

<SEQ ID NO: 116>

SEQ ID NO: 116 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: 117>

SEQ ID NO: 117 shows the nucleotide sequence of the light chain (estimated to be Ig lambda) constant region (CL) of a water buffalo antibody.

<SEQ ID NO: 118>

SEQ ID NO: 118 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG1).

<SEQ ID NO: 119>

SEQ ID NO: 119 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG1).

<SEQ ID NO: 120>

SEQ ID NO: 120 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG2).

<SEQ ID NO: 121>

SEQ ID NO: 121 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG2).

<SEQ ID NO: 122>

SEQ ID NO: 122 shows the amino acid sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG3).

<SEQ ID NO: 123>

SEQ ID NO: 123 shows the nucleotide sequence of the CH (CH1-CH3) of a water buffalo antibody (estimated to be IgG3).

<SEQ ID NO: 124>

SEQ ID NO: 124 shows the nucleotide sequence of primer boPD-L1-EGFP F.

<SEQ ID NO: 125>

SEQ ID NO: 125 shows the nucleotide sequence of primer boPD-L1-EGFP R.

CLAIMS

1. An anti-PD-L1 antibody comprising (a) a light chain comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2) and (b) a heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSGGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKDFD (SEQ ID NO: 5).
2. The antibody of claim 1, which is derived from rat.
3. The antibody of claim 2, which is 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. 6 and the heavy chain variable region has the amino acid sequence as shown in SEQ ID NO: 7.
5. The antibody of any one of claims 1 to 4, wherein the light chain constant region has the amino acid sequence of the constant region of kappa chain.
6. The antibody of any one of claims 1 to 5, wherein the heavy chain constant region has the amino acid sequence of the constant region of IgG2a.
7. The antibody of claim 5 or 6, wherein the light chain constant region has the amino acid sequence as shown in any one of SEQ ID NOS: 8, 10 to 12 and the heavy chain constant region has the amino acid sequence as shown in SEQ ID NO: 9 or 13.
8. The antibody of any one of claims 1 to 7 which has a four-chain structure comprising two light chains and two heavy chains.
9. A composition for detecting PD-L1, comprising the antibody of any one of claims 1 to 8 as an active ingredient.
10. The composition of claim 9 for use in diagnosis of cancers and/or inflammations.
11. The composition of claim 10, wherein the cancers and/or inflammations are selected from the group consisting of neoplastic diseases, leukemia, John'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.
12. The composition of claim 9 for use in selecting subject animals suitable for therapy with anti-PD-L1 antibodies.
13. A DNA encoding the anti-PD-L1 antibody of claim 1.

14. A vector comprising the DNA of claim 13.
15. A host cell transformed with the vector of claim 14.
16. A method of preparing an antibody, comprising culturing the host cell of claim 15 and collecting an anti-PD-L1 antibody from the resultant culture.
17. A DNA encoding the light chain of an anti-PD-L1 antibody, said light chain comprising CDR1 having the amino acid sequence of KSISKY (SEQ ID NO: 1), CDR2 having the amino acid sequence of SGS and CDR3 having the amino acid sequence of QQHNEYPLT (SEQ ID NO: 2).
18. A DNA encoding the heavy chain of an anti-PD-L1 antibody, said heavy chain comprising CDR1 having the amino acid sequence of GYTFTDYI (SEQ ID NO: 3), CDR2 having the amino acid sequence of INPDSSGN (SEQ ID NO: 4) and CDR3 having the amino acid sequence of ARGITMMVVISHWKFD (SEQ ID NO: 5).