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(54) **CANINE IL-4 IMMUNOREGULATORY PROTEINS AND USES THEREOF**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF proteins; to canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF nucleic acid molecules, including those that encode canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF proteins, respectively; to antibodies raised against such proteins; and to inhibitory compounds that regulate such proteins. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal.

10 Claims, No Drawings

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CANINE IL-4 IMMUNOREGULATORY PROTEINS AND USES THEREOF

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to prior pending U.S. Provisional Patent Application Serial No. 60/087,306, filed May 29, 1998, entitled "CANINE INTERLEUKIN-4 AND FLT-3 LIGAND PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF", which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins and/or inhibitors of such proteins or nucleic acid molecules. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies and/or inhibitors, as well as their use to regulate an immune response in an animal.

BACKGROUND OF THE INVENTION

Regulating immune responses in animals is important in disease management. Immune responses can be regulated by modifying the activity of immunoregulatory molecules and immune cells.

Several immunoregulatory molecules have been found in humans and other mammal species. Interleukin-4, produced by activated type 2 helper cells (T_H2 cells), has a number of functions. These functions include promotion of naive T cells and B cells to differentiate and proliferate. IL-4 promotes T_H2 differentiation and inhibits T_H1 development. FMS-like tyrosine kinase 3, (Flt-3 ligand) stimulates the expansion and mobilization of hematopoietic precursor cell stimulating activity. CD40 is a type I transmembrane protein expressed on antigen presenting cells, such as B lymphocytes, and other types of cells such as endothelial cells, epithelial cells, and fibroblasts. CD40 ligand (also known as CD154) is a type II transmembrane protein that is preferentially expressed on activated T lymphocytes. The CD40-CD154 interaction regulates diverse pathways of the immune system, including B cell proliferation, immunoglobulin production and class switching by B cells, activation and clonal expansion of T cells, activity of antigen presenting cells, growth and differentiation of epithelial cells, and regulation of inflammatory responses at mucosal and cutaneous sites. Interleukin-5 is produced by activated type 2 helper cells (T_H2), mast cells, and eosinophils. Its main functions include promotion of growth and differentiation of eosinophils and generation of cytotoxic T cells from thymocytes. Interleukin-13 is produced by T_H1 and T_H2 cells, and promotes growth and differentiation of B cells, up-regulation of MHC class II and CD23 expression on monocytes/macrophages and B cells; and inhibition of production of inflammatory cytokines such as IL-1 α , IL-1 β , IL-6, IL-8, IL-10, IL-12, among others. Interferon alpha is an antiviral protein that has three major functions: it inhibits

viral replication by activating cellular genes that destroy mRNA and inhibit protein translation, it induces MHC class I expression in non virally-infected cells, increasing resistance to NK cells, and can activate NK cells. GM-CSF, (granulocyte-macrophage colony-stimulating factor) stimulates the production of granulocytes and macrophages.

Prior investigators have disclosed sequences encoding feline IL-4 (Lemer et al., Genbank Accession No. U39634); porcine IL-4 (Zhou et al., Genbank Accession No. L12991); bovine IL-4 (Heussler, V. T., et al., Gene, vol. 114, pp. 273-278, 1992); ovine IL-4 (Seow, H.-F., et al., Gene, vol. 124, pp. 291-293, 1993); human IL-4 (Yokota, T., et al. Proc. Natl. Acad. Sci. U.S.A., vol. 83(16), pp. 5894-5898, 1986); and murine IL-4 (Sideras, P., et al., Adv. Exp. Med. Biol., vol. 213, pp. 227-236, 1987). Prior investigators have disclosed sequences encoding murine Flt-3 ligand (McClanahan et al., Genbank Accession No. U44024); and human Flt-3 ligand (Lyman et al., Blood, vol. 83, pp. 2795-2801, 1994). Prior investigators have disclosed sequences encoding human CD40 (Stamenkovic et al., EMBO J., vol. 8:1403-1410, 1989, GenBank Accession No. X60592), bovine CD40 (Hirano et al., Immunology, vol. 90, pp. 294-300, 1997, GenBank Accession No. U57745), and murine CD40 (Grimaldi et al., J. Immunol., vol. 143, pp. 3921-3926, 1992; Torres and Clark, J. Immunol., vol. 148, pp. 620-626, 1992, GenBank Accession No. M83312). Prior investigators have disclosed sequences encoding human CD154 (Graf et al., Eur. J. Immunol., vol. 22, pp. 3191-3194, 1992; Hollenbaugh, et al., EMBO J., vol. 11:4313-4321, 1992; Gauchat et al., FEBS lett., vol., 315, pp. 259-266, 1993; GenBank Accession Nos L07414, X68550, Z15017, X67878, respectively); bovine CD154 (Mertens et al., Immunogenetics, vol. 42, pp. 430-431, GenBank Accession No. Z48468); and murine CD154 (Armitage et al., Nature, vol. 357, pp. 80-82; 1992, GenBank Accession No. X65453). Prior investigators have disclosed sequences encoding feline interleukin-5 (Padrid et al., Am. J. Vet. Res., vol. 59, pp. 1263-1269, 1988, GenBank Accession No. AF025436) and human interleukin-5 (Azuma et al., Nucleic Acids Res., vol. 14, pp. 9149-9158, 1986, GenBank Accession No. X04688). Prior investigators have disclosed sequences encoding human interleukin-13 (McKenzie et al., Proc. Natl Acad. Sci. USA, vol. 90, pp. 3735-3739, 1993; Minty et al., Nature, vol. 362, pp. 248-250, 1993, GenBank Accession Nos L06801 and X69079, respectively); murine interleukin-13 (Brown et al., J. Immunol., vol. 142, pp. 679-687; 1989, GenBank Accession No. M23504); and rat interleukin-13 (Lakkis et al., Biochem. Biophys. Res. Commun., Vol. 197, pp. 612-618, 1993, GenBank Accession No. L26913). Prior investigators have disclosed sequences encoding feline interferon (Nakamura, N., Sudo, T., Matsuda, S., Yanai, A., Biosci. Biotechnol. Biochem. (1992) Vol: 56 pp 211-214, GenBank accession #E02521). Prior investigators have also disclosed sequences encoding feline GM-CSF (direct submission to GenBank, Accession No. AF053007)

There remains a need for compounds and methods to regulate an immune response by manipulation of the function of canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF.

SUMMARY OF THE INVENTION

The present invention relates to canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13,

feline interferon alpha, or feline GM-CSF nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins and/or inhibitors of such proteins or nucleic acid molecules. Identification of the nucleic acid molecules of the present invention is unexpected because initial attempts to obtain nucleic acid molecules using PCR were unsuccessful. After numerous attempts, the inventors discovered specific primers that were useful for isolating such nucleic acid molecules.

One embodiment of the present invention is an isolated nucleic acid molecule selected from the group consisting of: (a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21; or a homolog thereof, wherein said homolog has an at least about 50 contiguous nucleotide region identical in sequence to a 50 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21; (b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37 or a homolog thereof, wherein said homolog has an at least 40 contiguous nucleotide region identical in sequence to a 40 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37; (c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50, and/or a homolog thereof, wherein said homolog has an at least 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50; (d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59, and/or a homolog thereof, wherein said homolog has an at least 40 contiguous nucleotide region identical in sequence to a 40 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59; (e) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:60 and/or SEQ ID NO:62 and/or a homolog thereof, wherein said homolog has an at least 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:60 and/or SEQ ID NO:62; (f) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID

NO:67, SEQ ID NO:68, SEQ ID NO:69 and/or SEQ ID NO:71, and/or a homolog thereof, wherein said homolog has an at least 45 contiguous nucleotide region identical in sequence to a 45 nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69 and/or SEQ ID NO:71; (g) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79, and/or a homolog thereof, wherein said homolog has an at least 35 contiguous nucleotide region identical in sequence to a 35 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79; (h) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87, and/or a homolog thereof, wherein said homolog has an at least 45 contiguous nucleotide region identical in sequence to a 45 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87; (i) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106, and/or a homolog thereof, wherein said homolog has an at least 15 contiguous nucleotide region identical to a 15 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106 (j) an isolated nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:118; and/or (k) an isolated nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126.

Another embodiment of the present invention is an isolated nucleic acid molecule selected from the group consisting of: (a) a nucleic acid molecule having a nucleic acid sequence that is at least about 92 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21; (b) a nucleic acid molecule having a nucleic acid sequence that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37; (c) a nucleic acid molecule having a nucleic acid sequence that is at least about 75 percent identical to a nucleic acid

sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50; (d) a nucleic acid molecule having a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59; (e) a nucleic acid molecule having a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:60 and/or SEQ ID NO:62; (f) a nucleic acid molecule having a nucleic acid sequence that is at least about 85 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69 and/or SEQ ID NO:71; (g) a nucleic acid molecule having a nucleic acid sequence that is at least about 91 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79; (h) a nucleic acid molecule having a nucleic acid sequence that is at least about 90 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87; (i) a nucleic acid molecule having a nucleic acid sequence that is at least about 65 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106; (j) a nucleic acid molecule having a nucleic acid sequence that is selected from the group consisting of SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:122, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, and/or SEQ ID NO:118; and/or (k) a nucleic acid molecule having a nucleic acid sequence that is selected from the group consisting of SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, and/or SEQ ID NO:126.

Yet another embodiment of the present invention is an isolated nucleic acid molecule selected from the group consisting of: (a) a nucleic acid molecule having a nucleic acid sequence encoding an IL-4 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20; (b) a nucleic acid molecule having a nucleic acid sequence encoding a Flt-3 ligand protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34 and/or (ii) a protein comprising a fragment of at least 25 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34; (c) a nucleic acid molecule having a nucleic acid sequence encoding a Flt-3 ligand protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from

the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49 and/or (ii) a protein comprising a fragment of at least 25 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49; (d) a nucleic acid molecule having a nucleic acid sequence encoding a CD40 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:53 and/or SEQ ID NO:58 and/or (ii) a protein comprising a fragment of at least 30 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:53 and/or SEQ ID NO:58; (e) a nucleic acid molecule having a nucleic acid sequence encoding a CD40 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 60 percent identical to an amino acid sequence comprising SEQ ID NO:61 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence comprising SEQ ID NO:61; (f) a nucleic acid molecule having a nucleic acid sequence encoding a CD154 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 80 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70, and/or (ii) a protein comprising a fragment of at least 35 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70; (g) a nucleic acid molecule having a nucleic acid sequence encoding a CD154 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:73 and/or SEQ ID NO:78, and/or (ii) a protein comprising a fragment of at least 50 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:73 and/or SEQ ID NO:78; (h) a nucleic acid molecule having a nucleic acid sequence encoding an IL-5 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86; (i) a nucleic acid molecule having a nucleic acid sequence encoding an IL-13 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105 and/or (ii) a protein comprising a fragment of at least 15 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105; (j) a nucleic acid molecule having a nucleic acid sequence encoding an interferon alpha protein having an amino acid sequence that is selected from the group consisting of amino acid sequence SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117; (k) a nucleic acid molecule having a nucleic acid sequence encoding a GM-CSF protein having an amino acid sequence that is selected from the group consisting of amino acid sequence SEQ ID NO:120, SEQ ID NO:126, and/or (l) a nucleic acid molecule comprising a complement of any of said nucleic acid molecules as set forth in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), and/or (k), wherein said IL-4 protein elicits an immune response against an IL-4 protein selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20

and/or is a protein with interleukin-4 activity said Flt-3 ligand protein elicits an immune response against a Flt-3 ligand protein selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:44, and/or SEQ ID NO:49 and/or is a protein with Flt-3 ligand activity, said CD40 protein elicits an immune response against a CD40 protein selected from the group consisting of SEQ ID NO:53, SEQ ID NO:58, and/or SEQ ID NO:61 and/or is a protein with CD40 activity, said CD154 protein elicits an immune response against a CD154 protein selected from the group consisting of SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:73, and/or SEQ ID NO:78 and/or is a protein with CD154 activity, said IL-5 protein elicits an immune response against a IL-5 protein selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86 and/or is a protein with IL-5 activity, said IL-13 protein elicits an immune response against an IL-13 protein selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105 and/or is a protein with IL-13 activity, said interferon alpha protein elicits an immune response against an interferon alpha protein selected from the group consisting of SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117 and/or is a protein with interferon alpha activity, and/or said GM-CSF protein elicits an immune response against a GM-CSF protein selected from the group consisting of SEQ ID NO:120 and/or SEQ ID NO:125 and/or is a protein with GM-CSF activity.

The present invention also includes methods to produce any of the proteins of the present invention using nucleic acid molecules of the present invention and recombinantly using such nucleic acid molecules.

The present invention also includes an isolated protein selected from the group consisting of: (a) (i) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, and/or SEQ ID NO:19; and/or (ii) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20, wherein said isolated protein elicits an immune response against a canine IL-4 protein and/or has IL-4 activity; (b) (i) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:33, and/or SEQ ID NO:36; and/or (ii) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34, wherein said isolated protein is capable of eliciting an immune response against a canine Flt-3 ligand protein and/or has Flt-3 activity; (c) (i) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at

least 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:46, and/or SEQ ID NO:48; and/or (ii) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49, wherein said isolated protein is capable of eliciting an immune response against a feline Flt-3 ligand protein and/or has Flt-3 activity; (d) (i) an isolated protein of at least about 30 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 90 contiguous nucleotide region identical in sequence to a 90 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:55, and/or SEQ ID NO:57 and/or (ii) an isolated protein of at least about 30 amino acids in length, wherein said protein has an at least 30 contiguous amino acid region identical in sequence to a 30 contiguous amino acid region selected from the group consisting of SEQ ID NO:53, SEQ ID NO:58, wherein said isolated protein is capable of eliciting an immune response against a canine CD40 protein and/or has CD40 activity; (e) (i) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence comprising Seq id no:60; and/or (ii) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region comprising the amino acid sequence SEQ ID NO:61, wherein said isolated protein is capable of eliciting an immune response against a feline CD40 protein and/or has CD40 activity; (f) (i) an isolated protein of at least about 35 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 5 contiguous nucleotide region identical in sequence to a 105 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67, and/or SEQ ID NO:69; and/or (ii) an isolated protein of at least about 35 amino acids in length, wherein said protein has an at least 35 contiguous amino acid region identical in sequence to a 35 contiguous amino acid region selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70, wherein said isolated protein is capable of eliciting an immune response against a canine CD154 protein and/or has CD154 activity; (g) (i) an isolated protein of at least about 50 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 150 contiguous nucleotide region identical in sequence to a 150 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:75, and/or SEQ ID NO:77; and/or (ii) an isolated protein of at least about 50 amino acids in length, wherein said protein has an at least 50 contiguous amino acid region identical in sequence to a 50 contiguous amino acid region selected from the group consisting of SEQ ID NO:73 and/or SEQ ID NO:78, wherein said isolated protein is capable of eliciting an immune response against a feline CD154 protein and/or has CD154 activity; (h) (i) an isolated protein of at least about 20 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic

acid molecule has an at least contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:83, and/or SEQ ID NO:85; and/or (ii) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86, wherein said isolated protein is capable of eliciting an immune response against a canine IL-5 protein and/or has IL-5 activity; (i) an isolated protein of at least about 15 amino acids in length, wherein said protein is encoded by a nucleic acid molecule, wherein said nucleic acid molecule has an at least 45 contiguous nucleotide region identical in sequence to a 45 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, and/or SEQ ID NO:104; and/or (ii) an isolated protein of at least about 15 amino acids in length, wherein said protein has an at least 15 contiguous amino acid region identical in sequence to a 15 contiguous amino acid region selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105, wherein said isolated protein is capable of eliciting an immune response against a canine IL-13 protein and/or has IL-13 activity; (j) (i) an isolated protein encoded by a nucleic acid molecule selected from the group consisting of SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:113, and/or SEQ ID NO:116, and/or (ii) an isolated protein selected from the group consisting of SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117, wherein said isolated protein is capable of eliciting an immune response against a feline interferon alpha protein and/or has interferon alpha activity; (k) (i) an isolated protein encoded by a nucleic acid molecule selected from the group consisting of SEQ ID NO:119, SEQ ID NO:122, and/or SEQ ID NO:124, and/or (ii) an isolated protein selected from the group consisting of SEQ ID NO:120 and/or SEQ ID NO:125, wherein said isolated protein is capable of eliciting an immune response against a feline GM-CSF and/or has GM-CSF activity.

The present invention also includes an isolated protein selected from the group consisting of: (a) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20; (b) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34; (c) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49; and/or (d) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:53 and/or SEQ ID NO:58; (e) a protein having an amino acid sequence that is at least about 60 percent identical to an amino acid sequence comprising SEQ ID NO:61; (f) a protein having an amino acid sequence that is at least about 80 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70; (g) a protein having an amino acid sequence that is at least about 85 percent identical to the amino acid sequence SEQ ID NO:73 and/or SEQ ID NO:78; (h) a protein having an amino acid sequence that is at least about 85 percent

identical to an amino acid sequence selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86; (i) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105; (j) a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117; and/or (k) a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:120, and/or SEQ ID NO:125.

The present invention also includes isolated antibodies that selectively bind to a protein of the present invention.

One aspect of the present invention is a therapeutic composition that, when administered to an animal, regulates an immune response in said animal, said therapeutic composition comprising a therapeutic compound selected from the group consisting of: an immunoregulatory protein of the present invention; a mimotope of any of said immunoregulatory proteins; and a multimeric form of any of said immunoregulatory proteins; an isolated nucleic acid molecule of the present invention; an antibody that selectively binds to any of said immunoregulatory protein; and/or an inhibitor of a immunoregulatory protein activity identified by its ability to inhibit the activity of any of said immunoregulatory proteins. Yet another aspect of the present invention is a method to regulate an immune response in an animal comprising administering to the animal a therapeutic composition of the present invention.

The present invention also includes a method to produce an immunoregulatory protein, said method comprising culturing a cell capable of expressing said protein, said protein being encoded by a nucleic acid molecule of the present invention.

One embodiment of the present invention is a method to identify a compound capable of regulating an immune response in an animal, said method comprising: (a) contacting an isolated canine IL-4 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has T cell proliferation stimulating activity; and determining if said putative inhibitory compound inhibits said activity; (b) contacting an isolated canine Flt-3 ligand protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has dendritic precursor cell proliferation stimulating activity; and determining if said putative inhibitory compound inhibits said activity; (c) contacting an isolated feline Flt-3 ligand protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has dendritic precursor cell proliferation stimulating activity; and determining if said putative inhibitory compound inhibits said activity; (d) contacting an isolated canine CD40 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has CD40 ligand binding activity; and determining if said putative inhibitory compound inhibits said activity; (e) contacting an isolated feline CD40 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has CD40 ligand binding activity; and determining if said putative inhibitory compound inhibits said activity; (f) contacting an isolated canine CD154 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has B cell proliferation activity; and determining if

said putative inhibitory compound inhibits said activity; (g) contacting an isolated feline CD154 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has B cell proliferation activity; and determining if said putative inhibitory compound inhibits said activity; (h) contacting an isolated canine IL-5 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has TF-1 cell proliferation activity; and determining if said putative inhibitory compound inhibits said activity; (i) contacting an isolated canine IL-13 protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has TF-1 cell proliferation activity; and determining if said putative inhibitory compound inhibits said activity; (j) contacting an isolated feline IFN α protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has inhibition of proliferation of GM-CSF stimulated TF-1 cell activity; and determining if said putative inhibitory compound inhibits said activity; or (k) contacting an isolated feline GMCSF protein of the present invention with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has TF-1 cell proliferation activity; and determining if said putative inhibitory compound inhibits said activity.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins, isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecules, antibodies directed against canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins, and compounds derived therefrom that regulate the immune response of an animal (e.g. inhibitors, antibodies and peptides).

Canine IL-4 protein can refer to a canine IL-4 protein, including homologs thereof Canine Flt-3 ligand protein can refer to a canine Flt-3 ligand, including homologs thereof, and feline Flt-3 ligand can refer to feline Flt-3 ligand, including homologs thereof. Canine CD40 can refer to a canine CD40, including homologs thereof; feline CD40 can refer to a feline CD40, including homologs thereof Canine CD154 can refer to a canine CD154, including homologs thereof, feline CD154 can refer to a feline CD154, including homologs thereof. Canine IL-5 can refer to canine IL-5, including homologs thereof; canine IL-13 can refer to canine IL-13, including homologs thereof. Feline IFN α can refer to a feline IFN α , including homologs thereof, and feline GM-CSF can refer to a feline GM-CSF, including homologs thereof As used herein, the phrase "regulate an immune response" refers to modulating the activity of cells or molecules involved in an immune response. The term "regulate" can refer to increasing or decreasing an immune response. Regulation of an immune response can be determined using methods known in the art as well as methods disclosed herein. The term, "immunoregulatory protein" refers to a protein that can modulate the activity of cells or of molecules involved in an immune response. An immu-

noregulatory protein of the present invention refers to a canine IL-4, a canine and/or feline CD40, a canine and/or feline Flt3 ligand, a canine and/or feline CD154, a canine IL-5, a canine IL-13, a feline IFN α and/or a feline GM-CSF protein as described herein. As used herein, the terms isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins and/or isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecules refer to canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins and/or canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecules derived from mammals and, as such, can be obtained from their natural source, or can be produced using, for example, recombinant nucleic acid technology or chemical synthesis. Also included in the present invention is the use of these proteins, nucleic acid molecules, antibodies, and/or compounds derived therefrom as therapeutic compositions to regulate the immune response of an animal as well as in other applications, such as those disclosed below.

One embodiment of the present invention is an isolated protein that includes a canine IL-4 protein, a canine and/or feline Flt-3 ligand protein, a canine and/or feline CD40 protein, a canine and/or feline CD154 protein, a canine interleukin-5 protein, a canine interleukin-13 protein, a feline interferon alpha protein, and/or a feline GM-CSF protein. It is to be noted that the term "a" or "an" entity refers to one or more of that entity: for example, a protein refers to one or more proteins or at least one protein. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. According to the present invention, an isolated, or biologically pure, protein, is a protein that has been removed from its natural milieu. As such, "isolated" and/or "biologically pure" do not necessarily reflect the extent to which the protein has been purified. An isolated protein of the present invention can be obtained from its natural source, can be produced using recombinant DNA technology, or can be produced by chemical synthesis. Nucleic acid molecules of the present invention of known length isolated from *Canis familiaris* are denoted as follows: IL-4 is denoted as nCaIL-4_x, for example, nCaIL-4₅₄₉, wherein "#" refers to the number of nucleotides in that molecule; and in a similar fashion, Flt-3 ligand nucleic acid molecules are referred to as nCaFlt3L_x; CD40, nCaCD40_x; CD154, nCaCD154_x; IL-5, nCaIL-5_x; and IL-13, nCaIL-13_x. In a similar fashion, Flt-3 ligand nucleic acid molecules of the present invention of known length isolated from *Felis catus* are denoted as nFeFlt3L_x, CD40, nFeCD40_x; CD154, nFeCD154_x; IFN α , nFeIFN α _x; and GM-CSF (also denoted GMCSF), nFeGM-CSF_x. Similarly, proteins of the present invention of known length isolated from *Felis catus* are denoted as PFeFlt3I_x, PFeCD40_x, PFeCD154_x, PFeIFN α _x, and/or PFeGM-CSF_x; and proteins of the present invention of known length isolated from *Canis familiaris* are denoted PCaIL-4_x, PCaFlt3L_x, PCaCD40_x, PCaCD154_x, PCaIL-5_x, and/or PCaIL-13_x.

As used herein, an isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline

CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF ligand protein of the present invention (i.e., an canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively) can be a full-length protein or any homolog of such a protein. An isolated IL-4 protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against, (or to) an IL4 protein, bind to an IL-4 receptor, stimulate B cell differentiation or activation or stimulate production of immunoglobulin by a B cell. An isolated Flt-3 ligand protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against a Flt-3 ligand protein, bind to Flt-3 receptor or stimulate Flt-3 receptor-bearing hematopoietic stem cells, early hematopoietic progenitor cells or immature lymphocytes. An isolated CD40 protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against a CD40 protein, bind to CD154 or stimulate CD154-bearing B cells, T cells, and/or epithelial cells. An isolated CD154 protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response to a CD154 protein, bind to CD40 or stimulate CD40-bearing B cells, T cells, and/or epithelial cells. An isolated IL-5 protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response to an IL-5 protein, bind to an IL-5 receptor, and/or stimulate eosinophils and/or cause thymocytes to product cytotoxic T cells. An isolated IL-13 protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response to an IL-13 protein, bind to an IL-13 receptor, and/or stimulate B cells, up-regulate expression of MHC class II and/or CD23 on monocytes, macrophages and/or B cells; and/or inhibition of proinflammatory cytokines. An isolated interferon alpha protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response to an interferon alpha protein, bind to an interferon-alpha receptor, and/or activate NK cells and/or inhibit viral replication. An isolated GM-CSF protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response to a GM-CSF protein, bind to a GM-CSF receptor, and/or active granulocytes and/or macrophages. Examples of protein homologs of the present invention include immunoregulatory proteins of the present invention in which amino acids have been deleted (e.g., a truncated version of the protein, such as a peptide), inserted, inverted, substituted and/or derivatized (e.g., by glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitoylation, amidation and/or addition of glycerophosphatidyl inositol) such that the protein homolog includes at least one epitope capable of eliciting an immune response against the parent protein, of binding to an antibody directed against the parent protein and/or of binding to the parent's receptor, where the term parent refers to the longer and/or full-length protein that the homolog is derived from. That is, when the homolog is administered to an animal as an immunogen, using techniques known to those skilled in the art, the animal will produce an immune response against at least one epitope of an immunoregulatory protein of the

present invention, depending upon which protein is administered to an animal. The ability of a protein to effect an immune response can be measured using techniques known to those skilled in the art. As used herein, the term "epitope" refers to the smallest portion of a protein capable of selectively binding to the antigen binding site of an antibody. It is well accepted by those skilled in the art that the minimal size of a protein epitope capable of selectively binding to the antigen binding site of an antibody is about five or six to seven amino acids.

Homologs of immunoregulatory proteins of the present invention can be the result of natural allelic variation, including natural mutation. Protein homologs of the present invention can also be produced using techniques known in the art including, but not limited to, direct modifications to the protein and/or modifications to the gene encoding the protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

Immunoregulatory proteins of the present invention include variants of a full-length protein of a protein of the present invention. Such variants include proteins that are less than full-length. As used herein, variants of the present invention refer to nucleic acid molecules that are naturally-occurring as defined below, and may result from alternative RNA splicing, alternative termination of an amino acid sequence or DNA recombination. Examples of variants include allelic variants as defined below. It is to be noted that a variant is an example of a homolog of the present invention.

Immunoregulatory proteins of the present invention are encoded by nucleic acid molecules of the present invention. As used herein, an IL-4 nucleic acid molecule includes nucleic acid sequences related to a natural canine IL-4 gene. As used herein, a Flt-3 ligand nucleic acid molecule includes nucleic acid sequences related to a natural canine Flt-3 ligand gene. As used herein, a CD40 nucleic acid molecule includes nucleic acid sequences related to a natural CD40 gene. As used herein, a CD154 nucleic acid molecule includes nucleic acid sequences related to a natural CD154 gene. As used herein, an IL-5 nucleic acid molecule includes nucleic acid sequences related to a natural IL-5 gene. As used herein, an IL-13 nucleic acid molecule includes nucleic acid sequences related to a natural IL-13 gene. As used herein, an IFN α nucleic acid molecule includes nucleic acid sequences related to a natural IFN α gene. As used herein, a GM-CSF nucleic acid molecule includes nucleic acid sequences related to a natural GM-CSF gene. As used herein, a canine IL-4, a canine and/or feline CD40, a canine and/or feline Flt3 ligand, a canine and/or feline CD154, a canine IL-5, a canine IL-13, a feline IFN α , and/or a feline GM-CSF gene refers to the natural genomic elements that encode an canine IL-4, a canine and/or feline CD40, a canine and/or feline Flt3 ligand, a canine and/or feline CD154, a canine IL-5, a canine IL-13, a feline IFN α , and/or a feline GM-CSF protein, respectively, and includes all regions such as regulatory regions that control production of the protein encoded by the gene (such as, but not limited to, transcription, translation or post-translation control regions) as well as the coding region itself, and any introns or non-translated coding regions. As used herein, a gene that "includes" or "comprises" a sequence may include that sequence in one contiguous array, or may include the sequence as fragmented exons. As used herein, the term "coding region" refers to a continuous linear array of nucleotides that translates into a protein. A full-length coding region is that region that is translated into a full-length, i.e., a complete, protein as would be initially translated in its natural milieu, prior to any post-translational modifications.

In one embodiment, an IL-4 gene of the present invention includes the nucleic acid sequence SEQ ID NO:1, as well as the complement of SEQ ID NO:1. Nucleic acid sequence SEQ ID NO:1 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaIL-4₅₄₉, the production of which is disclosed in the Examples. Nucleic acid molecule nCaIL-4₅₄₉ comprises an apparently full-length coding region of canine IL-4. The complement of SEQ ID NO:1 (represented herein by SEQ ID NO:3) refers to the nucleic acid sequence of the strand fully complementary to the strand having SEQ ID NO:1, which can easily be determined by those skilled in the art. Likewise, a nucleic acid sequence complement of any nucleic acid sequence of the present invention refers to the nucleic acid sequence of the nucleic acid strand that is fully complementary to (i.e., can form a double helix with) the strand for which the sequence is cited. It should be noted that since nucleic acid sequencing technology is not entirely error-free, SEQ ID NO:1 (as well as other nucleic acid and protein sequences presented herein) represents an apparatus nucleic acid sequence of the nucleic acid molecule encoding an immunoregulatory protein of the present invention.

In another embodiment, a Flt-3 ligand gene of the present invention includes the nucleic acid sequence SEQ ID NO:6, as well as the complement represented by SEQ ID NO:8. Nucleic acid sequence SEQ ID NO:6 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nCaFlt3L₁₀₁₃, the production of which is disclosed in the Examples. Nucleic acid molecule nCaFlt3L₁₀₁₃ comprises an apparently full-length coding region of canine Flt-3 ligand.

In another embodiment, a Flt-3 ligand gene of the present invention includes the nucleic acid sequence SEQ ID NO:43, as well as the complement represented by SEQ ID NO:45. Nucleic acid sequence SEQ ID NO:43 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nFeFlt3L₉₄₂, the production of which is disclosed in the Examples. Nucleic acid molecule nFeFlt3L₉₄₂ comprises an apparently full-length coding region of feline Flt-3 ligand.

In another embodiment, a CD40 gene of the present invention includes the nucleic acid sequence SEQ ID NO:52, as well as the complement represented by SEQ ID NO:54. Nucleic acid sequence SEQ ID NO:52 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nCaCD40₁₄₂₅, the production of which is disclosed in the Examples. Nucleic acid molecule nCaCD40₁₄₂₅ comprises an apparently full-length coding region of canine CD40.

In another embodiment, a CD40 gene of the present invention includes the nucleic acid sequence SEQ ID NO:60, as well as the complement represented by SEQ ID NO:62. Nucleic acid sequence SEQ ID NO:60 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nFeCD40₃₃₆, the production of which is disclosed in the Examples. Nucleic acid molecule nFeCD40₃₃₆ comprises an apparent portion of the coding region of feline CD40.

In another embodiment, a CD154 gene of the present invention includes the nucleic acid sequence SEQ ID NO:64, as well as the complement represented by SEQ ID NO:66. Nucleic acid sequence SEQ ID NO:64 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nCaCD154₁₈₇₈, the production of which is disclosed in the Examples. Nucleic acid

molecule nCaCD154₁₈₇₈ comprises an apparently full-length coding region of canine CD154.

In another embodiment, a CD154 gene of the present invention includes the nucleic acid sequence SEQ ID NO:72, as well as the complement represented by SEQ ID NO:74. Nucleic acid sequence SEQ ID NO:72 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nFeCD154₈₈₅, the production of which is disclosed in the Examples. Nucleic acid molecule nFeCD154₈₈₅ comprises an apparently full-length coding region of feline CD154.

In another embodiment, an IL-5 gene of the present invention includes the nucleic acid sequence SEQ ID NO:80, as well as the complement represented by SEQ ID NO:82. Nucleic acid sequence SEQ ID NO:80 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nCaIL-5₆₁₀, the production of which is disclosed in the Examples. Nucleic acid molecule nCaIL-5₆₁₀ comprises an apparently full-length coding region of canine IL-5.

In another embodiment, an IL-13 gene of the present invention includes the nucleic acid sequence SEQ ID NO:91, as well as the complement represented by SEQ ID NO:93. Nucleic acid sequence SEQ ID NO:91 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nCaIL-13₁₃₀₂, the production of which is disclosed in the Examples. Nucleic acid molecule nCaIL-13₁₃₀₂ comprises an apparently full-length coding region of canine IL-13.

In another embodiment, an IFN α gene of the present invention includes the nucleic acid sequence SEQ ID NO:107, as well as the complement represented by SEQ ID NO:109. Nucleic acid sequence SEQ ID NO:107 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nFeIFN α _{567a}, the production of which is disclosed in the Examples. Nucleic acid molecule nFeIFN α _{567a} comprises an apparently full-length coding region of feline IFN α .

In another embodiment, a GM-CSF gene of the present invention includes the nucleic acid sequence SEQ ID NO:119, as well as the complement represented by SEQ ID NO:121. Nucleic acid sequence SEQ ID NO:119 represents the deduced sequence of the coding strand of a cDNA denoted herein as nucleic acid molecule nFeGM-CSF₄₄₄, the production of which is disclosed in the Examples. Nucleic acid molecule nFeGM-CSF₄₄₄ comprises an apparently full-length coding region of feline GM-CSF.

Additional immunoregulatory nucleic acid molecules and proteins of the present invention having specific sequence identifiers are described in Table 1.

TABLE 1

Sequence identification numbers (SEQ ID NOs) and their corresponding nucleic acid molecules or proteins.

SEQ ID NO	DESCRIPTION
1	nCaIL-4 ₅₄₀ coding strand
2	PCaIL-4 ₁₃₂
3	nCaIL-4 ₅₄₉ complementary strand
4	nCaIL-4 ₃₉₆ coding strand
5	nCaIL-4 ₃₉₆ complementary strand
6	nCaFlt3L ₁₀₁₃ coding strand
7	PCaFlt3L ₂₉₄
8	nCaFlt3L ₁₀₁₃ complementary strand
9	nCaFlt3L ₈₈₂ coding strand

TABLE 1-continued

Sequence identification numbers (SEQ ID NOs) and their corresponding nucleic acid molecules or proteins.	
SEQ ID NO	DESCRIPTION
10	nCaFlt3L ₈₈₂ complementary strand
19	nCaIL-4 ₃₂₄ coding strand
20	PCaIL-4 ₁₀₈
21	nCaIL-4 ₃₂₄ complementary strand
22	nCaFlt3L ₈₀₄ coding strand
23	PCaFlt3L ₂₆₈
24	nCaFlt3L ₈₀₄ complementary strand
25	nCaFlt3L ₉₈₅ coding strand
26	PCaFlt3L ₂₇₆
27	nCaFlt3L ₉₈₅ complementary strand
28	nCaFlt3L ₈₂₈ coding strand
29	nCaFlt3L ₈₂₈ complementary strand
30	nCaFlt3L ₇₅₀ coding strand
31	PCaFlt3L ₂₅₀
32	nCaFlt3L ₇₅₀ complementary strand
33	nCaFlt3L ₁₀₁₉ coding strand
34	PCaFlt3L ₃₁
35	nCaFlt3L ₁₀₁₉ complementary strand
36	nCaFlt3L ₉₃ coding strand
37	nCaFlt3L ₉₃ complementary strand
41	nFeFlt3L ₃₉₅ coding strand
42	nFeFlt3L ₇₉₃ coding strand
43	nFeFlt3L ₉₄₂ coding strand
44	PFeFlt3L ₂₉₁
45	nFeFlt3L ₉₄₂ complementary strand
46	nFeFlt3L ₈₇₃ coding strand
47	nFeFlt3L ₈₇₃ complementary strand
48	nFeFlt3L ₇₉₅ coding strand
49	PFeFlt3L ₂₆₅
50	nFeFlt3L ₇₉₅ complementary strand
51	nCaCD40 ₃₂₄ coding strand
52	nCaCD40 ₁₄₂₅ coding strand
53	PCaCD40 ₂₇₄
54	nCaCD40 ₁₄₂₅ complementary strand
55	nCaCD40 ₈₂₂ coding strand
56	nCaCD40 ₈₂₂ complementary strand
57	nCaCD40 ₇₆₅ coding strand
58	PCaCD40 ₂₅₅
59	nCaCD40 ₇₆₅ complementary strand
60	nFeCD40 ₃₃₆ coding strand
61	PFeCD40 ₁₁₂
62	nFeCD40 ₃₃₆ complementary strand
63	nCaCD154 ₃₉₀ coding strand
64	nCaCD154 ₁₈₇₈ coding strand
65	PCaCD154 ₂₆₀
66	nCaCD154 ₁₈₇₈ complementary strand
67	nCaCD154 ₇₈₀ coding strand
68	nCaCD154 ₇₈₀ complementary strand
69	nCaCD154 ₆₃₃ coding strand
70	PCaCD154 ₂₁₁
71	nCaCD154 ₆₅₃ complementary strand
72	nFeCD154 ₈₈₅ coding strand
73	PFeCD154 ₂₆₀
74	nFeCD154 ₈₈₅ complementary strand
75	nFeCD154 ₇₅₀ coding strand
76	nFeCD154 ₇₅₀ complementary strand
77	nFeCD154 ₈₃₃ coding strand
78	PFeCD154 ₄
79	nFeCD154 ₈₃₃ complementary strand
80	nCaIL-5 ₆₁₀ coding strand
81	PCaIL-5 ₁₃₄
82	nCaIL-5 ₆₁₀ complementary strand
83	nCaIL-5 ₄₀₂ coding strand
84	nIL-5 ₄₀₂ complementary strand
85	nCaIL-5 ₃₄₉ coding strand
86	PCaIL-5 ₁₁₅
87	nCaIL-5 ₃₄₅ complementary strand
88	nCaIL-13 ₁₆₆ coding strand
89	nCaIL-13 ₂₇₂ coding strand
90	nCaIL-13 ₂₇₈ coding strand
91	nCaIL-13 ₁₃₀₂ coding strand
92	PCaIL-13 ₁₃₁
93	nCaIL-13 ₁₃₀₂ complementary strand

TABLE 1-continued

Sequence identification numbers (SEQ ID NOs) and their corresponding nucleic acid molecules or proteins.	
SEQ ID NO	DESCRIPTION
94	nCaIL-13 ₃₉₃ coding strand
95	nCaIL-13 ₃₉₃ complementary strand
96	nCaIL-13 ₃₃₃ coding strand
97	PaIL-13 ₁₁₁
98	nCaIL-13 ₃₃₃ complementary strand
99	nCaIL-13 ₁₂₆₉ coding strand
100	PCaIL-13 ₁₁₀
101	nCaIL-13 ₁₂₆₉ complementary strand
102	nCaIL-13 ₃₉₀ coding strand
103	nCaIL-13 ₃₉₀ complementary strand
104	nCaIL-13 ₃₃₀ coding strand
105	PCaIL-13 ₁₁₀
106	nCaIL-13 ₃₃₀ complementary strand
107	nFeIFNa _{567a} coding strand
108	PFeIFNo _{189a}
109	nFeIFNo _{567a} complementary strand
110	nFeIFNo _{567b} coding strand
111	PFeIFNo _{180b}
112	nFeIFNo _{567b} complementary strand
113	nFeIFNo _{498a} coding strand
114	PFeIFNo _{166a}
115	nFeIFNo _{498a} complementary strand
116	nFeFeIFNo _{498b} coding strand
117	PFeIFNo _{166b}
118	nFeIFNo _{498b} complementary strand
119	nFeGMCSF ₄₄₄ coding strand
120	PFeGMCSF ₁₆₄
121	nFeGMCSF ₄₄₄ complementary strand
122	nFeGMCSF ₄₃₂ coding strand
123	nFeGMCSF ₄₃₂ complementary strand
124	nFeGMCSF ₃₈₁ coding strand
125	PFeGMCSF ₁₂₇
126	nFeGMCSF ₃₈₁ complementary strand

In another embodiment, an IL-4 gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, SEQ ID NO:21, and/or any other IL-4 nucleic acid sequence cited herein. In another embodiment, a Flt-3 ligand gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50 and/or any other Flt-3 ligand nucleic acid sequence cited herein. In another embodiment, a CD40 gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62 and/or any other CD40 nucleic acid sequence cited herein. In another embodiment, a CD154 gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:79 and/or any other CD154 nucleic acid sequence cited herein. In another embodiment, an IL-5 gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84,

SEQ ID NO:85, SEQ ID NO:87 and/or any other IL-5 nucleic acid sequence cited herein. In another embodiment, an IL-13 gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106 and/or any other IL-13 nucleic acid sequence cited herein. In another embodiment, an IFN α gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, and/or SEQ ID NO:118 and/or any other IFN α nucleic acid sequence cited herein. In another embodiment, a GM-CSF gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, and/or SEQ ID NO:126 and/or any other GM-CSF nucleic acid sequence cited herein. An allelic variant of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF gene, including the particular SEQ ID NO's cited herein, is a gene that occurs at essentially the same locus (or loci) in the genome as the gene including the particular SEQ ID NO's cited herein, but which, due to natural variations caused by, for example, mutation or recombination, has a similar but not identical sequence. Also included in the term allelic variant are allelic variants of cDNAs derived from such genes. Because natural selection typically selects against alterations that affect function, allelic variants usually encode proteins having similar activity to that of the protein encoded by the gene to which they are being compared. Allelic variants of genes or nucleic acid molecules can also comprise alterations in the 5' or 3' untranslated regions of the gene (e.g., in regulatory control regions), or can involve alternative splicing of a nascent transcript, thereby bringing alternative exons into juxtaposition. Allelic variants are well known to those skilled in the art and would be expected to be found within a given animal, since the respective genomes are diploid, and sexual reproduction will result in the reassortment of alleles.

The minimal size of an canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein homolog of the present invention is a size sufficient to be encoded by a nucleic acid molecule capable of forming a stable hybrid (i.e., hybridize under stringent hybridization conditions) with the complementary sequence of a nucleic acid molecule encoding the corresponding natural protein. Stringent hybridization conditions are determined based on defined physical properties of the gene to which the nucleic acid molecule is being hybridized, and can be defined mathematically. Stringent hybridization conditions are those experimental parameters that allow an individual skilled in the art to identify significant similarities between heterologous nucleic acid molecules. These conditions are well known to those skilled in the art. See, for example, Sambrook, et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, and Meinkoth, et al., 1984, *Anal. Biochem.* 138, 267-284, each of which is incorporated herein by this reference. As explained in detail in the cited references, the determination of hybridization conditions

involves the manipulation of a set of variables including the ionic strength (M. in moles/liter), the hybridization temperature ($^{\circ}$ C.), the concentration of nucleic acid helix destabilizing agents, such as formamide, the average length of the shortest hybrid duplex (n), and the percent G+C composition of the fragment to which an unknown nucleic acid molecule is being hybridized. For nucleic acid molecules of at least about 150 nucleotides, these variables are inserted into a standard mathematical formula to calculate the melting temperature, or T_m , of a given nucleic acid molecule. As defined in the formula below, T_m is the temperature at which two complementary nucleic acid molecule strands will disassociate, assuming 100% complementarity between the two strands:

$$T_m = 81.5^{\circ} \text{ C.} + 16.6 \log M + 0.41(\%G+C) - 500/n - 0.61(\% \text{formamide}).$$

For nucleic acid molecules smaller than about 50 nucleotides, hybrid stability is defined by the dissociation temperature (T_d), which is defined as the temperature at which 50% of the duplexes dissociate. For these smaller molecules, the stability at a standard ionic strength is defined by the following equation:

$$T_d = 4(G+C) + 2(A+T).$$

A temperature of 5° C. below T_d is used to detect hybridization between perfectly matched molecules.

Also well known to those skilled in the art is how base pair mismatch, i.e. differences between two nucleic acid molecules being compared, including non-complementarity of bases at a given location, and gaps due to insertion or deletion of one or more bases at a given location on either of the nucleic acid molecules being compared, will affect T_m or T_d for nucleic acid molecules of different sizes. For example, T_m decreases about 1° C. for each 1% of mismatched base pairs for hybrids greater than about 150 bp, and T_d decreases about 5° C. for each mismatched base pair for hybrids below about 50 bp. Conditions for hybrids between about 50 and about 150 base pairs can be determined empirically and without undue experimentation using standard laboratory procedures well known to those skilled in the art. These simple procedures allow one skilled in the art to set the hybridization conditions, by altering, for example, the salt concentration, the formamide concentration or the temperature, so that only nucleic acid hybrids with greater than a specified % base pair mismatch will hybridize. Stringent hybridization conditions are commonly understood by those skilled in the art to be those experimental conditions that will allow about 30% base pair mismatch, i.e., about 70% identity. Because one skilled in the art can easily determine whether a given nucleic acid molecule to be tested is less than or greater than about 50 nucleotides, and can therefore choose the appropriate formula for determining hybridization conditions, he or she can determine whether the nucleic acid molecule will hybridize with a given gene or specified nucleic acid molecule under stringent hybridization conditions and similarly whether the nucleic acid molecule will hybridize under conditions designed to allow a desired amount of base pair mismatch.

Hybridization reactions are often carried out by attaching the nucleic acid molecule to be hybridized to a solid support such as a membrane, and then hybridizing with a labeled nucleic acid molecule, typically referred to as a probe, suspended in a hybridization solution. Examples of common hybridization reaction techniques include, but are not limited to, the well-known Southern and northern blotting procedures. Typically, the actual hybridization reaction is done

under non-stringent conditions, i.e., at a lower temperature and/or a higher salt concentration, and then high stringency is achieved by washing the membrane in a solution with a higher temperature and/or lower salt concentration in order to achieve the desired stringency.

Preferred portions, or fragments, of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF, protein of the present invention include at least 15 amino acids, at least 20 amino acids, at least 25 amino acids, at least 30 amino acids, at least 35 amino acids, at least 40 amino acids, at least 45 amino acids, at least 50 amino acids, at least 60 amino acids, at least 75 amino acids or at least 100 amino acids. An IL-4, IL-5, and/or IL-13 protein of the present invention can include at least a portion of an IL-4, IL-5, and/or IL-13 protein that is capable of binding to an IL-4, IL-5, and/or IL-13 receptor, respectively. IL-4, IL-5, and IL-13 receptors are known to those of skill in the art, and are described in Janeway et al., in *Immunobiology, the Immune System in Health and Disease*, Garland Publishing, Inc., NY, 1996 (which is incorporated herein by this reference in its entirety). The IL-4, IL-5, and/or IL-13 receptor-binding portion of an IL-4, IL-5, and/or IL-13 protein, respectively, can be determined by incubating the protein with an isolated IL-4, IL-5, and/or IL-13 receptor, as appropriate, or a cell having an IL-4, IL-5, and/or IL-13 receptor on its surface, as appropriate, IL-4, IL-5, and/or IL-13 protein binding to purified IL-4, IL-5, and/or IL-13 receptor, respectively, can be determined using methods known in the art including Biacore® screening, confocal immunofluorescent microscopy, immunoprecipitation, gel chromatography, determination of inhibition of binding of antibodies that bind specifically to the IL-4, IL-5, and/or IL-13 binding domain of an IL-4, IL-5, and/or IL-13 receptor. ELISA using an IL-4, IL-5, and/or IL-13 receptor, respectively, labeled with a detectable tag such as an enzyme or chemiluminescent tag or yeast-2 hybrid technology. A Flt-3 ligand protein of the present invention can include at least a portion of a Flt-3 ligand protein that is capable of binding to Flt-3 receptor or stimulating Flt-3 receptor-bearing hematopoietic stem cells, early hematopoietic progenitor cells or immature lymphocytes. Flt-3 receptors are known to those of skill in the art, and are described in Drexler, *Leukemia*, vol. 10, pp. 588-599, 1996 (which is incorporated herein in its entirety by this reference). The Flt-3 receptor-binding portion of a Flt-3 ligand protein can be determined by incubating the protein with isolated Flt-3 receptor or a cell having a Flt-3 receptor on its surface. Flt-3 ligand protein binding to purified Flt-3 receptor can be determined using methods known in the art including Biacore® screening, confocal immunofluorescent microscopy, immunoprecipitation, gel chromatography, determination of inhibition of binding of antibodies that bind specifically to the Flt-3 ligand binding domain of a Flt-3 receptor. ELISA using a Flt-3 receptor labeled with a detectable tag such as an enzyme or chemiluminescent tag or yeast-2 hybrid technology. A CD40 and/or CD154 protein of the present invention can include at least a portion of a CD40 and/or CD154 protein that is capable of binding to a CD40 and/or CD154 receptor, respectively, or stimulating CD40 and/or CD154 receptor-bearing hematopoietic stem cells, early hematopoietic progenitor cells or immature lymphocytes. The CD40 and/or CD154 receptor-binding portion of a CD40 and/or CD154 protein can be determined by incubating the protein with isolated CD40 and/or CD154 receptor, as appropriate, or a cell having a CD40 and/or CD154 receptor on its surface, as

appropriate. CD40 and/or CD154 protein binding to CD154 and/or CD40, respectively, can be determined using methods known in the art including Biacore® screening, confocal immunofluorescent microscopy, immunoprecipitation, gel chromatography, determination of inhibition of binding of antibodies that bind specifically to the CD40 and/or CD154 binding domain of CD40 and/or CD154, as appropriate, ELISA using a CD40 and/or CD154 labeled with a detectable tag such as an enzyme or chemiluminescent tag or yeast-2 hybrid technology.

The present invention also includes mimetopes of canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins of the present invention. As used herein, a mimetope of an immunoregulatory protein of the present invention refers to any compound that is able to mimic the activity of such a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively, often because the mimetope has a structure that mimics the particular protein. Mimetopes can be, but are not limited to: peptides that have been modified to decrease their susceptibility to degradation such as all-D retro peptides; anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous immunogenic portions of an isolated protein (e.g., carbohydrate structures); and/or synthetic or natural organic molecules, including nucleic acids. Such mimetopes can be designed using computer-generated structures of proteins of the present invention. Mimetopes can also be obtained by generating random samples of molecules, such as oligonucleotides, peptides or other organic molecules, and screening such samples by affinity chromatography techniques using the corresponding binding partner.

One embodiment of an immunoregulatory protein of the present invention is a fusion protein that includes either a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein-containing domain, each attached to one or more fusion segments. Suitable fusion segments for use with the present invention include, but are not limited to, segments that can: link two or more immunoregulatory proteins of the present invention, to form multimeric forms of an immunoregulatory protein of the present invention; enhance a protein's stability; act as an immunopotentiator to enhance an immune response against a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein; and/or assist in purification of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein (e.g., by affinity chromatography). A suitable fusion segment can be a domain of any size that has the desired function (e.g., imparts increased stability, imparts increased immunogenicity to a protein, and/or simplifies purification of a protein). Fusion segments can be joined to amino and/or carboxyl termini of the IL-4-containing domain, or the Flt-3 ligand-containing domain, or the CD40-containing domain, or the CD154-containing domain, or the IL-5-containing domain, or the IL-13-containing domain, or the IFN α -containing domain, or GM-CSF-containing domain, of a protein and can be susceptible to cleavage in order to enable straightforward recovery of either canine interleukin-4, canine or

feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively. Fusion proteins are preferably produced by culturing a recombinant cell transformed with a fusion nucleic acid molecule that encodes a protein including the fusion segment attached to either the carboxyl and/or amino terminal end of an canine interleukin-4-, canine or feline Flt-3 ligand-, canine or feline CD40-, canine or feline CD154-, canine interleukin-5-, canine interleukin-13-, feline interferon alpha-, or feline GM-CSF-containing domain. Preferred fusion segments include a metal binding domain (e.g., a poly-histidine segment); an immunoglobulin binding domain (e.g., Protein A; Protein G; T cell; B cell; Fc receptor or complement protein antibody-binding domain); a sugar binding domain (e.g., a maltose binding domain); and/or a "tag" domain (e.g., at least a portion of -galactosidase, a strep tag peptide, a T7 tag peptide, a Flag™ peptide, or other domains that can be purified using compounds that bind to the domain, such as monoclonal antibodies). More preferred fusion segments include metal binding domains, such as a poly-histidine segment; a maltose binding domain; a strep tag peptide, such as that available from Biometra in Tampa, Fla.; and an S10 peptide.

A suitable fusion segment that links one IL-4 protein to another IL-4 protein, or one Flt-3 ligand protein to another Flt-3 ligand protein, or one CD40 protein to another CD40 protein, or one CD154 protein to another CD154 protein, or one IL-5 protein to another IL-5 protein to another IL-5 protein, or one IL-13 protein to another IL-13 protein, or one IFN α protein to another IFN α protein, or one GM-CSF protein to another GM-CSF protein, includes any amino acid sequence that enables such proteins to be linked while maintaining the biological function of either the canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins, respectively. Selection of a suitable linker is dependent upon how many proteins are to be linked to form one multimeric molecule and from where on either the canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF molecule the linker extends. Preferably, a linker fusion segment of the present invention comprises a peptide of from about 6 amino acid residues to about 40 residues, more preferably from about 6 residues to about 30 residues in length.

In another embodiment, an canine interleukin-4, canine or feline, Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein of the present invention also includes at least one additional protein segment that is capable of targeting either canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively, to a desired cell or receptive molecule. Such a multivalent targeting protein can be produced by culturing a cell transformed with a nucleic acid molecule comprising two or more nucleic acid domains joined together in such a manner that the resulting nucleic acid molecule is expressed as a multivalent targeting protein containing a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein or portion thereof and/or at least one targeting

compound capable of delivering the canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively, to a desired site in an animal.

Examples of multivalent targeting proteins include, but are not limited to, a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein of the present invention attached to one or more compounds that can bind to a receptive molecule on the surface of a cell located in an area of an animal where regulation of an immune response is desired. One of skill in the art can select appropriate targeting fusion segments depending upon the cell or receptive molecule being targeted.

Another example of a multivalent protein of the present invention includes, but is not limited to, a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein of the present invention attached to one or more proteins that are potentially antigenic in mammals. Thus, immunogenicity of the potentially antigenic protein could be enhanced by administering to a mammal together with an immunoregulatory protein of the present invention.

A naturally-occurring variant of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein of the present invention is preferably isolated from (including isolation of the natural protein or production of the protein by recombinant or synthetic techniques) from mammals, including but not limited to dogs (i.e., canids), cats (i.e., felids), horses (i.e., equids), humans, cattle, chinchillas, ferrets, goats, mice, minks, rabbits, raccoons, rats, sheep, squirrels, swine, chickens, ostriches, quail and/or turkeys as well as other furry animals, pets, zoo animals, work animals and/or food animals. Particularly preferred animals from which to isolate canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF proteins are dogs, cats, horses, and/or humans.

A preferred isolated protein of the present invention is a protein encoded by at least one of the following nucleic acid molecules: nCaIL-4₅₄₉, nCaIL-4₃₉₆, nCaIL-4₃₂₄, nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, nCaFlt3L₇₅₀, nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nFeFlt3L₈₇₃, nFeFlt3L₇₉₅, nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, nCaCD40₇₆₅, nFeCD40₃₃₆, nCaCD154₃₉₀, nCaCD154₈₇₈, nCaCD154₇₈₀, nCaCD154₆₃₃, nFeCD154₈₈₅, nFeCD154₇₈₀, nFeCD154₆₃₃, nCaIL-5₆₁₀, nCaIL-5₄₀₂, nCaIL-5₃₄₅, nCaIL-13₁₆₆, nCaIL-13₂₇₂, nCaIL-13₂₇₈, nCaIL-13₁₃₀₂, nCaIL-13₃₉₃, nCaIL-13₃₃₃, nCaIL-13₁₂₆₉, nCaIL-13₃₉₀, nCaIL-13₃₃₀, nFeIFN α _{567a}, nFeIFN α _{567b}, nFeIFN α _{498a}, nFeIFN α _{498b}, nFeGMCSF₄₄₄, nFeGMCSF₄₃₂, nFeGMCSF₃₈₁ and/or allelic variants of any of these nucleic acid molecules. Also preferred is an isolated protein that is encoded by a nucleic acid molecule the having nucleic acid sequence SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:19, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:57, SEQ ID

NO:60, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:80, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:119, SEQ ID NO:122, SEQ ID NO:124; and/or an allelic variant of such a nucleic acid molecule.

Translation of SEQ ID NO:1, the coding strand of nCaIL-4₅₄₉, yields a protein of about 132 amino acids, denoted herein as PCaIL-4₁₃₂, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having an initiation codon spanning from nucleotide 43 through nucleotide 45 of SEQ ID NO:1 and a stop codon spanning from nucleotide 439 through nucleotide 441 of SEQ ID NO:1.

Translation of SEQ ID NO:6, the coding strand of nCaFlt3L₁₀₁₃, yields a protein of about 294 amino acids, denoted herein as PCaFlt3L₂₉₄, the amino acid sequence of which is presented in SEQ ID NO:7, assuming an open reading frame having an initiation codon spanning from nucleotide 35 through nucleotide 37 of SEQ ID NO:6 and a stop codon spanning from nucleotide 917 through nucleotide 919 of SEQ ID NO:6.

Translation of SEQ ID NO:43, the coding strand for nFeFlt3L₉₄₂, yields a protein of about 291 amino acids, denoted herein as PFeFlt3L₂₉₁, the amino acid sequence of which is presented in SEQ ID NO:44, assuming an open reading frame having an initiation codon spanning from nucleotide 31 through nucleotide 33 of SEQ ID NO:43 and a stop codon spanning from nucleotide 904 through nucleotide 906 of SEQ ID NO:43.

Translation of SEQ ID NO:52, the coding strand for nCaCD40₁₄₂₅, yields a protein of about 274 amino acids, denoted herein as PCaCD40₂₇₄, the amino acid sequence of which is presented in SEQ ID NO:53, assuming an open reading frame having an initiation codon spanning from nucleotide 196 through nucleotide 198 of SEQ ID NO:52 and a stop codon spanning from about nucleotide 1018 through nucleotide 1020 of SEQ ID NO:52.

Translation of SEQ ID NO:60, the coding strand for nFeCD40₃₃₆, yields a protein of about 112 amino acids, denoted herein as PFeCD40₁₁₂, the amino acid sequence of which is presented in SEQ ID NO:61, assuming an open reading frame having an initiation codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:60.

Translation of SEQ ID NO:64, the coding strand for nCaCD154₁₈₇₈, yields a protein of about 260 amino acids, denoted herein as PCaCD154₂₆₀, the amino acid sequence of which is presented in SEQ ID NO:65, assuming an open reading frame having an initiation codon spanning from nucleotide 284 through nucleotide 286 of SEQ ID NO:64 and a stop codon spanning from nucleotide 1064 through nucleotide 1066 of SEQ ID NO:64.

Translation of SEQ ID NO:72, the coding strand for nFeCD154₈₈₅, yields a protein of about 260 amino acids, denoted herein as PFeCD154₂₆₀, the amino acid sequence of which is presented in SEQ ID NO:73, assuming an open reading frame having an initiation codon spanning from nucleotide 29 through nucleotide 31 of SEQ ID NO:72, and a stop codon spanning from nucleotide 809 through nucleotide 811 of SEQ ID NO:72.

Translation of SEQ ID NO:80, the coding strand for nCaIL-5₆₁₀, yields a protein of about 134 amino acids, denoted herein as PCaIL-5₁₃₄, the amino acid sequence of which is presented in SEQ ID NO:81, assuming an open

reading frame having an initiation codon spanning from nucleotide 29 through nucleotide 31 of SEQ ID NO:80, and a stop codon spanning from nucleotide 431 through nucleotide 433 of SEQ ID NO:80.

Translation of SEQ ID NO:91, the coding strand for nCaIL-13₁₃₀₂, yields a protein of about 131 amino acids, denoted herein as PCaIL-13₁₃₁, the amino acid sequence of which is presented in SEQ ID NO:92, assuming an open reading frame having an initiation codon spanning from nucleotide 52 through nucleotide 54 of SEQ ID NO:91 and a stop codon spanning from nucleotide 445 through nucleotide 447 of SEQ ID NO:91.

Translation of SEQ ID NO:107, the coding strand for nFeIFN α _{567a}, yields a protein of about 189 amino acids, denoted herein as PFeIFN α _{189a}, the amino acid sequence of which is presented in SEQ ID NO:108, assuming an open reading frame having an initiation codon spanning from nucleotide 1 through nucleotide 3 and a last codon prior to a stop codon spanning from nucleotide 565 through nucleotide 567 of SEQ ID NO:107.

Translation of SEQ ID NO:119, the coding strand for nFeGMCSF₄₄₄, yields a protein of about 144 amino acids, denoted herein as PFeGMCSF₁₄₄, the amino acid sequence of which is presented in SEQ ID NO:120, assuming an open reading frame having an initiation codon spanning from nucleotide 10 through nucleotide 12 of SEQ ID NO:119 and a stop codon spanning from nucleotide 442 through nucleotide 444 of SEQ ID NO:119.

Preferred IL-4 proteins of the present invention include proteins that are at least about 85%, preferably at least about 90%, and even more preferably at least about 95% identical to PCaIL-4₁₃₂, PCaIL-4₁₀₈, or fragments thereof. Preferred Flt-3 ligand proteins of the present invention include proteins that are at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to PCaFlt3L₂₉₄, PCaFlt3L₂₆₈, PCaFlt3L₂₇₆, PCaFlt3L₂₅₀, PCaFlt3L₃₁, and/or fragments thereof. Additional preferred Flt-3 ligand proteins of the present invention includes proteins that are at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to PFeFlt3L₂₉₁, PFeFlt3L₂₆₅ and/or fragments thereof. Preferred CD40 proteins of the present invention includes proteins that are at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to PCaCD40₂₇₄, PCaCD40₂₅₅ and/or fragments thereof. Additional preferred CD40 proteins of the present invention includes proteins that are at least about 60%, at least about 65%, preferably at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to PFeCD40₁₁₂ and/or fragments thereof. Preferred CD154 proteins of the present invention includes proteins that are at least about 80% identical, preferably at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to PCaCD154₂₆₀, PCaCD154₂₁₁ and/or fragments thereof. Additional preferred CD154 proteins of the present invention includes proteins that are at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to PFeCD154₂₆₀,

PFeCD154₂₁₁ and/or fragments thereof. Preferred IL-5 proteins of the present invention includes proteins that are at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to PCaIL-5₁₃₄, PCaIL-5₁₁₅ and/or fragments thereof. Preferred IL-13 proteins of the present invention includes proteins that are at least about 70% identical, preferably at least about 75% identical, more preferably at least about 80% identical, more preferably at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to PCaIL-13₁₃₁, PCaIL-13₁₁₁, PCaIL-13₁₃₀, PCaIL-13110, and/or fragments thereof. Preferred IFN α proteins of the present invention include PFeIFN α _{189a}, PFeIFN α _{189b}, PFeIFN α _{166a}, and/or PFeIFN α _{166b}. Preferred GM-CSF proteins of the present invention include PFeGMCSF₁₄₄, and/or PFeGMCSF₁₂₇.

More preferred are IL-4 proteins comprising PCaIL-4₁₃₂, PCaIL-4₁₀₈, and/or proteins encoded by allelic variants of a nucleic acid molecule encoding proteins PCaIL-4₁₃₂ and/or PCaIL-4₁₀₈. More preferred are Flt-3 ligand proteins comprising PCaFlt3L₂₉₄, PCaFlt3L₂₆₈, PCaFlt3L₂₇₆, PCaFlt3L₂₅₀, PCaFlt3L₃₁, PFeFlt3L₂₉₁, PFeFlt3L₂₆₅ and/or proteins encoded by allelic variants of a nucleic acid molecule encoding proteins PCaFlt3L₂₉₄, PCaFlt3L₂₆₈, PCaFlt3L₂₇₆, PCaFlt3L₂₅₀, PCaFlt3L₃₁, PFeFlt3L₂₉₁, and/or PFeFlt3L₂₆₅. More preferred are CD40 proteins comprising PCaCD40₂₇₄, PCaCD40₂₅₅, and/or PFeCD40₁₁₂ and/or proteins encoded by allelic variants of a nucleic acid molecule encoding proteins PCaCD40₂₇₄, PCaCD40₂₅₅, and/or PFeCD40₁₁₂. More preferred are CD154 proteins comprising PCaCD154₂₆₀, PCaCD154₂₁₁, PFeCD154₂₆₀, PFeCD154₂₁₁ and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of proteins PCaCD154₂₆₀, PCaCD154₂₁₁, PFeCD154₂₆₀, PFeCD154₂₁₁. More preferred are IL-5 proteins comprising PCaIL-5₁₃₄, PCaIL-5₁₁₅ and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of the proteins PCaIL-5₁₃₄ and/or PCaIL-5₁₁₅. More preferred are IL-13 proteins comprising PCaIL-13₁₃₁, PCaIL-13₁₁₁, PCaIL-13₁₃₀, PCaIL-13₁₁₀, and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of the proteins PCaIL-13₁₃₁, PCaIL-13₁₁₁, PCaIL-13₁₃₀, PCaIL-13₁₁₀.

Also preferred are IL-4 proteins of the present invention having amino acid sequences that are at least about 85%, preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:2, SEQ ID NO:20 and/or fragments thereof. Also preferred are Flt-3 ligand proteins of the present invention having amino acid sequences that are at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34 and/or fragments thereof. Additional preferred are Flt-3 ligand proteins of the present invention includes proteins that are at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and/or even more preferably at least about 95% identical to

SEQ ID NO:53, SEQ ID NO:58 and/or fragments thereof. Additional preferred CD40 proteins of the present invention includes proteins that are at least about 60%, at least about 65%, preferably at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:61 and/or fragments thereof. Preferred CD154 proteins of the present invention includes proteins that are at least about 80% identical, preferably at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:65, SEQ ID NO:70 and/or fragments thereof. Additional preferred CD154 proteins of the present invention includes proteins that are at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:73, SEQ ID NO:78 and/or fragments thereof. Preferred IL-5 proteins of the present invention includes proteins that are at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:81, SEQ ID NO:86 and/or fragments thereof. Preferred IL-13 proteins of the present invention includes proteins that are at least about 70% identical, preferably at least about 75% identical, more preferably at least about 80% identical, more preferably at least about 85% identical, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, SEQ ID NO:105, and/or fragments thereof. Preferred IFN α proteins of the present invention include SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, SEQ ID NO:117. Preferred GM-CSF proteins of the present invention include SEQ ID NO:120, SEQ ID NO:125.

More preferred are IL-4 proteins comprising the amino acid sequence SEQ ID NO:2, SEQ ID NO:20; and/or IL-4 proteins encoded by allelic variants of nucleic acid molecules encoding IL-4 proteins having the amino acid sequence SEQ ID NO:2, SEQ ID NO:20. More preferred are Flt-3 ligand proteins comprising SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31 and/or SEQ ID NO:34, SEQ ID NO:44, SEQ ID NO:49 and/or proteins encoded by allelic variants of a nucleic acid molecule encoding proteins SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:44, and/or SEQ ID NO:49. More preferred are CD40 proteins comprising SEQ ID NO:53, SEQ ID NO:58, SEQ ID NO:61 and/or proteins encoded by allelic variants of a nucleic acid molecule encoding proteins SEQ ID NO:53, SEQ ID NO:58 and/or SEQ ID NO:61. More preferred are CD154 proteins comprising SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:73, SEQ ID NO:78 and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of proteins SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:73, and/or SEQ ID NO:78. More preferred are IL-5 proteins comprising SEQ ID NO:81, SEQ ID NO:86 and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of the proteins SEQ ID NO:81, and/or SEQ ID NO:86. More preferred are IL-13 proteins comprising SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, SEQ ID NO:105, and/or proteins encoded by allelic variants of a nucleic acid molecule encoding one of the proteins SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105.

Percent identities between amino acid or nucleic acid sequences can be determined using standard methods known to those of skill in the art. It is known in the art that methods to determine the percentage identity and the number of gaps

are substantially similar when different methods for determining sequence similarity are used and when the degree of similarity is greater than 30% amino acid identity, as described by Johnson et al., *J. Mol. Biol.*, vol. 233, pages 716–738, 1993, and Feng et al., *J. Mol. Evol.*, vol. 21, pages 112–125, 1985, which are incorporated by reference herein in their entirety. Preferred methods to determine percentage identities between amino acid sequences and between nucleic acid sequences include comparisons using various computer programs such as GCG™ program (available from Genetics Computer Group, Madison, Wis.), DNAsis™ program (available from Hitachi Software, San Bruno, Calif.) or the MacVector™ program (available from the Eastman Kodak Company, New Haven, Conn.). Preferred settings for sequence comparisons using the DNAsis™ computer program or the GAP GCG™ program are disclosed herein in the Examples section.

Additional preferred IL-4 proteins of the present invention include proteins encoded by nucleic acid molecules comprising at least a portion of nCaIL-4₅₄₉, nCaIL-4₃₉₆, and/or nCaIL-4₃₂₄, as well as IL-4 proteins encoded by allelic variants of such nucleic acid molecules. Additional preferred Flt-3 ligand proteins of the present invention include proteins encoded by nucleic acid molecules comprising at least a portion of nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, nCaFlt3L₇₅₀, nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nCaFlt3L₈₇₃, and/or nFeFlt3L₇₉₅ as well as Flt-3 ligand proteins encoded by allelic variants of such nucleic acid molecules. Additional preferred CD40 proteins of the present invention include proteins encoded by nucleic acid molecules encoding at least a portion of nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, nCaCD40₇₆₅, and/or nFeCD40₃₃₆ as well as CD40 proteins encoded by allelic variants of such nucleic acid molecules. Additional preferred CD154 proteins of the present invention include proteins encoded by nucleic acid molecules encoding at least a portion of nCaCD154₃₉₀, nCaCD154₈₇₉, nCaCD154₇₈₀, nCaCD154₆₃₃, nFeCD154₈₈₅, nFeCD154₇₈₀, and/or nFeCD154₆₃₃ as well as CD154 proteins encoded by allelic variants of such nucleic acid molecules. Additional preferred IL-5 proteins of the present invention include proteins encoded by nucleic acid molecules encoding at least a portion of nCaIL-5₆₁₀, nCaIL-5₄₀₂, and/or nCaIL-5₃₄₅ as well as IL-5 proteins encoded by allelic variants of such nucleic acid molecules. Additional preferred IL-13 proteins of the present invention include proteins encoded by nucleic acid molecules encoding at least a portion of nCaIL-5₆₁₀, nCaIL-5₄₀₂, and/or nCaIL-5₃₄₅ as well as IL-13 proteins encoded by allelic variants of such nucleic acid molecules.

Also preferred are IL-4 proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:1, SEQ ID NO:4, and/or SEQ ID NO:19, as well as allelic variants of these nucleic acid molecules. Also preferred are Flt-3 ligand proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:46, and/or SEQ ID NO:48, as well as allelic variants of these nucleic acid molecules. Also preferred are CD40 proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:57, and/or SEQ ID NO:60, as well as allelic variants of these nucleic acid molecules. Also preferred are CD154 proteins encoded

by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, and/or SEQ ID NO:77, as well as allelic variants of these nucleic acid molecules. Also preferred are IL-5 proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:80, SEQ ID NO:83, and/or SEQ ID NO:85, as well as allelic variants of these nucleic acid molecules. Also preferred are IL-13 proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, and/or SEQ ID NO:104, as well as allelic variants of these nucleic acid molecules.

Another embodiment of the present invention is a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecule that includes one or more regulatory regions, full-length or partial coding regions, or combinations thereof. The minimal size of a nucleic acid molecule of the present invention is a size sufficient to allow the formation of stable hybrid (i.e., hybridization under stringent hybridization conditions) with the complementary sequence of another nucleic acid molecule. As such, the minimal size of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecule of the present invention is from about 12 to about 18 nucleotides in length.

In accordance with the present invention, an isolated nucleic acid molecule is a nucleic acid molecule that has been removed from its natural milieu (i.e., that has been subjected to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. As such, “isolated” does not reflect the extent to which the nucleic acid molecule has been purified. An isolated canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecule of the present invention can be isolated from its natural source or produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification or cloning) or chemical synthesis. Isolated canine, interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF, nucleic acid molecules can include, for example, natural allelic variants and/or nucleic acid molecules modified by nucleotide insertions, deletions, substitutions, and/or inversions in a manner such that the modifications do not substantially interfere with the nucleic acid molecule’s ability to encode an canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF protein of the present invention.

A canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, and/or feline GM-CSF ligand nucleic acid molecule homolog can be produced using a number of methods known to those skilled in the art, see, for example, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press: Sambrook et al., *ibid.*, is incorporated by reference herein in its entirety. For

example, nucleic acid molecules can be modified using a variety of techniques including, but not limited to, classic mutagenesis and recombinant DNA techniques such as site-directed mutagenesis, chemical treatment, restriction enzyme cleavage, ligation of nucleic acid fragments, PCR amplification, synthesis of oligonucleotide mixtures and ligation of mixture groups to “build” a mixture of nucleic acid molecules, and combinations thereof. Nucleic acid molecule homologs can be selected by hybridization with either a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecule or by screening the function of a protein encoded by the nucleic acid molecule (e.g., ability to elicit an immune response against at least one epitope of a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, respectively).

An isolated nucleic acid molecule of the present invention can include a nucleic acid sequence that encodes at least one canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein of the present invention, examples of such proteins being disclosed herein. Although the phrase “nucleic acid molecule” primarily refers to the physical nucleic acid molecule and the phrase “nucleic acid sequence” primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF ligand protein.

A preferred nucleic acid molecule of the present invention, when administered to an animal, is capable of regulating an immune response in an animal. As will be disclosed in more detail below, such a nucleic acid molecule can be, or encode, an antisense RNA, a molecule capable of triple helix formation, a ribozyme, or other nucleic acid-based drug compound. In additional embodiments, a nucleic acid molecule of the present invention can encode an immunoregulatory protein (e.g., a cell-bound or soluble protein of the present invention), the nucleic acid molecule being delivered to the animal, for example, by direct injection (i.e. as a genetic vaccine) or in a vehicle such as a recombinant virus vaccine or a recombinant cell vaccine.

One embodiment of the present invention is an IL-4 nucleic acid molecule comprising all or part (i.e., a fragment of the IL-4 nucleic acid molecule) of nucleic acid molecules nCaIL-4₅₄₉, nCaIL-4₃₉₆, and/or nCaIL-4₃₂₄, or allelic variants of these nucleic acid molecules. One embodiment of the present invention is a Flt-3 ligand nucleic acid molecule comprising all or part (i.e., a fragment of the Flt-3 ligand nucleic acid molecule) of nucleic acid molecules nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, nCaFlt3L₇₅₀, nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nFeFlt3L₈₇₃, and/or nFeFlt3L₇₉₅ and/or allelic variants of these nucleic acid molecules. One embodiment of the present invention is a CD40 nucleic acid molecule comprising all or part (i.e., a fragment of the CD40 nucleic acid molecule) of nucleic acid molecules nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, nCaCD40₇₆₅, and/or nFeCD40₃₃₆ and/or allelic variants of these nucleic acid molecules. One embodiment of the

present invention is a CD154 nucleic acid molecule comprising all or part of nucleic acid molecules nCaCD154₃₉₀, nCaCD154₁₈₇₈, nCaCD154₇₈₀, nCaCD154₆₃₃, nFeCD154₈₈₅, nFeCD154₇₈₀, and/or nFeCD154₆₃₃, and/or allelic variants of these nucleic acid molecules. One embodiment of the present invention is an IL-5 nucleic acid molecule comprising all or part of nucleic acid molecules nCaIL-5₆₁₀, nCaIL-5₄₀₂, and/or nCaIL-5₃₄₅, and/or allelic variants of these nucleic acid molecules. One embodiment of the present invention is an IL-13 nucleic acid molecule comprising all or part of nucleic acid molecules nCaIL-13₁₆₆, nCaIL13₂₇₂, nCaIL-13₂₇₈, nCaIL-13₁₃₀₂, nCaIL-13₃₉₃, nCaIL-13₃₃₃, nCaIL-13₁₂₆₉, nCaIL-13₃₉₀, and/or nCaIL-13₃₃₀, and/or allelic variants of these nucleic acid molecules. Another preferred nucleic acid molecule of the present invention includes at least a portion of (i.e., a fragment of the nucleic acid molecule) nucleic acid sequence SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124; and/or SEQ ID NO:126, as well as allelic variants of nucleic acid molecules having these nucleic acid sequences. Such nucleic acid molecules can include nucleotides in addition to those included in the SEQ ID NOs, such as, but not limited to, a full-length gene, a full-length coding region, a nucleic acid molecule encoding a fusion protein, and/or a nucleic acid molecule encoding a multivalent therapeutic compound.

One embodiment of an isolated nucleic acid molecule of the present invention is a nucleic acid molecule that can be any of the following: (a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21 and/or a homolog thereof, wherein said homolog has an at least 50 contiguous nucleotide region identical in sequence to a 50 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21; (b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33,

SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37, and/or a homolog thereof, wherein said homolog has an at least 40 contiguous nucleotide region identical in sequence to a 40 contiguous nucleotide region of a nucleic acid sequence having a nucleic acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37; (c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50, and/or a homolog thereof, wherein said homolog has an at least 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50; (d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59, and/or a homolog thereof, wherein said homolog has an at least 40 contiguous nucleotide region identical in sequence to a 40 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59; (e) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:60 and/or SEQ ID NO:62 and/or a homolog thereof, wherein said homolog has an at least 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:60 and/or SEQ ID NO:62; (f) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69 and/or SEQ ID NO:71, and/or a homolog thereof, wherein said homolog has an at least 45 contiguous nucleotide region identical in sequence to a 45 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, and/or SEQ ID NO:71; (g) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79, and/or a homolog thereof, wherein said homolog has an at least 35 contiguous nucleotide region identical in sequence to a 35 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79; (h) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87, and/or a homolog thereof, wherein said homolog has an at least 45 contiguous nucleotide region identical in sequence to a 45 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from

the group consisting of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85 and/or SEQ ID NO:87; (i) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106, and/or a homolog thereof, wherein said homolog has an at least 15 contiguous nucleotide region identical in sequence to a 15 contiguous nucleotide region of a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106; (j) an isolated nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, and/or SEQ ID NO:118, and/or (k) an isolated nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, and/or SEQ ID NO:126. The phrase, a homolog having an at least "x" contiguous nucleotide region identical in sequence to an "x" contiguous nucleotide region of a nucleic acid molecule selected from the group consisting of SEQ ID NO:"y", refers to an "x"-nucleotide in length nucleic acid molecule that is identical in sequence to an "x"-nucleotide portion of SEQ ID NO:"y", as well as to nucleic acid molecules that are longer in length than "x". The additional length may be in the form of nucleotides that extend from either the 5' or the 3' end(s) of the contiguous identical "x"-nucleotide portion. The 5' and/or 3' extensions can include one or more extensions that have no identity to an immunoregulatory molecule of the present invention, as well as extensions that show similarity or identity to cited nucleic acids sequences or portions thereof.

In another embodiment, an isolated nucleic acid molecule of the present invention can be any of the following: (a) a nucleic acid molecule having a nucleic acid sequence encoding an IL-4 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20; (b) a nucleic acid molecule having a nucleic acid sequence encoding a Flt-3 ligand protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34, and/or (ii) a protein comprising a fragment of at least 25 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34; (c) a nucleic acid molecule having a nucleic acid sequence encoding a Flt-3 ligand protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49 and/or

(ii) a protein comprising a fragment of at least 25 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:44 and/or SEQ ID NO:49; (d) a nucleic acid molecule having a nucleic acid sequence encoding a CD40 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:53 and/or SEQ ID NO:58 and/or (ii) a protein comprising a fragment of at least 30 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:53 and/or SEQ ID NO:58; (e) a nucleic acid molecule having a nucleic acid sequence encoding a CD40 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 60 percent identical to an amino acid sequence comprising SEQ ID NO:61 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence comprising SEQ ID NO:61; (f) a nucleic acid molecule having a nucleic acid sequence encoding a CD154 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 80 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70, and/or (ii) a protein comprising a fragment of at least 35 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:65 and/or SEQ ID NO:70; (g) a nucleic acid molecule having a nucleic acid sequence encoding a CD154 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:73 and/or SEQ ID NO:78, and/or (ii) a protein comprising a fragment of at least 50 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:73 and/or SEQ ID NO:78; (h) a nucleic acid molecule having a nucleic acid sequence encoding an IL-5 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86 and/or (ii) a protein comprising a fragment of at least 20 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86; (i) a nucleic acid molecule having a nucleic acid sequence encoding an IL-13 protein selected from the group consisting of (i) a protein having an amino acid sequence that is at least about 70 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105 and/or (ii) a protein comprising a fragment of at least 15 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105; (j) a nucleic acid molecule having a nucleic acid sequence encoding an interferon alpha protein having an amino acid sequence that is selected from the group consisting of amino acid sequence SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117, (k) a nucleic acid molecule having a nucleic acid sequence encoding a GMCSF protein having an amino acid sequence that is selected from the group consisting of amino acid sequence SEQ ID NO:120, SEQ ID NO:126 and/or (l) a nucleic acid molecule comprising a complement of any of the before-mentioned nucleic acid sequences, wherein said IL-4 protein elicits an immune response against an IL-4 protein selected from the group consisting of SEQ ID NO:2 and/or SEQ ID NO:20 and/or is a protein with interleukin-4 activity, said Flt-3 ligand protein elicits an immune response against a

Flt-3 ligand protein selected from the group consisting of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:44, and/or SEQ ID NO:49 and/or is a protein with Flt-3 ligand activity, said CD40 protein elicits an immune response against a CD40 protein selected from the group consisting of SEQ ID NO:53, SEQ ID NO:58, and/or SEQ ID NO:61 and/or is a protein with CD40 activity, said CD154 protein elicits an immune response against a CD154 protein selected from the group consisting of SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:73, and/or SEQ ID NO:78 and/or is a protein with CD154 activity, said IL-5 protein elicits an immune response against a IL-5 protein selected from the group consisting of SEQ ID NO:81 and/or SEQ ID NO:86 and/or is a protein with IL-5 activity, said IL-13 protein elicits an immune response against an IL 13 protein selected from the group consisting of SEQ ID NO:92, SEQ ID NO:97, SEQ ID NO:100, and/or SEQ ID NO:105 and/or is a protein with IL-13 activity, said interferon alpha protein elicits an immune response against an interferon alpha protein selected from the group consisting of SEQ ID NO:108, SEQ ID NO:111, SEQ ID NO:114, and/or SEQ ID NO:117 and/or is a protein with interferon alpha activity, and said GMCSF protein elicits an immune response against a GMCSF protein selected from the group consisting of SEQ ID NO:120 and/or SEQ ID NO:125 and/or is a protein with GM-CSF activity.

In one embodiment, an IL-4 nucleic acid molecule of the present invention encodes a protein that is at least about 85%, preferably at least about 90%, preferably at least about 92%, and even more preferably at least about 95% identical to P_{Ca}IL-4₁₃₂ and/or P_{Ca}IL-4₁₀₈. In one embodiment, a Flt-3 ligand nucleic acid molecule of the present invention encodes a protein that is at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Ca}Flt3L₂₉₄, P_{Ca}Flt3L₂₆₈, P_{Ca}Flt3L₂₇₆, P_{Ca}Flt3L₂₅₀, and/or P_{Ca}Flt3L₃₁. In one embodiment, a Flt-3 ligand nucleic acid molecule of the present invention encodes a protein that is at least about 75%, more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Fe}Flt3L₂₉₁, and/or P_{Fe}Flt3L₂₆₅. In one embodiment, a CD40 nucleic acid molecule of the present invention encodes a protein that is at least about P_{Ca}CD40₂₇₄, and/or P_{Ca}CD40₂₅₅. In one embodiment, a CD40 nucleic acid molecule of the present invention encodes a protein that is at least about 60%, preferably at least about 65%, preferably at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Fe}CD40₁₁₂. In one embodiment, a CD154 nucleic acid molecule of the present invention encodes a protein that is at least about 80%, at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Ca}CD154₂₆₀, and/or P_{Ca}CD154₂₁₁. In one embodiment, a CD154 nucleic acid molecule of the present invention encodes a protein that is at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Fe}CD154₂₆₀, P_{Fe}CD154₂₁₁. In one embodiment, an IL-5 nucleic acid molecule of the present invention encodes a protein that is at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to P_{Ca}IL-5₁₃₄, and/or P_{Ca}IL-5₁₁₅. In one

embodiment, an IL-13 nucleic acid molecule of the present invention encodes a protein that is at least about 70%, at least about 75%, at least about 80%, preferably at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to PCaIL-13₁₃₁, PCaIL-13₁₁₁, PCaIL-13₁₃₀, PCaIL-13₁₁₀. Even more preferred is a nucleic acid molecule encoding PCaIL-4₁₃₂, PCaIL-4₁₀₈, PCaFlt3L₂₉₄, PCaFlt3L₂₆₈, PCaFlt3L₂₇₆, PCaFlt3L₂₅₀, PCaFlt3L₃₁, PFeFlt3L₂₉₁, PFeFlt3L₂₆₅, PCaCD40₂₇₄, PCaCD40₂₅₅, PFeCD40₁₁₂, PCaCD154₂₆₀, PCaCD154₂₁₁, PFeCD154₂₆₀, PFeCD154₂₁₁, PCaIL-5₁₃₄, PCaIL-5₁₁₅, PCaIL-13₁₃₁, PCaIL-13₁₁₁, PCaIL-13₁₃₀, PCaIL-13₁₁₀ and/or an allelic variant of such a nucleic acid molecule.

In another embodiment, an IL-4 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 85%, preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:2, SEQ ID NO:20. The present invention also includes an IL-4 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:2, and/or SEQ ID NO:20, as well as allelic variants of an IL-4 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a Flt-3 ligand nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34. The present invention also includes a Flt-3 ligand nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:31, and/or SEQ ID NO:34, as well as allelic variants of a Flt-3 ligand nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a Flt-3 ligand nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 75%, more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:44, and/or SEQ ID NO:49. The present invention also includes a Flt-3 ligand nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:44, and/or SEQ ID NO:49, as well as allelic variants of a Flt-3 ligand nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a CD40 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:53 and/or SEQ ID NO:58. The present invention also includes a CD40 nucleic acid molecule encoding a protein having at least a portion of SEQ ID

NO:53 and/or SEQ ID NO:58, as well as allelic variants of a CD40 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a CD40 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 60%, preferably at least about 65%, preferably at least about 70%, preferably at least about 75%, even more preferably at least about 80%, even more preferably at least about 85%, even more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:60. The present invention also includes a CD40 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:60, as well as allelic variants of a CD40 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a CD154 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about at least about 80%, at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67, and/or SEQ ID NO:69. The present invention also includes a CD154 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67, and/or SEQ ID NO:69, as well as allelic variants of a CD154 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a CD154 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:72, SEQ ID NO:75, and/or SEQ ID NO:77. The present invention also includes a CD154 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:72, SEQ ID NO:75, and/or SEQ ID NO:77, as well as allelic variants of a CD154 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, an IL-5 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about at least about 85%, at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:80, SEQ ID NO:83, and/or SEQ ID NO:85. The present invention also includes an IL-5 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:80, SEQ ID NO:83, and/or SEQ ID NO:85, as well as allelic variants of an IL-5 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, an IL-13 nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about at least about 70%, at

least about 75%, at least about 80%, preferably at least about 85%, more preferably at least about 90%, and even more preferably at least about 95% identical to SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, and/or SEQ ID NO:104. The present invention also includes an IL-13 nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, and/or SEQ ID NO:104, as well as allelic variants of an IL-13 nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, an IL-4 nucleic acid molecule of the present invention is at least about 90%, and preferably at least about 95% identical to nCaIL-4₅₄₉. Even more preferred is a nucleic acid molecule comprising nCaIL4₅₄₉, nCaIL-4₃₉₆, nCaIL-4₃₂₄, and/or an allelic variant of such a nucleic acid molecule. In another embodiment, a Flt-3 ligand nucleic acid molecule of the present invention is at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nCaFlt3L₁₀₁₃. Even more preferred is a nucleic acid molecule comprising nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, and/or nCaFlt3L₇₅₀, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, a Flt-3 ligand nucleic acid molecule of the present invention is at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nFeFlt3L₉₄₂. Even more preferred is a nucleic acid molecule comprising nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nFeFlt3L₈₇₃, and/or nFeFlt3L₇₉₅, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, a CD40 nucleic acid molecule of the present invention is at least about 70%, at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, and/or nCaCD40₇₆₅, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, a CD40 nucleic acid molecule of the present invention is at least about 70%, at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nFeCD40₃₃₆, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, a CD154 nucleic acid molecule of the present invention is at least about 85%, preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nCaCD154₃₉₀, nCaCD154₁₈₇₈, nCaCD154₇₈₀, CaCD154₆₃₃, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, a CD154 nucleic acid molecule of the present invention is at least about 91%, and preferably about 95% identical to nFeCD154₈₈₅, nFeCD154₇₈₀, and/or nFeCD154₆₃₃, and/or an allelic variant of such a nucleic acid molecule. In one embodiment, an IL-5 molecule of the present invention is at least about 90% and preferably at least about 95% identical to nCaIL-5₆₁₀, nCaIL-5₄₀₂, and/or nCaIL-5₃₄₅, and/or an allelic variant of such a nucleic acid molecule. In another embodiment, an IL-13 molecule of the present invention is at least about

65%, at least about 70%, preferably at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to nCaIL-13₁₆₆, nCaIL-13₂₇₂, nCaIL-13₂₇₈, nCaIL-13₁₃₀₂, nCaIL13₃₉₃, nCaIL-13₃₃₃, nCaIL13₁₂₆₉, nCaIL-13₃₉₀, and/or nCaIL13₃₃₀, and/or an allelic variant of such a nucleic acid molecule.

In another embodiment, an IL-4 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 90%, and preferably at least about 95% identical to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21. The present invention also includes an IL-4 nucleic acid molecule comprising at least a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, and/or SEQ ID NO:21, as well as allelic variants of such IL4 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In another embodiment, a Flt-3 ligand nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 75%, preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37. The present invention also includes a Flt-3 ligand- nucleic acid molecule comprising at least a portion of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:36, and/or SEQ ID NO:37, as well as allelic variants of such Flt-3 ligand nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a Flt-3 ligand nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50. The present invention also includes a Flt-3 ligand- nucleic acid molecule comprising at least a portion of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, and/or SEQ ID NO:50, as well as allelic variants of such Flt-3 ligand nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a CD40 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 70%, at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59. The present invention also includes a CD40 nucleic acid molecule comprising at least

a portion of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and/or SEQ ID NO:59, as well as allelic variants of such CD40 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a CD40 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 70%, at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to SEQ ID NO:60 and/or SEQ ID NO:62. The present invention also includes a CD40 nucleic acid molecule comprising at least a portion of SEQ ID NO:60 and/or SEQ ID NO:62, as well as allelic variants of such CD40 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a CD154 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 85%, preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical to SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, and/or SEQ ID NO:71. The present invention also includes a CD154 nucleic acid molecule comprising at least a portion of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, and/or SEQ ID NO:71, as well as allelic variants of such CD154 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a CD154 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 91%, and preferably about 95% identical to SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79. The present invention also includes a CD154 nucleic acid molecule comprising at least a portion of SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and/or SEQ ID NO:79, as well as allelic variants of such CD154 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, an IL-5 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 90% and preferably at least about 95% identical to SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87. The present invention also includes an IL-5 nucleic acid molecule comprising at least a portion of SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and/or SEQ ID NO:87, as well as allelic variants of such IL-5 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, an IL-13 nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 65%, at least about 70%, preferably at least about 75%, more preferably at least about 80%, more preferably at least about 85%, more preferably at least about 90% and even more preferably at least about 95% identical

to SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106. The present invention also includes an IL-13 nucleic acid molecule comprising at least a portion of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and/or SEQ ID NO:106, as well as allelic variants of such IL-13 nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, an IFN α nucleic acid molecule of the present invention is identical to SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:116, and/or SEQ ID NO:118.

In another embodiment, a GM-CSF nucleic acid molecule of the present invention is identical to SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, and/or SEQ ID NO:126.

Knowing the nucleic acid sequences of certain immunoregulatory nucleic acid molecules of the present invention allows one skilled in the art to, for example, (a) make copies of those nucleic acid molecules, (b) obtain nucleic acid molecules including at least a portion of such nucleic acid molecules (e.g., nucleic acid molecules including full-length genes, full-length coding regions, regulatory control sequences, truncated coding regions), and/or (c) obtain other immunoregulatory nucleic acid molecules. Such nucleic acid molecules can be obtained in a variety of ways including screening appropriate expression libraries with antibodies of the present invention; traditional cloning techniques using oligonucleotide probes of the present invention to screen appropriate libraries; and PCR amplification of appropriate libraries or DNA using oligonucleotide primers of the present invention. Preferred libraries to screen or from which to amplify nucleic acid molecules include mammalian cDNA libraries as well as genomic DNA libraries. Similarly, preferred DNA sources from which to amplify nucleic acid molecules include mammalian cDNA and genomic DNA. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., *ibid*.

The present invention also includes nucleic acid molecules that are oligonucleotides capable of hybridizing, under stringent hybridization conditions, with complementary regions of other, preferably longer, nucleic acid molecules of the present invention such as those comprising canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecules. Oligonucleotides of the present invention can be RNA, DNA, or derivatives of either. The minimum size of such oligonucleotides in the size required for formation of a stable hybrid between an oligonucleotide and a complementary sequence on a nucleic acid molecule of the present invention. A preferred oligonucleotide of the present invention has a maximum size of about 100 nucleotides. The present invention includes oligonucleotides that can be used as, for example, probes to identify nucleic acid molecules, primers to produce nucleic acid molecules, or therapeutic reagents to inhibit canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine

interleukin-13, feline interferon alpha, or feline GM-CSF protein production or activity (e.g., as antisense-, triplex formation-, ribozyme- and/or RNA drug-based reagents). The present invention also includes the use of such oligo-

nucleotides to protect animals from disease using one or more of such technologies. Appropriate oligonucleotide-containing therapeutic compositions can be administered to an animal using techniques known to those skilled in the art. One embodiment of the present invention includes a recombinant vector, which includes at least one isolated nucleic acid molecule of the present invention, inserted into any vector capable of delivering the nucleic acid molecule into a host cell. Such a vector contains heterologous nucleic acid sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid molecules of the present invention and that preferably are derived from a species other than the species from which the nucleic acid molecule(s) are derived. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a virus or a plasmid. Recombinant vectors can be used in the cloning, sequencing, and/or otherwise manipulating immunoregulatory nucleic acid molecules of the present invention.

One type of recombinant vector, referred to herein as a recombinant molecule, comprises a nucleic acid molecule of the present invention operatively linked to an expression vector. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression vector in a manner such that the molecule is able to be expressed when transformed into a host cell. As used herein, an expression vector is a DNA or RNA vector that is capable of transforming a host cell and of effecting expression of a specific nucleic acid molecule. Preferably, the expression vector is also capable of replicating within the host cell. Expression vectors can be either prokaryotic or eukaryotic, and are typically viruses or plasmids. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention, including in bacterial, fungal, parasite, insect, other animal, and plant cells. Preferred expression vectors of the present invention can direct gene expression in bacterial, yeast, insect and mammalian cells, and more preferably in the cell types disclosed herein, more preferably in vivo.

In particular, expression vectors of the present invention contain regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the recombinant cell and that control the expression of nucleic acid molecules of the present invention. In particular, recombinant molecules of the present invention include transcription control sequences. Transcription control sequences are sequences which control the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those which control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in at least one of the recombinant cells of the present invention. A variety of such transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in bacterial, yeast, helminth and/or other endoparasite, insect and mammalian cells, such as, but not limited to, *tac*, *lac*, *trp*, *trc*, *oxy-pro*, *omp/lpp*, *rrnB*, bacteriophage lambda (such as lambda *p_L* and lambda *p_R* and fusions that include such promoters), bacteriophage T7, T7lac, bacteriophage T3, bacteriophage SP6, bacteriophage

SPO1, metallothionein, alpha-mating factor, Pichia alcohol oxidase, alphavirus subgenomic promoter, antibiotic resistance gene, baculovirus. Heliothis zea insect virus, vaccinia virus, herpesvirus, raccoon poxvirus, other poxvirus, adenovirus, cytomegalovirus (such as immediate early promoter), simian virus 40, retrovirus, actin, retroviral long terminal repeat. Rous sarcoma virus, heat shock, phosphate and nitrate transcription control sequences as well as other sequences capable of controlling gene expression in prokaryotic or eukaryotic cells. Additional suitable transcription control sequences include tissue-specific promoters and enhancers as well as lymphokine-inducible promoters (e.g., promoters inducible by interferons or interleukins). Transcription control sequences of the present invention can also include naturally occurring transcription control sequences naturally associated with mammals, such as dog, cat, horse or human transcription control sequences.

Suitable and preferred nucleic acid molecules to include in recombinant vectors of the present invention are as disclosed herein. Preferred nucleic acid molecules to include in recombinant vectors, and particularly in recombinant molecules, include nCaIL-4₅₄₉, nCaIL-4₃₉₆, nCaIL-4₃₂₄, nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, nCaFlt3L₇₅₀, nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nFeFlt3L₈₇₃, nFeFlt3L₇₉₅, nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, nCaCD40₇₆₅, nFeCD40₃₃₆, nCaCD154₃₉₀, nCaCD154₈₇₈, nCaCD154₇₈₀, nCaCD154₆₃₃, nFeCD154₈₈₅, nFeCD154₇₈₀, nFeCD154₆₃₃, nCaIL-5₆₁₀, nCaIL-5₄₀₂, nCaIL-5₃₄₅, nCaIL-13₁₆₆, nCaIL-13₂₇₂, nCaIL-13₂₇₈, nCaIL-13₁₃₀₂, nCaIL-13₃₉₃, nCaIL-13₃₃₃, nCaIL-13₁₂₆₉, nCaIL-13₃₉₀, nCaIL-13₃₃₀, nFeIFN α _{567a}, nFeIFN α _{567b}, nFeIFN α _{498a}, nFeIFN α _{498b}, nFeGMCSF₄₄₄, nFeGMCSF₄₃₂, and/or nFeGMCSF₃₈₁.

Recombinant molecules of the present invention may also (a) contain secretory signals (i.e., signal segment nucleic acid sequences) to enable an expressed parasitic helminth protein of the present invention to be secreted from the cell that produces the protein and/or (b) contain fusion sequences which lead to the expression of nucleic acid molecules of the present invention as fusion proteins. Examples of suitable signal segments include any signal segment capable of directing the secretion of a protein of the present invention. Preferred signal segments include, but are not limited to, tissue plasminogen activator (t-PA), interferon, interleukin, growth hormone, histocompatibility and viral envelope glycoprotein signal segments. Suitable fusion segments encoded by fusion segment nucleic acids are disclosed herein. In addition, a nucleic acid molecule of the present invention can be joined to a fusion segment that directs the encoded protein to the proteasome, such as a ubiquitin fusion segment. Eukaryotic recombinant molecules may also include intervening and/or untranslated sequences surrounding and/or within the nucleic acid sequences of nucleic acid molecules of the present invention.

Another embodiment of the present invention includes a recombinant cell comprising a host cell transformed with one or more recombinant molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism. Transformed nucleic acid molecules of the present invention can remain extrachromosomal or can integrate into one or

more sites within a chromosome of the transformed (i.e., recombinant) cell in such a manner that their ability to be expressed is retained. Preferred nucleic acid molecules with which to transform a cell include immunoregulatory nucleic acid molecules of the present invention disclosed herein. Particularly preferred nucleic acid molecules with which to transform a cell include nCaIL-4₅₄₉, nCaIL-4₃₉₆, nCaIL-4₃₂₄, nCaFlt3L₁₀₁₃, nCaFlt3L₈₈₂, nCaFlt3L₈₀₄, nCaFlt3L₈₂₈, nCaFlt3L₉₈₅, nCaFlt3L₁₀₁₉, nCaFlt3L₉₃, nCaFlt3L₇₅₀, nFeFlt3L₃₉₅, nFeFlt3L₇₉₃, nFeFlt3L₉₄₂, nFeFlt3L₈₇₃, nFeFlt3L₇₉₅, nCaCD40₃₂₁, nCaCD40₁₄₂₅, nCaCD40₈₂₂, nCaCD40₇₆₅, nFeCD40₃₃₆, nCaCD154₃₉₀, nCaCD154₈₇₈, nCaCD154₇₈₀, nCaCD154₆₃₃, nFeCD154₈₈₅, nFeCD154₇₈₀, nFeCD154₆₃₃, nCaIL-5₆₁₀, nCaIL-5₄₀₂, nCaIL-5₃₄₅, nCaIL-13₁₆₆, nCaIL-13₂₇₂, nCaIL-13₂₇₈, nCaIL13₁₃₀₂, nCaIL-13₃₉₃, nCaIL-13₃₃₃, nCaIL13₁₂₆₉, nCaIL-13₃₉₀, nCaIL-13₃₃₀, nFeIFN α _{567a}, nFeIFN α _{567b}, nFeIFN α _{498a}, nFeIFN α _{498b}, nFeGMCSF₄₄₄, nFeGMCSF₄₃₂, and/or nFeGMCSF₃₈₁.

Suitable host cells to transform include any cell that can be transformed with a nucleic acid molecule of the present invention. Host cells can be either untransformed cells or cells that are already transformed with at least one nucleic acid molecule (e.g., nucleic acid molecules encoding one or more proteins of the present invention and/or other proteins useful in the production of multivalent vaccines). Host cells of the present invention either can be endogenously (i.e., naturally) capable of producing immunoregulatory proteins of the present invention or can be capable of producing such proteins after being transformed with at least one nucleic acid molecule of the present invention. Host cells of the present invention can be any cell capable of producing at least one protein of the present invention, and include bacterial, fungal (including yeast), parasite (including helminth, protozoa and ectoparasite), other insect, other animal and plant cells. Preferred host cells include bacterial, mycobacterial, yeast, helminth, insect and mammalian cells. More preferred host cells include Salmonella, Escherichia, Bacillus, Listeria, Saccharomyces, Spodoptera, Mycobacteria, Trichoplusia, BHK (baby hamster kidney) cells, MDCK cells (Madin-Darby canine kidney cell line), CRFK cells (Crandell feline kidney cell line), CV-1 cells (African monkey kidney cell line used, for example, to culture racoon poxvirus), COS (e.g., COS-7) cells, chinese hamster ovary (CHO) cells, Ltk cells and Vero cells. Particularly preferred host cells are Escherichia coli, including E. coli K-12 derivatives; Salmonella typhi; Salmonella typhimurium, including attenuated strains such as UK-1₀₃₉₈₇ and SR-11₀₄₀₇₂; Spodoptera frugiperda; Trichoplusia ni; BHK cells; MDCK cells; CRFK cells; CV-1 cells; COS cells; Vero cells; and non-tumorigenic mouse myoblast G8 cells (e.g., ATCC CRL 1246). Additional appropriate mammalian cell hosts include other kidney cell lines, other fibroblast cell lines (e.g., human, murine or chicken embryo fibroblast cell lines), myeloma cell lines. Chinese hamster ovary cells, mouse NIH/3T3 cells, LMTK³¹ cells and/or HeLa cells. In one embodiment, the proteins may be expressed as heterologous proteins in myeloma cell lines employing immunoglobulin promoters.

A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules of the present invention operatively linked to an expression vector containing one or more transcription control sequences, examples of which are disclosed herein.

A recombinant cell of the present invention includes any cell transformed with at least one of any nucleic acid

molecule of the present invention. Suitable and preferred nucleic acid molecules as well as suitable and preferred recombinant molecules with which to transfer cells are disclosed herein.

5 Recombinant cells of the present invention can also be co-transformed with one or more recombinant molecules including any of canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF nucleic acid molecule encoding one or more proteins of the present invention and/or one or more other nucleic acid molecules encoding other therapeutic compounds, as disclosed herein (e.g., to produce multi-valent vaccines).

10 Recombinant DNA technologies can be used to improve expression of transformed nucleic acid molecules by manipulating, for example, the number of copies of the nucleic acid molecules within a host cell, the efficiency with which those nucleic acid molecules are transcribed, the efficiency with which the resultant transcripts are translated, and the efficiency of post-translational modifications. Recombinant techniques useful for increasing the expression of nucleic acid molecules of the present invention include, but are not limited to, operatively linking nucleic acid molecules to high-copy number plasmids, integration of the nucleic acid molecules into one or more host cell chromosomes, addition of vector stability sequences to plasmids, substitutions or modifications of transcription control signals (e.g., promoters, operators, enhancers), substitutions or modifications of translational control signals (e.g., ribosome binding sites, Shine-Dalgarno sequences), modification of nucleic acid molecules of the present invention to correspond to the codon usage of the host cell, deletion of sequences that destabilize transcripts, and use of control signals that temporally separate recombinant cell growth from recombinant enzyme production during fermentation. The activity of an expressed recombinant protein of the present invention may be improved by fragmenting, modifying, or derivatizing nucleic acid molecules encoding such a protein.

15 Isolated immunoregulatory proteins of the present invention can be produced in a variety of ways, including production and/or recovery of natural proteins, production and/or recovery of recombinant proteins, and/or chemical synthesis of the proteins. In one embodiment, an isolated protein of the present invention is produced by culturing a cell capable of expressing the protein under conditions effective to produce the protein, and recovering the protein. A preferred cell to culture is a recombinant cell of the present invention. Effective culture conditions include, but are not limited to, effective media, bioreactor, temperature, pH and oxygen conditions that permit protein production. An effective medium refers to any medium in which a cell is cultured to produce an immunoregulatory protein of the present invention. Such medium typically comprises an aqueous medium having assimilable carbon, nitrogen and phosphate sources, and appropriate salts, minerals, metals and other nutrients, such as vitamins. Cells of the present invention can be cultured in conventional fermentation bioreactors, shake flasks, test tubes, microtiter dishes, and petri plates. Culturing can be carried out at a temperature, pH and oxygen content appropriate for a recombinant cell. Such culturing conditions are within the expertise of one of ordinary skill in the art.

20 Depending on the vector and host system used for production, resultant proteins of the present invention may either remain within the recombinant cell; be secreted into

the fermentation medium; be secreted into a space between two cellular membranes, such as the periplasmic space in *E. coli*; or be retained on the outer surface of a cell or viral membrane.

The phrase "recovering the protein", as well as similar phrases, refers to collecting the whole fermentation medium containing the protein and need not imply additional steps of separation or purification. Proteins of the present invention can be purified using a variety of standard protein purification techniques, such as, but not limited to, affinity chromatography, ion exchange chromatography, filtration, electrophoresis, hydrophobic interaction chromatography, gel filtration chromatography, reverse phase chromatography, concanavalin A chromatography, chromatofocusing and/or differential solubilization. Proteins of the present invention are preferably retrieved in "substantially pure" form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the protein as a therapeutic composition or diagnostic. A therapeutic composition for animals, for example, should exhibit no substantial toxicity and preferably should be capable of stimulating the production of antibodies in a treated animal.

The present invention also includes isolated (i.e., removed from their natural milieu) antibodies that selectively bind to an immunoregulatory protein of the present invention and/or a mimetope thereof (e.g., anti-IL-4 antibodies, anti-Flt-3 ligand antibodies, anti-CD40 antibodies, anti-CD154 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IFN α antibodies, and/or anti-GM-CSF antibodies). As used herein, the term "selectively binds to" an immunoregulatory protein of the present invention, refers to the ability of antibodies of the present invention to preferentially bind to specified proteins and/or mimetopes thereof of the present invention. Binding can be measured using a variety of methods standard in the art including enzyme immunoassays (e.g., ELISA), immunoblot assays, etc.; see, for example, Sambrook et al., *ibid.*, and Harlow, et al., 1988, *Antibodies, a Laboratory Manual*, Cold Spring Harbor Labs Press; Harlow et al., *ibid.*, is incorporated by this reference herein in its entirety. An anti-IL-4 antibody of the present invention preferably selectively binds to an IL-4 protein in such a way as to inhibit the function of that protein. An anti-Flt-3 ligand antibody of the present invention preferably selectively binds to a Flt-3 ligand- protein in such a way as to inhibit the function of that protein. An anti-CD40 antibody of the present invention preferably selectively binds to a CD40 protein in such a way as to inhibit the function of that protein. An anti-CD154 antibody of the present invention preferably selectively binds to a CD154 protein in such a way as to inhibit the function of that protein. An anti-IL-5 antibody of the present invention preferably selectively binds to an IL-5 protein in such a way as to inhibit the function of that protein. An anti-IL-13 antibody of the present invention preferably selectively binds to an IL-13 protein in such a way as to inhibit the function of that protein. An anti-IFN α antibody of the present invention preferably selectively binds to an IFN α protein in such a way as to inhibit the function of that protein. An anti-GM-CSF antibody of the present invention preferably selectively binds to a GM-CSF protein in such a way as to inhibit the function of that protein.

Isolated antibodies of the present invention can include antibodies in serum, or antibodies that have been purified to varying degrees. Antibodies of the present invention can be polyclonal or monoclonal, or can be functional equivalents such as antibody fragments and/or genetically-engineered antibodies, including single chain antibodies or chimeric antibodies that can bind to one or more epitopes.

A preferred method to produce antibodies of the present invention includes (a) administering to an animal an effective amount of a protein, peptide and/or mimetope thereof of the present invention to produce the antibodies and (b) recovering the antibodies. In another method, antibodies of the present invention are produced recombinantly using techniques as heretofore disclosed to produce any of the immunoregulatory proteins of the present invention. Antibodies raised against defined proteins or mimetopes can be advantageous because such antibodies are not substantially contaminated with antibodies against other substances that might otherwise cause interference in a diagnostic assay or side effects if used in a therapeutic composition.

Antibodies of the present invention have a variety of potential uses that are within the scope of the present invention. For example, such antibodies can be used (a) as reagents in assays to detect an immunoregulatory protein of the present invention, (b) as reagents in assays to modulate cellular activity through an immunoregulatory protein of the present invention (e.g., mimicking ligand binding to a canine interleukin-4, canine or feline Flt-3 ligand, canine or feline CD40, canine or feline CD154, canine interleukin-5, canine interleukin-13, feline interferon alpha, or feline GM-CSF protein, as appropriate), and/or (c) as tools to screen expression libraries and/or to recover desired proteins of the present invention from a mixture of proteins and other contaminants. Furthermore, antibodies of the present invention can be used to target compounds (e.g., nucleic acid molecules, drugs or proteins) to antigen presenting cells. Targeting can be accomplished by conjugating (i.e., stably joining) such antibodies to the compounds using techniques known to those skilled in the art. Suitable compounds are known to those skilled in the art.

One embodiment of the present invention is a therapeutic composition that, when administered to an animal in an effective manner, is capable of regulating an immune response in an animal. Therapeutic compositions of the present invention can include at least one of the following therapeutic compounds: an isolated IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein of the present invention and/or a mimetope thereof; an isolated IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF nucleic acid molecule of the present invention; an isolated antibody that selectively binds to an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein of the present invention; an inhibitor of canine IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF function identified by its ability to bind to an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein, respectively, of the present invention; such an inhibitor can inhibit binding of the respective immunoregulatory protein with its respective receptor, or inhibit the activity the respective protein. Methods to perform such assays to measure binding and/or activity of an immunoregulatory protein of the present invention are known to those of skill in the art, and are described, for example, in Janeway et al., *ibid.* As used herein, a therapeutic compound refers to a compound that, when administered to an animal in an effective manner, is able to treat, ameliorate, and/or prevent a disease. Examples of proteins, nucleic acid molecules, antibodies and/or inhibitors of the present invention are disclosed herein.

The present invention also includes a therapeutic composition comprising at least one IL-4-, Flt-3 ligand-, CD40-, CD154-, IL-5-, IL-13-, IFN α -, and/or GM-CSF-based compound of the present invention in combination with at least one additional therapeutic compound. Examples of such compounds are disclosed herein.

Therapeutic compositions of the present invention can be administered to any animal susceptible to such therapy, preferably to mammals, and more preferably to dogs, cats, humans, ferrets, horses, cattle, sheep and/or other pets, economic food animals and/or zoo animals. Preferred animals include dogs, cats, horses and/or humans.

A therapeutic composition of the present invention is administered to an animal in an effective manner such that the composition is capable of regulating an immune response in that animal. Therapeutic compositions of the present invention can be administered to animals prior to onset of a disease (i.e., as a preventative vaccine) and/or can be administered to animals after onset of a disease in order to treat the disease (i.e., as a therapeutic vaccine). Preferred diseases to prevent and/or treat include autoimmune diseases, allergic reactions, infectious diseases, tumor development, inflammatory diseases and/or graft rejection. In one embodiment, a therapeutic composition of the present invention is administered with an antigen to enhance an immune response against that antigen.

Therapeutic compositions of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and/or other aqueous physiologically balanced salt solutions. Non-aqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include suspensions containing viscosity enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer and/or Tris buffer, while examples of preservatives include thimerosal, o-cresol, formalin and/or benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

In one embodiment of the present invention, a therapeutic composition can include an adjuvant. Adjuvants are agents that are capable of enhancing the immune response of an animal to a specific antigen. Suitable adjuvants include, but are not limited to, cytokines, chemokines, and/or compounds that induce the production of cytokines and/or chemokines (e.g., granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin 2 (IL-2), interleukin-3 (IL-3), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 12 (IL-12), interferon gamma, interferon gamma inducing factor I (IGIF), transforming growth factor beta, RANTES (regulated upon activation, normal T cell expressed and presumably secreted), macrophage inflammatory proteins (e.g., MIP-1 alpha and MIP-1 beta), and Leishmania elongation initiating factor (LEIF)); bacterial components (e.g., endotoxins, in particular superantigens, exotoxins and cell wall components); aluminum-based salts; calcium-based salts; silica; polynucleotides; toxoids; serum proteins, viral coat proteins; block copolymer adjuvants (e.g., Hunter's Titermax™ adjuvant (Vaxcel™, Inc. Norcross, Ga.), Ribit adjuvants (Ribit ImmunoChem Research, Inc., Hamilton, Mont.); and saponins and their derivatives (e.g., Quil A (Superfos Biosector A/S, Denmark). Protein adjuvants of the present

invention can be delivered in the form of the protein themselves or of nucleic acid molecules encoding such proteins using the methods described herein.

In one embodiment of the present invention, a therapeutic composition can include a carrier. Carriers include compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to, polymeric controlled release vehicles, biodegradable implants, liposomes, bacteria, viruses, other cells, oils, esters, and glycols.

One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises a composition of the present invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an animal, form a solid or a gel in situ. Preferred controlled release formulations are biodegradable (i.e., bioerodible).

A preferred controlled release formulation of the present invention is capable of releasing a composition of the present invention into the blood of the treated animal at a constant rate sufficient to attain therapeutic dose levels of the composition to regulate an immune response in an animal. The therapeutic composition is preferably released over a period of time ranging from about 1 to about 12 months. A controlled release formulation of the present invention is capable of effecting a treatment preferably for at least about 1 month, more preferably for at least about 3 months, even more preferably for at least about 6 months, even more preferably for at least about 9 months, and even more preferably for at least about 12 months.

Therapeutic compositions of the present invention can be administered to animals prior to and/or after onset of disease. Acceptable protocols to administer therapeutic compositions in an effective manner include individual dose size, number of doses, frequency of dose administration, and/or mode of administration. Determination of such protocols can be accomplished by those skilled in the art. A suitable single dose is a dose that is capable of regulating the immune response in an animal when administered one or more times over a suitable time period. For example, a preferred single dose of a protein, mimotope or antibody therapeutic composition is from about 1 microgram (μg) to about 10 milligrams (mg) of the therapeutic composition per kilogram body weight of the animal. Booster vaccinations can be administered from about 2 weeks to several years after the original administration. Booster administrations preferably are administered when the immune response of the animal becomes insufficient to protect the animal from disease. A preferred administration schedule is one in which from about 10 μg to about 1 mg of the therapeutic composition per kg body weight of the animal is administered from about one to about two times over a time period of from about 2 weeks to about 12 months. Modes of administration can include, but are not limited to, subcutaneous, intradermal, intravenous, intranasal, intraocular, oral, transdermal and/or intramuscular routes.

According to one embodiment, a nucleic acid molecule of the present invention can be administered to an animal in a fashion to enable expression of that nucleic acid molecule into a therapeutic protein or therapeutic RNA (e.g., antisense

RNA, ribozyme, triple helix forms or RNA drug) in the animal. Nucleic acid molecules can be delivered to an animal in a variety of methods including, but not limited to, (a) administering a naked (i.e., not packaged in a viral coat or cellular membrane) nucleic acid as a genetic vaccine (e.g., as naked DNA or RNA molecules, such as is taught, for example in Wolff et al., 1990, Science 247, 1465–1468) or (b) administering a nucleic acid molecule packaged as a recombinant virus vaccine or as a recombinant cell vaccine (i.e., the nucleic acid molecule is delivered by a viral or cellular vehicle).

A genetic (i.e., naked nucleic acid) vaccine of the present invention includes a nucleic acid molecule of the present invention and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A genetic vaccine of the present invention can comprise one or more nucleic acid molecules of the present invention in the form of, for example, a dicistronic recombinant molecule. Preferred genetic vaccines include at least a portion of a viral genome (i.e., a viral vector). Preferred viral vectors include those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picomaviruses, and/or retroviruses, with those based on alphaviruses (such as Sindbis or Semliki forest virus), species-specific herpesviruses and/or poxviruses being particularly preferred. Any suitable transcription control sequence can be used, including those disclosed as suitable for protein production. Particularly preferred transcription control sequences include cytomegalovirus immediate early (preferably in conjunction with Intron-A), Rous sarcoma virus long terminal repeat, and tissue-specific transcription control sequences, as well as transcription control sequences endogenous to viral vectors if viral vectors are used. The incorporation of a “strong” polyadenylation signal is also preferred.

Genetic vaccines of the present invention can be administered in a variety of ways, with intramuscular, subcutaneous, intradermal, transdermal, intranasal and/or oral routes of administration being preferred. A preferred single dose of a genetic vaccine ranges from about 1 nanogram (ng) to about 600 μg , depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized and/or topically. Genetic vaccines of the present invention can be contained in an aqueous excipient (e.g., phosphate buffered saline) alone or in a carrier (e.g., lipid-based vehicles).

A recombinant virus vaccine of the present invention includes a recombinant molecule of the present invention that is packaged in a viral coat and that can be expressed in an animal after administration. Preferably, the recombinant molecule is packaging- or replication-deficient and/or encodes an attenuated virus. A number of recombinant viruses can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picomaviruses, and/or retroviruses. Preferred recombinant virus vaccines are those based on alphaviruses (such as Sindbis virus), raccoon poxviruses, species-specific herpesviruses and/or species-specific poxviruses. An example of methods to produce and use alphavirus recombinant virus vaccines are disclosed in U.S. Pat. No. 5,766,602 by Xiong et al., issued Jun. 16, 1998, which is incorporated by this reference herein in its entirety.

When administered to an animal, a recombinant virus vaccine of the present invention infects cells within the immunized animal and directs the production of a therapeu-

tic protein or RNA nucleic acid molecule that is capable of protecting the animal from disease caused by a parasitic helminth as disclosed herein. For example, a recombinant virus vaccine comprising an immunoregulatory nucleic acid molecule of the present invention is administered according to a protocol that results in the regulation of an immune response in an animal. A preferred single dose of a recombinant virus vaccine of the present invention is from about 1×10^4 to about 1×10^8 virus plaque forming units (pfu) per kilogram body weight of the animal. Administration protocols are similar to those described herein for protein-based vaccines, with subcutaneous, intramuscular, intranasal, intraocular and/or oral administration routes being preferred.

A recombinant cell vaccine of the present invention includes recombinant cells of the present invention that express at least one protein of the present invention. Preferred recombinant cells for this embodiment include Salmonella, E. coli, Listeria, Mycobacterium, S. frugiperda, yeast, (including Saccharomyces cerevisiae and Pichia pastoris), BHK, CV-1, myoblast G8, COS (e.g., COS-7), Vero, MDCK and CRFK recombinant cells. Recombinant cell vaccines of the present invention can be administered in a variety of ways but have the advantage that they can be administered orally, preferably at doses ranging from about 10^8 to about 10^{12} cells per kilogram body weight. Administration protocols are similar to those described herein for protein-based vaccines. Recombinant cell vaccines can comprise whole cells, cells stripped of cell walls or cell lysates.

The efficacy of a therapeutic composition of the present invention to regulate the immune response in an animal can be tested in a variety of ways including, but not limited to, detection of cellular immunity within the treated animal, determining lymphocyte or dendritic cell activity, detection of immunoglobulin levels, determining hematopoietic stem cell or hematopoietic early progenitor cell development, determining dendritic cell development or challenge of the treated animal with an infectious agent to determine whether the treated animal is resistant to disease. In one embodiment, therapeutic compositions can be tested in animal models such as mice. Such techniques are known to those skilled in the art.

One embodiment of the present invention is an inhibitory compound. Preferably, such an inhibitory compound is derived from an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein of the present invention. Examples of inhibitory compounds include an antibody of the present invention, that is administered to an animal in an effective manner (i.e., is administered in an amount so as to be present in the animal at a titer that is sufficient, upon interaction of that antibody with a native IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein, to decrease the activity of such proteins in an animal, at least temporarily). Oligonucleotide nucleic acid molecules of the present invention can also be administered in an effective manner, thereby reducing expression of either an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein, in order to interfere with the protein activity targeted in accordance with the present invention. Peptides of an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF protein of the present invention can also be administered in an effective manner, thereby reducing binding of IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF proteins to the appropriate receptor, in order to interfere with the protein activity targeted in accordance with the present invention. An inhibitory compound of an IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or

GM-CSF function can be identified using IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF proteins of the present invention, respectively.

One embodiment of the present invention is a method to identify a compound capable of inhibiting IL-4 function. Such a method includes the steps of: (a) contacting (e.g., combining, mixing) an isolated IL-4 protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the IL-4 protein binds to IL-4 receptor or stimulates T cells in a T cell proliferation assay, and (b) determining if the putative inhibitory compound inhibits the binding of IL-4 protein to IL-4 receptor or the stimulation of T cells in a T cell proliferation assay. Another embodiment of the present invention is a method to identify a compound capable of inhibiting Flt-3 ligand function. Such a method includes the steps of: (a) contacting an isolated Flt-3 ligand protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the Flt-3 ligand protein binds to Flt-3 receptor or stimulates dendritic precursor cells in a proliferation assay, and (b) determining if the putative inhibitory compound inhibits the binding of Flt-3 ligand protein to Flt-3 receptor or the stimulation of dendritic precursor cells in a proliferation assay. Another embodiment of the present invention is a method to identify a compound capable of inhibiting CD40 function. Such a method includes the steps of (a) contacting an isolated CD40 protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the CD40 protein binds to a CD40 binding partner (e.g., CD154) and (b) determining if the putative inhibitory compound inhibits the binding of CD40 protein to the CD40 binding partner. A CD40 binding partner is a molecule that selectively binds to CD40 protein. Likewise, a binding partner for any other immunoregulatory protein of the present invention includes molecules that selectively bind to that particular immunoregulatory protein. Another embodiment of the present invention is a method to identify a compound capable of inhibiting CD154 function. Such a method includes the steps of (a) contacting an isolated CD154 protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the CD154 protein binds to a CD154 binding partner (e.g., CD40) and (b) determining if the putative inhibitory compound inhibits the binding of CD154 protein to the CD154 binding partner. Yet another embodiment of the present invention is a method to identify a compound capable of inhibiting IL-5 function. Such a method includes the steps of: (a) contacting an isolated IL-5 protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the IL-5 protein binds to IL-5 receptor or stimulates T cells in a T cell proliferation assay, and (b) determining if the putative inhibitory compound inhibits the binding of IL-5 protein to IL-5 receptor or the stimulation of T cells in a T cell proliferation assay. Another embodiment of the present invention is a method to identify a compound capable of inhibiting IL-13 function. Such a method includes the steps of: (a) contacting an isolated IL-13 protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the IL-13 protein binds to IL-13 receptor or stimulates T cells in a T cell proliferation assay, and (b) determining if the putative inhibitory compound inhibits the binding of IL-13 protein to IL-13 receptor or the stimulation of T cells in a T cell proliferation assay. Another embodiment of the present invention is a method to identify a

compound capable of inhibiting IFN α function. Such a method includes the steps of: (a) contacting an isolated IFN α protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the IFN α protein binds to IFN α receptor or inhibits proliferation of GM-CSF stimulated TF-1 cells, and (b) determining if the putative inhibitory compound inhibits the binding of IFN α protein to IFN α receptor or inhibits proliferation of GM-CSF stimulated TF-1 cells. Another embodiment of the present invention is a method to identify a compound capable of inhibiting GM-CSF function. Such a method includes the steps of: (a) contacting an isolated GM-CSF protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of said compound, the GM-CSF protein bind to GM-CSF receptor or stimulates T cells in a T cell proliferation assay, and (b) determining if the putative inhibitory compound inhibits the binding of GM-CSF protein to GM-CSF receptor or the stimulation of T cells in a T cell proliferation assay.

Putative inhibitory compounds to screen include small organic molecules, antibodies (including mimetopes thereof), and/or ligand analogs. Such compounds are also screened to identify those that are substantially not toxic in host animals.

Preferred IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF, proteins to inhibit are those produced by dogs, cats, horses or humans, even more preferred IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF proteins to inhibit are those produced by domestic dogs or cats. A particularly preferred inhibitor of the present invention is capable of regulating an immune response in an animal. It is also within the scope of the present invention to use inhibitors of the present invention to target diseases involving undesired immune activity in animals. Compositions comprising inhibitors of IL-4, Flt-3 ligand, CD40, CD154, IL-5, IL-13, IFN α , and/or GM-CSF function can be administered to animals in an effective manner to regulate the immune response in the animals, and preferably to prevent autoimmune disease, allergy, infectious disease, inflammation or prevent graft rejection in animals, or to treat animals with such diseases. Effective amounts and/or dosing regimens can be determined using techniques known to those skilled in the art.

It is also within the scope of the present invention to use isolated proteins, mimetopes, nucleic acid molecules and/or antibodies of the present invention as diagnostic reagents. Methods to use such diagnostic reagents are well known to those skilled in the art, see, for example, Janeway, et al., *ibid.*, and/or PCT Publication No. WO 98/23964, published Jun. 4, 1998.

The following examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention.

EXAMPLES

It is to be noted that the examples include a number of molecular biology, microbiology, immunology and biochemistry techniques considered to be familiar to those skilled in the art. Disclosure of such techniques can be found, for example, in Sambrook et al., *ibid.*, and Ausubel, et al., 1993, *Current Protocols in Molecular Biology*, Greene/Wiley Interscience, New York, N.Y., and related references. Ausubel, et al. *ibid.* is incorporated by reference herein in its entirety.

Example 1

This example describes the isolation and sequencing of canine interleukin-4 (IL-4) nucleic acid molecules of the

present invention. This example also describes expression of recombinant canine IL-4 in *E. coli* and mammalian cells; development of monoclonal and polyclonal antibodies to *E. coli*-expressed canine IL-4; and bioactivity of mammalian-expressed canine IL-4.

A. Isolation and Sequencing of a Canine IL-4 Nucleic Acid Molecule.

Initial attempts to isolate a canine IL-4 nucleic acid molecule using various primers corresponding to putative conserved regions of IL-4 nucleic acid molecules failed. Forward and reverse primers were then designed using a sequence tag site (IL-4sts) described by Venta et al. in GenBank. The forward primer was designated as IL-4stsA, having the nucleic acid sequence 5' CTATTAATGG GTCTCACCTC CCAA CT 3', designated herein as SEQ ID NO:11. The reverse primer was designated as prIL-4stsB, having the nucleic acid sequence 5' TCAACTCGGT GCA-CAGAGTC TTGG 3', designated herein as SEQ ID NO:12. The primers were used to amplify PCR products from a *C. familiaris* mitogen activated PBMC cDNA library that was constructed in the Uni-ZAP® XR vector (available from Stratagene Cloning Systems, La Jolla, Calif.), using Stratagene's ZAP-cDNA® Synthesis Kit and the manufacturer's protocol. The mRNA was isolated from *C. familiaris* peripheral blood mononuclear cells about 4 hours after they were activated by a polyclonal activating agent in culture. Four PCR products were produced that had the expected size range. The PCR products were cloned and sequenced using standard techniques. A portion of one of the four products was found to be somewhat homologous with an IL-4 nucleic acid sequence reported in GenBank.

To identify a cDNA encoding a full-length canine IL-4 protein, the PCR product showing some homology with the IL-4 sequence reported in GenBank was used to generate an about 549 base pair DNA fragment as follows. The PCR product was labeled with ³²P and used as a probe to screen the canine PBMC cDNA library. Hybridization was done at about 6×SSC, 5×Denhardt's solution, 0.5% SDS, 100 μg/ml of ssDNA and 100 μg/ml of tRNA, at about 68° C., for about 36 hr. (the compositions of SSC and Denhardt's are described in Sambrook et al., *ibid.*). The filters were washed 3 times, for about 30 minutes per wash, at about 55° C. in about 2×SSC, 0.2% SDS, followed by a final wash of about 30 minutes in the same buffer except using about 1×SSC. Positive clones were isolated and the cDNA inserts were sequenced for both strands using vector flanking primers and gene-specific internal primers. Sequence analysis was performed using the GAP program of GCG (available from the University of Wisconsin) using the alignment settings of: gap weight set at 50, length weight set at 3, and average match set at 10 for nucleic acid sequence comparisons; and gap weight set at 12, length weight set at 4, and average match set at 2.912 for amino acid sequence comparisons.

A cDNA nucleic acid molecule was isolated, referred to herein as nCaIL-4₅₄₉, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:1. The complement of SEQ ID NO:1 is represented herein by SEQ ID NO:3. Translation of SEQ ID NO:1 suggests that nucleic acid molecule nCaIL-4₅₄₉ encodes a full-length IL-4 protein of about 132 amino acids, denoted herein as PCaIL-4₁₃₂, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having an initiation codon spanning from nucleotide 43 through nucleotide 45 of SEQ ID NO:1 and a stop codon spanning from nucleotide 439 through nucleotide 441 of SEQ ID NO:1. The coding region encoding PCaIL-4₁₃₂ is

presented herein as nCaIL-4₃₉₆, which has the nucleotide sequence SEQ ID NO:4 (the coding strand) and SEQ ID NO:5 (the complementary strand). A putative signal sequence coding region extends from nucleotide 43 through nucleotide 114 of SEQ ID NO:1. The proposed mature protein (i.e., canine IL-4 protein from which the signal sequence has been cleaved), denoted herein as PCaIL-4₁₀₈, contains about 108 amino acids, extending from residue 25 through residue 132 of SEQ ID NO:2; PCaIL-4₁₀₈ amino acid sequence is represented herein as SEQ ID NO:20. The nucleic acid molecule encoding PCaIL-4₁₀₈ is denoted herein as nCaIL-4₃₂₄, extending from nucleotide 115 through nucleotide 438 of SEQ ID NO:1, nCaIL-4₃₂₄ has a coding sequence denoted SEQ ID NO:19 and a complementary sequence denoted SEQ ID NO:21.

Comparison of nucleic acid sequence SEQ ID NO:1 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:1 showed the most homology, i.e., about 89.3% identity, with a feline IL-4 gene. Comparison of amino acid sequence SEQ ID NO:2 with amino acid sequences reported in GenBank indicates that SEQ ID NO:2 showed the most homology, i.e., about 82.6% identity, with a feline IL-4 protein. Sequence analysis was performed using the GCG GAP program as described above.

B. Expression of Recombinant Canine IL-4 in *E. coli* and Mammalian Cells

i. *E. coli* Expression

A recombinant molecule capable of expressing the mature form of canine IL-4, denoted herein as pGEX-nCaIL-4₃₂₇, was produced as follows. A 340-nucleotide fragment was PCR amplified from nucleic acid molecule nCaIL-4₅₄₉ (having coding strand SEQ ID NO:1) using the following primer sequences: positive strand 5' TGAATTCGGA CAT-**AACTTCA ATATTAC** 3' (SEQ ID NO:38) (EcoRI site in bold) and 5' TCTCGAGATT CAGCTTCATG **CCTGTA** 3' (SEQ ID NO:39) (XhoI site in bold). The resulting 340-base pair fragment was digested with EcoRI and XhoI restriction enzymes (available from New England Biolabs, Beverly, Mass.), according to the manufacturer's directions, and gel-purified using standard techniques. The digested 340-base pair fragment, now 327 base pairs, was then ligated into pGEX-6P-1 (available from Amersham Pharmacia, Piscataway, N.J.), which had been previously digested with EcoRI and XhoI and gel purified, to produce recombinant molecule pGEX-nCaIL-4₃₂₇. Recombinant molecules of pGEX produce the protein of interest as a glutathione s-transferase (GST) fusion protein. The recombinant molecule pGEX-nCaIL-4₃₂₇ was transformed into DH5alpha cells (available from Life Technologies, Gaithersburg, Md.), a recombination deficient strain of *E. coli*, to produce recombinant cell DH5-pGEX-nCaIL-4₃₂₇. The recombinant cells were screened for presence of insert by PCR and confirmed by enzyme restriction analysis and nucleic acid sequencing, using standard techniques. Several clonal recombinant molecules were transformed into BL21 cells (available from Amersham Pharmacia, Piscataway, N.J.), a protease deficient strain of *E. coli*, to produce recombinant cell BL21-pGEX-nCaIL-4₃₂₇. These recombinant cells were screened, and the clone with the highest level of protein yield was selected for scaling up for larger-scale protein production. The resultant recombinant protein is referred to herein as *E. coli*PCaIL-4₁₀₉.

To produce and purify *E. coli*PCaIL-4₁₀₉, bacterial cultures of recombinant cell BL21:pGEX-nCaIL-4₃₂₇ were grown in shake flasks at 37° C. and induced with 0.1 mM IPTG (isopropyl-β-D-thiogalactopyranoside), (available

from Sigma Chemical Company, St. Louis, Mo.) when OD_{600nm} reached about 0.8 units. Growth was allowed to continue for about 4 hours; then bacteria were harvested by centrifugation at $4000\times g$ (times gravity) for 20 minutes. The bacterial pellet was washed and resuspended in phosphate buffered saline (PBS) (for recipe, see Sambrook et al. *ibid.*), then lysed by exposure to gaseous nitrogen pressure in a Parr pressure vessel (available from Parr Instrument Co., Moline, Ill.), according to the manufacturer's instructions. Cell debris was removed by centrifugation at $10,000\times g$ for 20 minutes. The IL-4-GST fusion protein E. coliPCaIL-4₁₀₉ was purified from the supernatant by allowing incubation with glutathione-conjugated resin, removing unbound proteins and then removing the GST tag with PRESCISSION™ protease; all reagents were available from Amersham Pharmacia and all were used according to the manufacturer's directions.

Concentration and purity of E. coliPCaIL-4₁₀₉ were estimated by BCA Protein Assay kit (available from Pierce, Rockford, Ill.) and SDS-PAGE followed by Coomassie staining, respectively. The purified material exhibited a single band of approximately 14 kilodaltons (kD) by Coomassie stained SDS-PAGE.

ii. CHO Cell Expression

A recombinant molecule denoted herein as pCMV-nCaIL-4₃₉₀, capable of expressing a full length form of canine IL-4 (including signal sequence) was produced as follows. A 422-nucleotide fragment was PCR amplified from nucleic acid molecule nCaIL-4₁₄₉. Using the following primers: 5' **CCCAAGCTTA TGGGTCTCACC TCCCAAC** (HindIII site in bold), denoted SEQ ID NO:40, and 3' **CCTCGAGATT CAGCTTTCATGCTGTGTA** (XhoI site in bold), denoted SEQ ID NO:127. The 422-base pair PCR product was digested with the restriction endonucleases HindIII and xhoI, both available from New England Biolabs. The resulting 399-base pair product encoding full-length canine IL-4 was gel purified using standard techniques and ligated into the cytomegalovirus (CMV) immediate-early transcription control region of the pCMV-Int A plasmid vector that had been digested with HindIII and XhoI (available from New England Biolabs), and gel purified, to produce the recombinant molecule pCMV-nCaIL-4₃₉₉. The pCMV-Int A plasmid vector was generated as referenced by J. E. Osorio et al., 1999, Vaccine 17, 1109–1116. Briefly, vector pRc/RSV, (available from Invitrogen Corp., San Diego, Calif.) was cleaved with restriction enzyme PvuII (available from New England Biolabs), and the 2963-base pair PvuII fragment was gel purified. The fragment was self-ligated to form the vector pRc/RSV(Pvu), which contains a Rous Sarcoma Virus (RSV) long terminal repeat, a multiple cloning site, a bovine growth hormone polyadenylation sequence, a bacterial origin of replication, and an ampicillin resistance gene. Vector pRc/RSV(Pvu) was restriction enzyme digested using HindIII and NruI. A HindIII/SspI fragment containing the HCMV intermediate early promoter and first intron (i.e. intron A) was ligated into the digested pRc/RSV(Pvu) vector to produce the vector pCMV-Int A.

Stable expression of CaIL-4 in mammalian cells was carried out by transfecting the recombinant molecule pCMV-nCaIL-4₃₉₉ into Chinese Hamster Ovary cells, (CHO, available from ATCC) as follows. Six-well polystyrene tissue culture plates (available from Corning Costar, Acton, Mass.) were seeded with approximately 5×10^5 cells/well in 2 milliliter (ml) cell culture media, consisting of Minimal Essential Media (MEM) supplemented with 100 mM L-glutamine, 100 mM gentamicin, and 10% fetal

bovine serum (FBS), (all available from Life Technologies). Cells were grown to about 80% confluence (for about 18 hours) before transfection. The recombinant molecules to be transfected were purified using the Plasmid Midi Kit (available from Qiagen, Valencia, Calif.) and used according to the manufacturer's instructions. The recombinant molecule pCMV-nCaIL-4₃₉₉ was linearized using the restriction enzyme PvuI (available from New England Biolabs). The plasmid pcDNA3, (available from Invitrogen), which contains the neomycin resistance gene, was linearized using the restriction enzyme EcoRI. Approximately 2 μ g of pCMV-nCaIL-4₃₉₉ was mixed with about 2 ng of linearized pcDNA3 in about 100 μ l OPTIMEM™ media, available from Life Technologies. About 10 μ l Lipofectamine, (available from Life Technologies) was mixed with 100 μ l OPTIMEM. The nucleic acid molecule-containing mixture was then added to the Lipofectamine mixture and incubated at room temperature for about 45 minutes. After incubation, about 0.8 ml OPTIMEM was added, and the mixture was overlaid onto the CHO cells which had been previously rinsed with OPTIMEM. Cells were incubated for about 5 hours at 37° C. 5% CO₂, 95% relative humidity. Approximately 1 ml of cell culture media as described previously, with 20% FBS, was added and the cells were incubated overnight. The media was changed at 24 hours, and at 72 hours post transfection, the cells were split 1:4 and put into fresh cell culture media containing about 500 μ g/ml geneticin (G418, available from Life Technologies). The media was changed every 3–5 days. After several weeks, G418 resistant colonies were trypsinized using sterile filter papers, 5–6 mm in diameter that were soaked in trypsin, which were then placed over individual wells of 24 well plates that contained separated widely spaced colonies of CHO cells. After 3 days, the papers were removed. The resulting recombinant cells are referred to herein as CHO-pCMV-nCaIL-4₃₉₉. The recombinant cells were then expanded and tested for the presence of nIL-4399 RNA by RT-PCR and tested for the presence of PCaIL-4₁₃₃ protein by Western blot analysis. Westerns were developed with rabbit anti-E. coliPCaIL-4₁₀₉ serum and 607.1 monoclonal antibody, a monoclonal antibody that selectively binds to E. coliPCaIL-4₁₀₉ protein. See Example 1C for a description of how these antibodies were produced.

C. Monoclonal and Polyclonal Antibodies to Recombinant canine IL-4 (i.e., Anti-canine IL-4 Antibodies)

The following describes the development of monoclonal and polyclonal antibodies that selectively bind to E. coliPCaIL-4₁₀₉.

Female Balb/C mice, 6–8 weeks old, were injected subcutaneously, at about 4 sites, with a total of 25 μ g E. coliPCaIL-4₁₀₉ (produced as described in Example 1Bi) in Freund's Complete Adjuvant (day 0). Fourteen days later, the mice received an intraperitoneal boost of 25 μ g E. coliPCaIL-4₁₀₉ in Freund's Incomplete Adjuvant (day 14). Fourteen days later, serum was tested for antibody titer to E. coliPCaIL-4₁₀₉ by ELISA (day 28). Three days prior to fusion, mice were boosted intravenously with 20 μ g E. coliPCaIL-4₁₀₉ in PBS (day 35). Splenocytes were harvested from mice demonstrating the highest serum titer by ELISA and depleted of CD4+ and CD8+ cells. This depletion was achieved by incubation of the splenocytes with biotinylated rat anti-mouse CD4 and anti-mouse CD8 monoclonal antibodies, available from PharMingen, San Diego, Calif. Antibody-labeled cells were then removed by incubation with M-280 streptavidin coated magnetic beads,

available from Dynal, Oslo, Norway. Depleted splenocytes were fused to SP2/0 cells (available from ATCC) using 50% polyethylene glycol in unsupplemented Iscove's Modified Dulbecco's Media (IMDM), following established protocols; see, for example, Harlow E., and Lane D., eds., 1995, *Antibodies, A Laboratory Manual*, Monoclonal Antibodies, Cold Spring Harbor Laboratories; Harlow et al. *ibid.*, is incorporated by reference herein in its entirety. Fused cells were plated in 96-well plates using IMDM cell culture media, (available from Life Technologies, Inc., Rockville, Md.), which was supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 1xnonessential amino acids, 1xMEM amino acids, 0.05 mg/ml gentamicin, and 0.5 mM β -mercaptoethanol (all reagents available from Life Technologies). Additionally, 100 μ M hypoxanthine, 0.4 μ M aminopterin, and 16 μ M thymidine, all available from Sigma Chemical Corporation, St Louis, Mo., were added.

After about 7 days, wells positive for hybridoma growth were screened by ELISA to E. coliPCaIL-4₁₀₉. Immulon II 96-well plates (available from VWR, Denver, Colo.) were coated, overnight, with 100 ng/ml E. coliPCaIL-4₁₀₉ in 0.1 M carbonate/bicarbonate buffer, Ph 9.6. After blocking the wells with 20% FBS in Tris buffered saline (TBS), culture supernatants were allowed to bind. Presence of anti-E. coliPCaIL-4₁₀₉ mouse antibody was detected with polyclonal goat anti-mouse IgG conjugated to horseradish peroxidase, (available from KPL, Gaithersburg, Md.), and color developed with 3,3',5,5'-tetramethylbenzidine dihydrochloride (TMB), available from Pierce, Rockford, Ill. Specificity of the ELISA reactivity was verified by Western blot analysis to E. coliPCaIL-4₁₀₉, developed with polyclonal goat anti-mouse IgG conjugated to alkaline phosphatase and nitro-blue tetrazolium/5-bromo-4-chloro-3'-indolyphosphate p-toluidine salt substrate (NBT/BCIP, available from Sigma). Western blots exhibited a single band of approximately 14 kD. Immunoglobulin isotype of the monoclonal antibodies was determined using IsoStrips, available from Boehringer Mannheim, Indianapolis, Ind. Twenty-three monoclonal antibodies were generated to E. coliPCaIL-4₁₀₉, 22 of which were of the IgM isotype and one of which was IgG1, and is referred to herein as 607.1.

Polyclonal rabbit serum was produced by repeated immunization (over a 10 month period) of a male, New Zealand White rabbit 12–16 months old. Initial immunization was 50 μ g E. coliPCaIL-4₁₀₉ (prepared as described in Example 1bi) in Freund's Complete Adjuvant, at several sites subcutaneously and intradermally. One month later, and at one month intervals thereafter, the rabbit was boosted intradermally with 50 μ g E. coliPCaIL-4₁₀₉ in Freund's Incomplete Adjuvant. Serum was collected bi-weekly and titers monitored by ELISA and Western blot to E. coliPCaIL-4₁₀₉. Serum that selectively bound to E. coliPCaIL-4₁₀₉ protein is referred to as anti-E. coliPCaIL-4₁₀₉ serum.

D. Bioactivity of Mammalian-expressed Canine IL-

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The following describes a bioassay to detect the expression of canine IL-4 protein expressed in the supernatants from CHO-pCMV-nCaIL-4₃₉₉ recombinant cells by screening for production of CD23.

About 100 μ l Ramos cells, available from ATCC, at a concentration of about 3.5×10^3 cells/ml were seeded into 96-well flat bottom plates, available from Becton Dickinson, Franklin Lakes, N.J.). These cells were grown in RPMI media supplemented with 100 mM L-glutamine,

gentamicin, and 10% FBS (called TCM). The Ramos cells were then treated in 5% CO₂ for 37° C. for approximately 48 h. with one of the following:

Group Treatment

- 1 TCM
- 2 CHO-pCMV (a transfectant cell line containing the empty pCMV vector) supernatant (1:4 final dilution in TCM)
- 3 CHO-pCMV-nCaIL-4₃₉₉ supernatant (1:20 final dilution in TCM)

Triplicate samples for each treatment group were pooled for staining to look for increased expression of CD23 (one of the reported effects of IL-4). Briefly, 1×10^5 cells from each treatment group were incubated in phosphate buffered saline (PBS) containing 30% FBS for 15–30 min on ice. The cells were collected and incubated with the following:

Condition	Primary Incubation	Secondary Location
A	PBS	Goat anti mouse PE
B	Mouse anti human CD23	Goat anti mouse PE

Condition Primary Incubation Secondary Incubation
 Mouse anti-human CD23 monoclonal antibody, available from Pharmingen, was used at about 10 μ g/ml. Goat (Fab'2) anti mouse IgG PE, available from Southern Biotechnologies was used at about 2.5 μ g/ml. These reagents were diluted in PBS with 5% FBS. Primary incubations were performed for 30–60 minutes on ice, and secondary incubations were performed for 20–30 min on ice. Three washes of PBS/5% FBS were performed in between each incubation. Cells were then analyzed on a flow cytometer (e.g., MoFlow Desk Top System, available from Cytomation, Ft. Collins, Colo.) with the fluorescein gate set at 10^1 . The results are shown below in Table 2.

TABLE 2

Induction of CD23 on Ramos cells post-treatment with supernatants from CHO-pCMV-nCaIL-4 ₃₉₉		
Treatment	Condition	% positive
1	A	0
	B	1
2	A	8
	B	1
3	A	3
	B	99

Table 2 shows that the canine IL-4 expressed by the CHO transfectant CHO-pCMV-nCaIL-4₃₉₉ is biologically active, demonstrated by its ability to induce expression of CD23 in Ramos cells.

Example 2

This example describes the isolation and sequencing of certain canine Flt-3 ligand and feline Flt-3 nucleic acid molecules and proteins of the present invention. The example also describes expression of a canine Flt-3 ligand protein of the present invention in CHO cells, as well as detection of the expressed canine Flt-3 ligand protein.

A. Canine Flt-3 Ligand Nucleic Acid Molecules and Proteins.

i. This example describes the isolation and sequencing of certain canine Flt-3 ligand nucleic acid molecules and proteins of the present invention.

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A canine Flt-3 ligand nucleic acid molecule was produced as follows. A pair of primers was initially used to amplify DNA from the *C. familiaris* mitogen activated PBMC cDNA library described above in Example 1. A forward primer referred to as FLT3F1, having the nucleic acid sequence 5' CTGGCGCCAG CCTGGAGCCC 3', designated herein as SEQ ID NO:13 was used in combination with a reverse primer referred to herein as FLT3B1, having the nucleic acid sequence 5' GGGAGATGTT GGTCTGGACG 3', referred to herein as SEQ ID NO:14 to amplify Flt-3 ligand DNA from the cDNA library by polymerase chain reaction (PCR). The primers were designed using conserved regions of IL-4 cDNA sequences from other species in the public databases corresponding to the positions shown below:

Database	Accession number	Nucleotides	Animal
gb	U04806	102-121	human
gb	L23636	41-60	mouse
gb	U04806	77-458	human
gb	L23636	419-400	mouse

A 360-base pair (bp) PCR product was generated in the above reaction that was purified, radiolabeled and used as a probe to screen the cDNA library. Hybridization was performed in 6×SSC, 5×Denhardt's solution, 0.5% SDS, 100 µg/ml ssDNA and 100 µg/ml of tRNA, at 68° C., for about 36 hr. The filters were washed 3 times, for about 30 minutes per wash, at 55° C. in 2×SSC, 0.1% SDS, followed by a final wash in 0.25×SSC, for about 30 minutes, at 55° C. Several positive phage clones were identified and shown to produce PCR products when used as templates in combination with the FLT3F1 and FLT3B1 primers. The DNA inserts in the phage clones were sequenced using standard techniques and failed to yield any clones containing DNA inserts having a portion homologous to published Flt-3 ligand sequences. The 360-bp PCR fragment generated above was then cloned into the vector pcDNA 2.1 (available from Invitrogen Corp., San Diego, Calif.). Several independent colonies were generated and the sequences of their inserts determined. One clone was identified that which contained insert sequence having a portion, that was somewhat homologous to published human or murine Flt-3 ligand sequence.

Two canine Flt-3 ligand-specific primers were then designed using the nucleic acid sequence obtained using the 360-bp PCR product described above.

Primer	Sequence	SEQ ID NO
DFLB1	5'GACCAGGCGCCAGAACGC 3'	SEQ ID NO:15
DFLF1	5'CGGTCACCATCCGCAAGC 3'	SEQ ID NO:16

The 5' region of a Flt-3 ligand nucleic acid molecule was PCR amplified from the cDNA library using the DFLB1 primer in combination with the 5' T3 vector primer from the Uni-ZAP® XR vector (available from Stratagene). The 3' region of a Flt-3 ligand nucleic acid molecule was PCR amplified from the cDNA library using the DFLF1 in combination with the 3' T7 primer from the Uni-ZAP® XR vector (available from Stratagene). A 855-bp PCR product was obtained representing the 5' region of a Flt-3 ligand nucleic acid molecule. A 265-bp PCR product was obtained representing the 3' region of a Flt-3 ligand nucleic acid molecule. Both the 855-bp PCR product and 265-bp PCR

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product were cloned and sequenced using standard methods. Additional canine Flt-3 ligand-specific primers were designed using the nucleic acid sequence obtained from the sequence of the 855-bp PCR product and 265-bp PCR products.

Primer	Sequence	SEQ ID NO
DFLB2	5'TGGCAAGGCAGTGGCCTC 3'	SEQ ID NO:17
DFLF2	5'GCCGAGATGATAGTGCTGGC 3'	SEQ ID NO:18

A 546-bp PCR product was generated using the primer DFLF2 in combination with the primer DFLB2 to amplify a PCR product from the cDNA library. The 546-bp PCR product was then purified, radiolabelled and used as a probe to screen the cDNA library. Hybridization was performed in 6×SSC, 5×Denhardt's solution, 0.5% SDS, 100 µg/ml of ssDNA and 100 µg/ml of tRNA, at 68° C. for about 36 hr. The filters were washed in 1.25×SSC, for about 30 minutes, at 55° C. Four cDNA clones encoding full-length canine Flt-3 ligand were isolated. Nucleic acid sequence was obtained using standard techniques.

A Flt-3 ligand clone was isolated, referred to herein as nCaFlt3L₁₀₁₃, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:6. The complement of SEQ ID NO:6 is represented herein by SEQ ID NO:8. Translation of SEQ ID NO:6 suggests that nucleic acid molecule nCaFlt3L₁₀₁₃ encodes a full-length Flt-3 ligand protein of about 294 amino acids, denoted herein as PCaFlt3L₂₉₄, the amino acid sequence of which is presented in SEQ ID NO:7, assuming an open reading frame having an initiation codon spanning from nucleotide 35 through nucleotide 37 of SEQ ID NO:6 and a stop codon spanning from nucleotide 917 through nucleotide 919 of SEQ ID NO:6. The coding region encoding PCaFlt3L₂₉₄ is presented herein as nCaFlt3L₈₈₂, which has the nucleotide sequence SEQ ID NO:9 (the coding strand) and SEQ ID NO:10 (the complementary strand). A putative signal sequence coding region extends from nucleotide 35 through nucleotide 112 of SEQ ID NO:6. The proposed mature protein (i.e., canine Flt-3 ligand protein from which the signal sequence has been cleaved), denoted herein as PCaFlt3L₂₆₈ (SEQ ID NO:23), contains about 268 amino acids, extending from residue 27 through residue 294 of SEQ ID NO:7. The nucleic acid molecule encoding PCaFlt3L₂₆₈ is denoted herein as nCaFlt3L₈₀₄, extending from nucleotide 113 through nucleotide 916 of SEQ ID NO:6, nCaFlt3L₈₀₄ has a coding sequence denoted SEQ ID NO:22 and a complementary sequence denoted SEQ ID NO:24.

Below is a description of the identification of alternatively spliced Canis Flt3 ligand transcripts. Besides cDNA clones such as nucleic acid molecule nCaFlt3L₁₀₁₃ encoding the full-length canine FLT3 ligand protein, two splice variants of canine Flt3 ligand cDNA clones were also isolated, using the same hybridization conditions as mentioned previously in this Example. One such variant (Clone 1), denoted herein as nCaFlt3L₉₈₅, has a coding strand the nucleic acid sequence of which is represented as SEQ ID NO:25. The complement of SEQ ID NO:25 is represented herein by SEQ ID NO:27. Translation of SEQ ID NO:25 suggests that nucleic acid molecule nCaFlt3L₉₈₅ encodes a Flt-3 ligand protein of 276 amino acids, denoted herein as PCaFlt3L₂₇₆, the amino acid sequence of which is represented by SEQ ID NO:26, assuming an open reading frame having an initiation

codon spanning from nucleotide 74 through nucleotide 76 of SEQ ID NO:25 and a stop codon spanning from nucleotide 902 through nucleotide 904 of SEQ ID NO:25. The coding region encoding PCaFlt3L₂₇₆ is represented herein as nCaFlt3L₈₂₈, which has the nucleotide sequence SEQ ID NO:28 (the coding strand) and SEQ ID NO:29 (the complementary strand). Alignment of nucleic acid molecules nCaFlt3L₈₁₂ and nCaFlt3L₈₂₈ indicates that the nucleic acid molecules are identical except for a deletion in nCaFlt3L₈₂₈, which spans from nucleotide 343 through nucleotide 396 of nCaFlt3L₈₈₂. Accordingly, nCaFlt3L₈₂₈ encodes 18 fewer amino acids than nCaFlt3L₈₈₂. The deletion in PCaFlt3L₂₇₆, which spans from residue 115 through residue 132 of PCaFlt3L₂₉₄, occurs between helix III and helix IV of the canine Flt3 ligand protein inferred from alignment with the human and mouse Flt3 ligand protein (Lyman et al., Cell, vol. 75, pp. 1157–1167, 1993; Hannum et al., Nature, vol. 368, pp. 643–648, 1994; Lyamn et al., Blood, vol. 83, pp. 2795–2801, 1994). In addition, the alignment shows that there are 39 more nucleotides in the 5' untranslated region of nucleic acid molecule nCaFlt3L₉₈₅ (nucleotides 1 to 39) than nucleic acid molecule nCaFlt3L₁₀₁₃ and there are 2 more nucleotides in the 3' untranslated region of nucleic acid molecule nCaFlt3L₉₈₅ (nucleotides 922 to 923) than nucleic acid molecule nCaFlt3L₁₀₁₃. The remaining sequences between nCaFlt3L₉₈₅ and nCaFlt3L₁₀₁₃ are identical. A putative mature form of nCaFlt3L₉₈₅ (without the signal sequence) is predicted. The putative signal sequence coding region extends from nucleotide 74 to nucleotide 151 of SEQ ID NO:25. The proposed mature protein, denoted herein as PCaFlt3L₂₅₀, represented by SEQ ID NO:31, contains about 250 amino acids, extending from residue 27 through residue 276 of SEQ ID NO:26. The nucleic acid molecule encoding PCaFlt3L₂₅₀, extending from nucleotide 152 through nucleotide 901 of SEQ ID NO:6, denoted herein as nCaFlt3L₇₅₀, is represented by SEQ ID NO:30 (the coding strand) and SEQ ID NO:32 (the complement strand).

A second variant (Clone 19) is represented by nucleic acid molecule nCaFlt3L₁₀₁₉, the coding strand of which is denoted herein as SEQ ID NO:33. The complement of SEQ ID NO:33 is denoted herein as SEQ ID NO:35. Translation of SEQ ID NO:33 suggests that nCaFlt3L₁₀₁₉ encodes a Flt-3 ligand protein of 31 amino acids, PCaFlt3L₃₁, denoted SEQ ID NO:34, assuming an initiation codon spanning from nucleotide 74 through nucleotide 76 and a stop codon spanning nucleotide 167 through nucleotide 169 of SEQ ID NO:33. The coding region encoding PCaFlt3L₃₁ is represented herein as nCaFlt3L₉₃, which has the nucleotide sequence SEQ ID NO:36 (the coding strand) and SEQ ID NO:37 (the complementary strand). Alignment of nucleic acid molecules nCaFlt3L₉₈₅ and nCaFlt3L₁₀₁₉ indicates the presence of an insertion of 91 nucleotides in nCaFlt3L₁₀₁₉. The insertion spans nucleotide 107 through nucleotide 198 of nCaFlt3L₁₀₁₉. A stop codon is found in this insertion in frame with the predicted initiation codon, which span nucleotide 74 through nucleotide 76 of SEQ ID NO:6. Since this insertion (with an in-frame stop codon) occurs in or close to the signal peptide, it is likely that nucleic acid molecule nCaFlt3L₁₀₁₉ encodes a nonfunctional Flt-3 ligand protein.

Comparison of nucleic acid sequence SEQ ID NO:6 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:6 showed the most homology, i.e., about 69.8% identity, with a human Flt-3 ligand gene. Comparison of amino acid sequence SEQ ID NO:7 with amino acid sequences reported in GenBank indicates that SEQ ID NO:7 showed the most homology, i.e. about 71% identity, with a human Flt-3 ligand protein. Sequence analysis was per-

formed with DNAsis™ using the alignment settings of: gap penalty set at 5; number of top diagonals set at 5; fixed gap penalty set at 10; K-tuple set at 2; window size set at 5 and floating gap penalty set at 10.

ii. This example describes the production of a recombinant molecule encoding a full length canine Flt-3 ligand protein and expression of that protein by a recombinant cell of the present invention.

A recombinant molecule, denoted herein as pCMV-nCaFlt3L₈₈₂ and capable of expressing a full length form of Flt-3 ligand, was produced as follows. Nucleic acid molecule nCaFlt3L₈₈₂ was digested with the restriction endonucleases EcoRI and XbaI, gel purified and ligated into pCMV-Int A (prepared by methods described in Example 1) to produce recombinant molecule pCMV-nCaFlt3L₈₁₂. Insert size and identity were confirmed by restriction digestion, PCR, and sequencing analyses.

Stable transfectants expressing the recombinant molecule pCMV-nCaFlt3L₈₈₂ were established in Chinese Hamster Ovary cells (CHO, available from ATCC) as follows. Briefly, six-well polystyrene tissue culture plates were seeded with approximately 4×10^5 cells per well in 2 ml of MEM (available from Life Technologies, Gaithersburg, Md.) supplemented with 100 mM L-glutamine, gentamicin, and 10% FBS (TCM). Cells were grown to about 80% confluence (about 18 hr). The recombinant molecule to be transfected was prepared using the Qiagen Endotoxin-Free Plasmid Maxi Kit as per the manufacturer's instructions. The recombinant molecule was linearized with the restriction enzyme PvuI, extracted with phenol, and precipitated with isopropanol. The plasmid pcDNA 3, available from Invitrogen, which contains the neomycin resistance gene, was linearized with the restriction enzyme EcoRI. Approximately 1 μ g of recombinant plasmid DNA and 100 ng of pcDNA3 were mixed with about 100 μ l OptiMEM medium, available from Life Technologies. About 10 μ l Lipofectamine (available from Life Technologies) was mixed with 100 μ l OptiMEM. The DNA-containing mixture was then added to the Lipofectamine mixture and incubated at room temperature for about 30 min. After incubation, about 800 μ l of OptiMEM was added, and the entire mixture was overlaid onto the CHO cells that had been rinsed with OptiMEM. Cells were incubated for 6 hours at 37° C., 5% CO₂, 95% relative humidity. Approximately 1 ml of TCM with 20% FBS was added, and the cells were incubated overnight. The media was changed after about 24 hr. About 72 hr post transfection, the cells were split 1:4 and put into selection TCM containing 500 μ g/ml Geneticin (G418), available from Life Technologies. The medium was changed every 3–5 days. After several weeks, G418-resistant colonies were trypsinized, and the cells were plated into 24 well plates. The resulting recombinant cells are referred to herein as CHO-pCMV-nCaFlt3L₈₈₂. The recombinant cells were then expanded for testing.

iii. The following describes the detection of expression of a canine Flt-3 ligand protein of the present invention by CHO-pCMV-nCaFlt3L₈₈₂, a recombinant cell of the present invention.

Recombinant cells CHO-pCMV-nCaFlt3L₈₈₂, produced as described in Example 2, part (B)(ii) above, were tested for surface expression of canine Flt-3 ligand using a cross-reactive goat anti-human Flt-3 ligand polyclonal antibody as follows. Briefly, 1×10^5 CHO-pCMV-nCaFlt3L₈₈₂ cells or CHO-pCMV cells (i.e., cells transfected with an empty vector as described in Example 1) were incubated in phosphate buffered saline (PBS) containing 30% fetal bovine

serum (FBS) for about 30 min on ice. The cells were then spun down and treated with the following:

Condition	Primary Incubation	Secondary Incubation
1	PBS	Rabbit (Fab' 2) anti sheep (H + L) FITC
2	Goat anti-human Flt3 ligand	Rabbit (Fab' 2) anti sheep (H + L) FITC

Goat anti-human Flt3 ligand, available from R and D Systems, Minneapolis, Minn. was used at about 20 μ g/ml. Rabbit (Fab' 2) anti sheep (H+L) FITC, available from Southern Biotechnology Associates, Inc., was used at about 10 μ g/ml. These reagents were diluted in PBS/5%FBS. All incubations were in 50 μ l for about 1 hr on ice with 2 washes of PBS/5%FBS in between each incubation. Cells were then analyzed on a flow cytometer (e.g., MoFlow Desk Top System, available from Cytomation, Ft. Collins, Colo.) with the fluorescein gate set at 10¹. The results are shown below in Table 3.

TABLE 3

Expression of canine Flt3 ligand on CHO transfectants.		
Cells	% positive	
	Condition 1	Condition 2
CHO-pCMV	1	1
CHO-pCMV nCaFlt3L ₈₈₂	2	48
CHO-pCMV nCaFlt3L ₈₈₂	1	20

Table 3 shows that canine Flt3 ligand is expressed on the surface of the CHO transfectants.

B. Feline Flt-3 Ligand Nucleic Acid Molecules and Proteins.

This example describes the production of certain feline Flt-3 ligand nucleic acid molecules and proteins of the present invention.

A nucleic acid molecule encoding a feline Flt-3 ligand was isolated from a feline PBMC cDNA library as follows. A *Felis catus* mitogen activated PBMC cDNA library was constructed in the Uni-Zap-R XRTM vector, available from Stratagene, La Jolla, Calif., using Stratagene's Zap cDNA-RTM Synthesis Kit and the manufacturer's protocol using mRNA isolated from *F. catus* peripheral blood mononuclear cells about 4 hours after they were activated by a polyclonal activating agent in culture. PCR amplification to isolate a feline Flt 3 ligand nucleic acid molecule was conducted according to the following set of steps: one initial denaturation step at 95° C. for 3 minutes; then 35 cycles of the following; 94° C. for 30 seconds, 53.8° C. for 30 seconds, and 72° C. for 105 seconds; then one final extension step at 72° C. for 8 minutes. A 395 nucleotide cDNA fragment containing the 5' end of feline Flt3 ligand coding region, denoted nFeFlt3L₃₉₅, was amplified from the feline PMBC cDNA library using the following primers: vector primer T3 having nucleic acid sequence 5' AATTAACCCT CAC-TAAAGGG 3' (SEQ ID NO:142) (available from Stratagene) and the antisense primer having SEQ ID NO:14, described in Example 2A. The nucleic acid sequence of the coding strand of nFeFlt3L₃₉₅ is denoted SEQ ID NO:41. A 793-nucleotide cDNA fragment containing the 3' end of feline Flt3 ligand coding region, denoted nFeFlt3L₇₉₃, was

isolated using sense primer 2 having the nucleic acid sequence 5' CACAGYCCCA TCTCCTCC 3' (where Y was either T or C) denoted herein as SEQ ID NO:151, in conjunction with vector primer T7 having the nucleic acid sequence 5' GTAATACGAC TCACTATAGG GC 3' (SEQ ID NO:152). The nucleic acid sequence of the coding strand of nFeFlt3L₇₉₃ is denoted SEQ ID NO:42. Nucleic acid molecules nFeFlt3L₃₉₃ and nFeFlt3L₇₉₃ overlap by 246 nucleotides and form a composite sequence encoding a Flt3 ligand protein that is similar in length to that of PCaFlt3L₂₉₄. This composite feline Flt3 ligand cDNA is referred to herein as nFeFlt3L₉₄₂, the coding strand of which was shown to have nucleic acid sequence SEQ ID NO:43. The reverse complement of SEQ ID NO:43 is referred to herein as SEQ ID NO:45. Translation of SEQ ID NO:43 suggests that nucleic acid molecule nFeFlt3L₉₄₂ encodes a Flt3 ligand protein of 291 amino acids, denoted herein as PFeFlt3L₂₉₁, the amino acid sequence of which is presented in SEQ ID NO:44, assuming an open reading frame having an initiation codon spanning from nucleotide 31 through nucleotide 33 of SEQ ID NO:43 and a stop codon spanning from nucleotide 904 through nucleotide 906 of SEQ ID NO:43. The coding region encoding PFeFlt3L₂₉₁, not including the termination codon, is presented herein as nFeFlt3L₈₇₃, which has the nucleotide sequence SEQ ID NO:46 (the coding strand) and SEQ ID NO:47 (the complementary strand). A putative signal sequence coding region extends from nucleotide 31 to nucleotide 108 of SEQ ID NO:43. The proposed mature protein, denoted herein as PFeFlt3L₂₆₅, denoted SEQ ID NO:49, contains about 265 amino acids, extending from residue 27 through residue 291 of SEQ ID NO:44. The nucleic acid molecule encoding PFeFlt3L₂₆₅, is denoted herein as nFeFlt3L₇₉₅, (SEQ ID NO:48) extending from nucleotide 109 through nucleotide 903 of SEQ ID NO:43. SEQ ID NO:48 has a complementary strand denoted SEQ ID NO:50.

Sequence alignment indicates that nucleic acid sequence SEQ ID NO:43 shares the highest (67.8%) identity with the nucleic acid sequence of human Flt-3 ligand (GenBank accession numbers U04806 and U03858). Amino acid sequence SEQ ID NO:44 shares the highest (70.2%) identity with human Flt-3 ligand protein (GenBank accession numbers U04806 and U03858).

Example 3.

This example describes the isolation and sequencing of certain canine CD40 and feline CD40 nucleic acid molecules and proteins of the present invention.

A. Canine CD40 Nucleic Acid Molecules and Proteins

This example describes the production of certain canine CD40 nucleic acid molecules and proteins of the present invention.

A canine CD40 nucleic acid molecule of the present invention was produced by PCR amplification as follows. A 321-nucleotide canine CD40 nucleic acid molecule, denoted nCaCD40₃₂₁, was amplified from a canine PBMC cDNA library, prepared as described in Example 1, using two degenerate oligonucleotide primers designed in accordance with conserved regions of human, bovine, rabbit, and mouse CD40 gene sequences available in GenBank; sense primer, 5' TGCCCRSTCG GCTTCTTCTC C 3', denoted herein as SEQ ID NO:128; and antisense primer, 5' CGACTCTCTT TRCCRTCCTC CTG 3', denoted herein as SEQ ID NO:129, where R was either A or G and S was either G or C. PCR

conditions were as follows: one initial denaturation step at 95° C. for 3 minutes; then 35 cycles of the following: 94° C. for 30 seconds, then 53° C. for 30 seconds, then 72° C. for 105 seconds; followed by one final extension at 72° C. for 5 minutes. The resulting PCR product, i.e., nCaCD40₃₂₁, with a coding strand represented by SEQ ID NO:51, was radiolabeled using standard techniques and used to screen the canine PBMC cDNA library, under the following hybridization conditions: hybridized in 6×SSC, 5×Denhardt's solution, 0.5% SDS, 100 µg/ml single stranded DNA, 100 µg/ml tRNA for 36 hours at 68° C., followed by a wash of 0.1% SDS, 1×SSC at 55° C. for 60 minutes. A clone (Clone 18B) containing a 1425-nucleotide canine CD40 nucleic acid molecule, denoted nCaCD40₁₄₂₅, was obtained. The nucleic acid sequence of the coding strand of nCaCD40₁₄₂₅ is represented as SEQ ID NO:52. The reverse complement of SEQ ID NO:52 is referred to herein as SEQ ID NO:54. Translation of SEQ ID NO:52 suggests that nucleic acid molecule nCaCD40₁₄₂₅ encodes a canine CD40 protein of 274 amino acids, denoted herein as PCaCD40₂₇₄, the amino acid sequence of which is presented in SEQ ID NO:53, assuming an open reading frame having an initiation codon spanning from nucleotide 196 through nucleotide 198 of SEQ ID NO:52 and a stop codon spanning from nucleotide 1018 through nucleotide 1020 of SEQ ID NO:52. The coding region encoding PCaCD40₂₇₄, not including the termination codon, is presented herein as nCaCD40₈₂₂, which has the nucleotide sequence SEQ ID NO:55 (the coding strand) and SEQ ID NO:56 (the complementary strand).

A putative signal sequence coding region extends from nucleotide 196 through nucleotide 252 of SEQ ID NO:52. The proposed mature protein, denoted herein as PCaCD40₂₅₅, represented by SEQ ID NO:58, contains about 255 amino acids, extending from residue 20 through residue 274 of SEQ ID NO:53. The nucleotide sequence encoding PCaCD40₂₅₅, which extends from nucleotide 253 through nucleotide 1017 of SEQ ID NO:52, is denoted herein as nucleic acid molecule nCaCD40₇₆₅, represented by SEQ ID NO:57 (the coding strand) and SEQ ID NO:59 (the complement strand).

Sequence analysis was performed with DNAsis™ using the alignment settings of: gap penalty set at 5; number of top diagonals set at 5; fixed gap penalty set at 10; k-tuple set at 2; window size set at 5 and floating gap penalty set at 10. At the amino acid level, PCaCD40₂₇₄ shares 65.3%, 50.1%, and 42.3% identity with the CD40 proteins of human, bovine, and mouse, respectively (Stamenkovic et al., EMBO J., vol. 8:1403–1410, 1989; Hirano et al., Immunology, vol. 90, pp. 294–300, 1997; Grimaldi et al., J. Immunol., vol. 143, pp. 3921–3926; Torres and Clark, J. Immunol., vol. 148, pp. 620–626). At the nucleotide level, nCaCD40₁₄₂₅ shares 69.3%, 69.4%, and 40.4% identity with the cDNA sequences of human, bovine, and mouse CD40, respectively.

B. Feline CD40 Nucleic Acid Molecules and Proteins

This example describes the isolation and sequencing of certain nucleic acid molecules of the present invention that encode certain feline CD40 proteins of the present invention.

A 336-nucleotide feline CD40 nucleic acid molecule, denoted nFeCD40₃₃₆, was amplified from a feline PBMC cDNA library, prepared as described in Example 2, using PCR conditions and primers as described in Example 3A, i.e., a sense primer having SEQ ID NO:128; and an antisense

primer having SEQ ID NO:129. The resulting PCR product, i.e., nFeCD40₃₃₆, was shown to have a coding strand the nucleic acid sequence of which is represented as SEQ ID NO:60. The reverse complement of SEQ ID NO:60 is referred to herein as SEQ ID NO:62. Translation of SEQ ID NO:60 suggests that nucleic acid molecule nFeCD40₃₃₆ encodes a partial CD40 protein of 112 amino acids, denoted herein as PFeCD40₁₁₂, the amino acid sequence of which is presented in SEQ ID NO:61, assuming an open reading frame spanning from nucleotide 1 through nucleotide 336 of SEQ ID NO:60.

Comparison of nucleic acid sequence SEQ ID NO:60 with nucleic acid molecules reported in GenBank indicates that SEQ ID NO:60 showed the most homology, i.e. 67.2% identity, with a human CD40 gene. Comparison of amino acid sequence SEQ ID NO:61 with amino acid sequences reported in GenBank indicates that SEQ ID NO:61 showed the most homology, i.e. about 54.4% identity, with a human CD40 protein. Sequence analysis was performed using the GCG GAP program as described above.

Example 4

This example describes the isolation and sequencing of certain canine CD154 (canine CD40 ligand) and feline CD154 (feline CD40 ligand) nucleic acid molecules and proteins of the present invention.

A. Canine CD154 (CD40 Ligand) Nucleic Acid Molecules and Proteins

The following describes the isolation and sequencing of certain cDNA nucleic acid molecules encoding certain canine CD154 (CD40 ligand) proteins of the present invention.

A canine CD154 nucleic acid molecule of the present invention was produced by PCR amplification as follows. A 390-nucleotide canine CD40 nucleic acid molecule, denoted nCaCD154₃₉₀, was amplified from a canine PBMC cDNA library, prepared as described in Example 1, using two degenerate oligonucleotide primers designed in accordance with human CD154 gene sequences available in GenBank; sense primer, 5' CCTCAAATTG CGGCACATGT C 3', denoted herein as SEQ ID NO:130; and antisense primer, 5' CTGTTTCAGAG TTTGAGTAAG CC 3', denoted herein as SEQ ID NO:131. PCR conditions used for canine CD154 cDNA amplification were standard conditions for PCR amplification (Sambrook, et al., *ibid.*). The resulting PCR product, i.e., nCaCD154₃₉₀, with a coding strand represented by SEQ ID NO:63, was radiolabeled using standard techniques and used to screen the canine PBMC cDNA library, under the hybridization conditions described in Example 3. A clone containing a 1878-nucleotide canine CD154 nucleic acid molecule, denoted nCaCD154₁₈₇₈, was obtained. The nucleic acid sequence of the coding strand of nCaCD154₁₈₇₈ is represented as SEQ ID NO:64. The reverse complement of SEQ ID NO:64 is referred to herein as SEQ ID NO:66. Translation of SEQ ID NO:64 suggests that nucleic acid molecule of nCaCD154₁₈₇₈ encodes a CD154 protein of 260 amino acids, denoted herein as PCaCD154₂₆₀, the amino acid sequence of which is presented in SEQ ID NO:65, assuming an open reading frame having an initiation codon spanning from nucleotide 284 through nucleotide 286 of SEQ ID NO:64 and a stop codon spanning from nucleotide 1064 through nucleotide 1066 of SEQ ID NO:64. The coding region encoding PCaCD154₂₆₀, not including the termination codon, is presented herein as nCaCD154₇₈₀, which has the nucleotide sequence SEQ ID

NO:67 (the coding strand) and SEQ ID NO:68 (the complementary strand).

A putative signal/membrane anchor sequence coding region extends from nucleotide 284 through nucleotide 430 of SEQ ID NO:64. The proposed soluble CD154 protein, denoted herein as PCaCD154₂₁₁, represented by SEQ ID NO:70, contains about 211 amino acids, extending from residue 50 through residue 260 of SEQ ID NO:65. The nucleotide sequence encoding PCaCD154₂₁₁, which extends from nucleotide 431 through nucleotide 1063 of SEQ ID NO:64, is denoted herein as nucleic acid molecule nCaCD154₆₃₃, represented by SEQ ID NO:69 (the coding strand) and SEQ ID NO:71 (the complement strand).

Sequence analysis was performed with DNAsis™ using the alignment settings of: gap penalty set at 5; number of top diagonals set at 5; fixed gap penalty set at 10; k-tuple set at 2; window size set at 5 and floating gap penalty set at 10. At the amino acid level, PCaCD154₂₆₀ shares 78.0%, 77.6%, and 67.6% identity with the CD154 proteins of human, bovine, and mouse, respectively (Graf et al., *Eur. J. Immunol.*, vol. 22, pp. 3191–3194, 1992; Hollenbaugh, et al., *EMBO J.*, vol. 11:4313–4321, 1992; Gauchat et al., *FEBS Lett.*, vol., 315, pp. 259–266, 1993; Mertens et al., *Immunogenetics*, vol. 42, pp. 430–431; Armitage et al., *Nature*, vol. 357, pp. 80–82; 1992). At the nucleotide level, nCaCD154₁₈₇₈, shares 81.1%, 81.5%, and 74.4% identity with the sequences of human, bovine, and mouse CD154 cDNAs, respectively.

B. Feline CD154 (CD40 ligand) Nucleic Acid Molecules and Proteins

This example describes the isolation and sequencing of certain nucleic acid molecules encoding certain feline CD154 (CD40 ligand) proteins of the present invention.

A feline CD154 nucleic acid molecule was isolated by PCR amplification from a feline PBMC cDNA library, prepared as described in Example 2, using Amplitaq DNA polymerase (available from PE Applied Biosystems Inc, Foster City, Calif.) under the following PCR protocol; one initial denaturation step at 95° C. for 5 minutes; then 40 cycles of the following: 94° C. for 45 seconds, then 48° C. for 45 seconds, then 72° C. for 120 seconds; followed by a final extension at 72° C. for 7 minutes. The forward and reverse primers used were based on human CD154 cDNA sequences outside the open reading frame in the 5' and 3' untranslated regions, respectively, so that the open reading frame in the PCR product contained only feline sequences. The sequence of the forward primer was 5' GAAGATACCA TTTCAACTTT AACACAGC 3' SEQ ID NO:132, and that of the reverse primer was 5' TGCTGTATTG TGAA-GACTCC CAGC 3' SEQ ID NO:133. PCR products were cloned into the TA cloning vector (available from Invitrogen Corporation, Carlsbad, Calif.), and the resulting clones were sequenced using an ABI Prism™ Model 377 Automatic DNA Sequencer (available from PE Applied Biosystems Inc.). DNA sequencing reactions were performed using Prism™ dRhodamine Terminator Cycle Sequencing Ready Reaction kits (available from PE Applied Biosystems Inc.).

The PCR product was sequenced and found to contain 885 nucleotides, and is denoted as nFeCD154₈₈₅. The nucleotide sequence of the coding strand of nFeCD154₈₈₅ is represented herein as SEQ ID NO:72, and its complement is denoted SEQ ID NO:74. Translation of the open reading frame in SEQ ID NO:72 suggests that nFeCD154₈₈₅ encodes a protein containing 260 amino acids, referred to herein as PFeCD154₂₆₀, the amino acid sequence of which

is presented as SEQ ID NO:73, assuming an open reading frame in which the first codon spans from nucleotide 29 through nucleotide 31 of SEQ ID NO:72, and the stop codon spans from nucleotide 809 through nucleotide 811 of SEQ ID NO:72. The encoded protein has a predicted molecular weight of 28.6 kDa for the precursor protein and 27.2 kDa for the mature protein. The coding region encoding PFeCD154₂₆₀, not including the termination codon, is presented herein as nFeCD154₇₈₀, which has the nucleotide sequence SEQ ID NO:75 (the coding strand) and SEQ ID NO:76 (the complementary strand).

A putative signal/membrane anchor sequence coding region extends from nucleotide 29 through nucleotide 175 of SEQ ID NO:72. The proposed soluble feline CD154 protein, denoted herein as PFeCD154₂₁₁, represented by SEQ ID NO:78, contains about 211 amino acids, extending from residue 50 through residue 260 of SEQ ID NO:73. The nucleotide sequence encoding PFeCD154₂₁₁, denoted herein as nFeCD154₆₃₃ which extends from nucleotide 176 through nucleotide 808 of SEQ ID NO:72, is represented herein by SEQ ID NO:77 (the coding strand) and SEQ ID NO:79 (the complementary strand).

Comparison of feline CD154 nucleotide and amino acid sequences with those of other species published in GenBank reveals that the feline CD154 nucleotide sequence SEQ ID NO:75 is 86%, 88% and 75% identical to the human, bovine and murine CD154 gene sequences, respectively (Genbank accession number L07414, Z48469 and X56453 respectively). At the amino acid sequence level, SEQ ID NO:73 is 81%, 82%, and 67% identical to the human, bovine and murine CD154 amino acid sequences, respectively. Hydrophobicity analysis of feline CD154 proteins results in a pattern similar to those of human, bovine and murine CD154 proteins. A putative N-glycosylation site was identified at position 239 in PFeCD154₂₆₀ that is conserved in the human, bovine and murine amino acid sequences. Five cysteine residues are present in the feline CD154 protein sequence SEQ ID NO:73. Four of the five residues, located at positions 72, 84, 177 and 217 of PFeCD154₂₆₀, are conserved in all four species and are likely involved in disulfide bond formation. The cysteine residue located at position 193 of PFeCD154₂₆₀ is present in all but the murine sequence.

Example 5

This example describes the isolation and sequencing of certain canine IL-5 nucleic acid molecules and proteins of the present invention. This example also describes expression of canine IL-5 in a *Pichia* expression system.

A. Isolation and Sequencing of Canine IL-5 Nucleic Acid Molecules and Proteins

A canine IL-5 cDNA nucleic acid molecule encoding a canine IL-5 protein was isolated by PCR amplification from a canine PBMC cDNA library (prepared as described in Example 1) using PCR conditions as described in Example 4B and the following primers. Degenerate oligonucleotide primers were designed in accordance with conserved regions of human and cat IL-5 gene sequences available in GenBank; sense primer, 5' ATGCACTTTC TTTGCC 3', denoted herein as SEQ ID NO:134; antisense primer 1, 5' CTGGAG-GAAA AKACTTCRAT GATTCTGATA TCTGAAATAT AT 3', denoted herein as SEQ ID NO:135; and antisense primer 2, 5' CTGACYCTTK STTGGSCCTC ATTCTCA 3', denoted herein as SEQ ID NO:136, where K was G or T, R was either A or G, S was either G or C, and Y was either T or C.

An about 610-nucleotide canine IL-5 nucleic acid molecule, denoted nCaIL-5₆₁₀, was obtained using primers having SEQ ID NO:134 and SEQ ID NO:135, respectively. The sequence of the coding strand of nCaIL-5₆₁₀ is represented herein as SEQ ID NO:80. The reverse complement of SEQ ID NO:80 is referred to herein as SEQ ID NO:82. Translation of SEQ ID NO:80 suggests that nucleic acid molecule nCaIL-5₆₁₀ encodes an IL-5 protein of 134 amino acids, denoted herein as PCaIL-5₁₃₄, the amino acid sequence of which is presented in SEQ ID NO:81, assuming an open reading frame having an initiation codon spanning from nucleotide 29 through nucleotide 31 of SEQ ID NO:80 and a stop codon spanning from nucleotide 431 through nucleotide 433 of SEQ ID NO:80. The coding region encoding PCaIL-13₁₃₄, not including the termination codon, is presented herein as nCaIL-5₄₀₂, which has the nucleotide sequence SEQ ID NO:83 (the coding strand) and SEQ ID NO:84 (the complementary strand).

An about 488-nucleotide fragment, denoted herein as nCaIL-5₄₈₈, isolated by PCR with primers having SEQ ID NO:134 and SEQ ID NO:136, respectively, corresponds to nucleotide 1 through nucleotide 488 of nCaIL-5₆₁₀.

A putative signal sequence coding region extends from nucleotide 29 through nucleotide 85 of SEQ ID NO:80. The proposed mature protein, denoted herein as PCaIL-5₁₁₅, represented by SEQ ID NO:86, contains about 115 amino acids, extending from residue 20 through residue 134 of SEQ ID NO:81. The nucleotide sequence encoding PCaIL-5₁₁₅, which extends from nucleotide 86 through nucleotide 430 of SEQ ID NO:80, is denoted herein as nucleic acid molecule nCaIL-5₃₄₅, represented by SEQ ID NO:85 (coding strand) and SEQ ID NO:87 (the complement strand).

Sequence analysis was performed with DNAsis™ using the alignment settings of: gap penalty set at 5; number of top diagonals set at 5; fixed gap penalty set at 10; k-tuple set at 2; window size set at 5 and floating gap penalty set at 10. At the amino acid level, PCaIL-5₁₃₄ shared 82.8% and 57.4% identity with feline and human IL-5 proteins, respectively (Padrid et al., *Am. J. Vet. Res.*, vol. 59, pp. 1263–1269, 1998; Azuma et al., *Nucleic Acids Res.*, vol. 14, pp. 9149–9158, 1986). At the nucleotide level, nCaIL-5₆₁₀ shared 81.7% and 75% identity with the cDNA sequences of the feline and human IL-5, respectively.

B. Expression of Canine IL-5 in Pichia

This example describes the expression in Pichia of a canine IL-5 cDNA fragment, namely a canine IL-5 nucleic acid molecule denoted nCaIL-5₃₄₈, the coding strand of which consists of nucleotides 86–433 of SEQ ID NO:80, and as such, encodes a predicted mature canine IL-5 protein having SEQ ID NO:86. Nucleic acid molecule nCaIL-5₃₄₈, was PCR amplified from nCaIL-5₆₁₀ using sense primer 5' GGGCTCGAGA AAAGATTTGC TGTAGAAAAT CCCATG 3' denoted herein as SEQ ID NO:137, with nucleotides 16–36 corresponding to nucleotides 86–106 of SEQ ID NO:80; and antisense primer 5' CCCGCGCCG CTCAACTTTC CGGTGTCCAC TC 3', denoted herein as SEQ ID NO:138, with nucleotides 12–32 corresponding to the reverse complement of nucleotides 413–433 of SEQ ID NO:80. To facilitate cloning, an XhoI site (shown in bold) was added to the sense primer and a NotI site (shown in bold) was added to the antisense primer. The PCR-amplified fragment was digested with restriction endonucleases XhoI and NotI, gel purified and ligated into pPICZαA plasmid vector, available from Invitrogen, that has been digested by Aho I and Not I and gel purified, to produce recombinant

molecule pPICZαA-nCaIL-5₃₄₈. The insert in the recombinant molecule was verified by DNA sequencing. The recombinant molecule was used to transform Pichia pastoris strain X-33 by electroporation to produce recombinant cell Pichia-pPICZαA-nCaIL-5₃₄₈. Recombinant cell Pichia-pPICZαA-nCaIL-5₃₄₈ was cultured using techniques known to those skilled in the art and IL-5 expression was induced with methanol. The supernatant was recovered and submitted to SDS-PAGE. Silver staining of the resultant gel indicated a band of about 18 kDa only seen in the supernatant of Pichia transformed with recombinant molecule pPICZαA-nCaIL-5₃₄₈.

Example 6

This example describes the isolation and sequencing of certain canine IL-13 nucleic acid molecules and proteins of the present invention. This example also describes expression of canine IL-13 in E. coli.

A. Isolation and Sequencing of Canine IL-13 Nucleic Acid Molecules and Proteins

A canine IL-13 cDNA nucleic acid molecule encoding a canine IL-13 protein was isolated by PCR amplification from a canine PBMC cDNA library (prepared as described in Example 1) using the following primers and PCR conditions: Degenerate oligonucleotide primers were designed in accordance with conserved regions of human and cat IL-5 gene sequences available in GenBank; sense primer, 5' GTCMTKGCTC TYRCTIGCCT TGG 3', denoted herein as SEQ ID NO:139; antisense primer 1, 5' AASTGGGCY ACYTCGATTT TGG 3', denoted herein as SEQ ID NO:140; antisense primer 2, 5' GTGATGTTGM YCAGTCCTC 3', denoted herein as SEQ ID NO:141, where M was either A or C, K was G or T, R was either A or G, S was either G or C, and Y was either T or C. PCR conditions used were as follows: One initial denaturation step at 95° C. for 3 minutes; then 38 cycles of the following: 94° C. for 30 seconds, 51.8° C. for 45 seconds, then 72° C. for 105 seconds; then a final extension at 72° C. for 5 minutes.

An about 272-nucleotide canine IL-13 nucleic acid molecule, denoted nCaIL-13₂₇₂ and having a coding strand represented by SEQ ID NO:89, was PCR amplified using primers having nucleic acid sequences of SEQ ID NO:139 and SEQ ID NO:140, respectively. An about 166-nucleotide canine IL-13 nucleic acid molecule, denoted nCaIL-13₁₆₆ and having a coding strand represented by SEQ ID NO:88, was isolated using primers having nucleic acid sequences of SEQ ID NO:142 (see Example 2B) and SEQ ID NO:141, respectively. Nucleic acid molecules nCaIL-13₂₇₂ and nCaIL-13₁₆₆ form an overlapping composite fragment of 383 nucleotides, denoted nCaIL-13₃₈₃. Two canine IL-13 specific primers (i.e., sense primer, 5' ATGGCGCTCT GGT-TGACTGT 3', denoted herein as SEQ ID NO:143; and antisense primer, 5' GGCTTTTGAG AGCACAGTGC 3', denoted herein as SEQ ID NO:144) were derived from nCaIL-13₃₈₃ and were used to isolate a 278-nucleotide fragment, denoted nCaIL-13₂₇₈ and having a coding strand represented by SEQ ID NO:90. Nucleic acid molecule nCaIL-13₂₇₈ was radiolabeled and used to screen the canine PBMC cDNA library under the following hybridization conditions: hybridization took place in 6×SSC, 5×Denhardt's solution, 0.5% SDS, 100 μg/ml single stranded DNA, 100 μg/ml tRNA, for 36 hours at 60° C.; the final wash solution was 0.1% SDS, 0.125×SSC at 60° C. for 30 minutes. Two clones were selected, namely clone 80 and clone 78.

Sequence analysis of Clone 80 indicated that the clone includes an about 1302-nucleotide canine IL-13 nucleic acid molecule referred to herein as nCaIL-13₁₃₀₂, the coding strand of which was shown to have nucleic acid sequence SEQ ID NO:91. The reverse complement of SEQ ID NO:91 is referred to herein as SEQ ID NO:93. Translation of SEQ ID NO:91 suggests that nucleic acid molecule nCaIL-13₁₃₀₂ encodes an IL-13 protein of 131 amino acids, denoted herein as PCaIL-13₁₃₁, the amino acid sequence of which is presented in SEQ ID NO:92, assuming an open reading frame having an initiation codon spanning from nucleotide 52 through nucleotide 54 of SEQ ID NO:91 and a stop codon spanning from nucleotide 445 through nucleotide 447 of SEQ ID NO:91. The coding region encoding PCaIL-13₁₃₁, not including the termination codon, is presented herein as nCaIL-13₃₉₃, which has the nucleotide sequence SEQ ID NO:94 (the coding strand) and SEQ ID NO:95 (the complementary strand).

A putative signal sequence coding region extends from nucleotide 52 to nucleotide 111 of SEQ ID NO:91. The proposed mature protein, denoted herein as PCaIL-13₁₁₁, represented by SEQ ID NO:97, contains 111 amino acids, extending from residue 21 through residue 131 of SEQ ID NO:91. The nucleotide sequence encoding PCaIL-13₁₁₁, which extends from nucleotide 112 through nucleotide 444 of SEQ ID NO:91, is denoted herein as nucleic acid molecule nCaIL-13₃₃₃, represented by SEQ ID NO:96 (coding strand) and SEQ ID NO:98 (the complement strand).

Sequence analysis of Clone 78 indicated that the clone includes an about 1269-nucleotide canine IL-13 nucleic acid molecule referred to herein as nCaIL-13₁₂₆₉, the coding strand of which was shown to have nucleic acid sequence SEQ ID NO:99. The reverse complement of SEQ ID NO:99 is referred to herein as SEQ ID NO:101. Translation of SEQ ID NO:99 suggests that nucleic acid molecule nCaIL-13₁₂₆₉ encodes an IL-13 protein of 130 amino acids, denoted herein as PCaIL-13₁₃₀, the amino acid sequence of which is presented in SEQ ID NO:100, assuming an open reading frame having an initiation codon spanning from nucleotide 57 through nucleotide 59 of SEQ ID NO:99 and a stop codon spanning from nucleotide 447 through nucleotide 449 of SEQ ID NO:99. The coding region encoding PCaIL-13₁₃₀, not including the termination codon, is represented herein as nCaIL-13₃₉₀, which has the nucleotide sequence SEQ ID NO:102 (the coding strand) and SEQ ID NO:103 (the complementary strand). PCaIL-13₁₃₀ is missing one amino acid compared to PCaIL-13₁₃₃, namely amino acid position Q97 of PCaIL-13₁₃₃.

A putative signal sequence coding region extends from nucleotide 57 to nucleotide 116 of SEQ ID NO:99. The proposed mature protein, denoted herein as PCaIL-13₁₁₀, represented by SEQ ID NO:105, contains 110 amino acids, extending from residue 21 through residue 130 of SEQ ID NO:100. The nucleotide sequence encoding PCaIL-13₁₁₀, which extends from nucleotide 117 through nucleotide 446 of SEQ ID NO:99, is denoted herein as nucleic acid molecule nCaIL-13₃₃₀, represented by SEQ ID NO:104 (coding strand) and SEQ ID NO:106 (the complement strand).

Sequence analysis was performed with DNAsis™ using the alignment settings of: gap penalty set at 5; number of top diagonals set at 5; fixed gap penalty set at 10; k-tuple set at 2; window size set at 5 and floating gap penalty set at 10. At the amino acid level, PCaIL-13₁₃₁ shared 61.7%, 39.6%, 36.6% identity with the IL-13 proteins of human, mouse, and rat (Brown et al., J. Immunol., vol. 142, pp 679–687, 1989; Lakkis et al., Biochem, Biophys, Res. Commun., Vol. 197, pp. 612–618, 1993; McKenzie et al., Proc. Natl Acad.

Sci. USA, vol. 90, pp. 3735–3739, 1993; Minty et al., Nature, vol. 362, pp. 248–250, 1993), respectively. At the nucleotide level, nCaIL-13₁₃₀₂ shared 56.0%, 57.1%, and 45.9% identity with the sequences of human, rat, and mouse IL-13 cDNAs, respectively.

B. Expression of Canine IL-13 in E. coli

This example describes the expression in E. coli of a canine IL-13 cDNA fragment, namely a canine IL-13 nucleic acid molecule denoted nCaIL-13₃₃₆, the coding strand of which consists of nucleotides 112–447 of SEQ ID NO:91, and as such, encodes a predicted mature canine IL-13 protein having SEQ ID NO:97. Nucleic acid molecule nCaIL-13₃₃₆ was PCR amplified from nCaIL-13₁₃₀₂ using sense primer 5' CCCCATATGA GCCCTGTGAC TCCCTC-CCC 3' denoted herein as SEQ ID; 145, with nucleotides 10–29 corresponding to nucleotides 112–1131 of SEQ ID NO:91; and antisense primer 5' GGGGAATTCT CATCT-GAAAT TTCCATGGCG 3', denoted herein as SEQ ID NO:146, with nucleotides 10–30 corresponding to the reverse complement of nucleotides 427–447 of SEQ ID NO:91. To facilitate cloning, an NdeI site (shown in bold) was added to the sense primer and an EcoRI site (shown in bold) was added to the antisense primer. The resulting PCR fragment was digested with restriction endonucleases NdeI and EcoRI, gel purified and ligated into λcro plasmid vector, the production of which is described in U.S. Pat. No. 5,569,603 by Tripp et al., issued Oct. 29, 1996, that had been digested by NdeI and EcoRI and gel purified to produce recombinant molecule pλcro-nCaIL-13₃₃₆. The insert in the recombinant molecule was verified by DNA sequencing. Recombinant molecule pλcro-nCaIL-13₃₃₆ was used to transform E. coli strain HCE101 (BL21), thereby producing BL21-pλcro-nCaIL-13₃₃₆. PCaIL-13₁₁₁ was produced under conditions as described in U.S. Pat. No. 5,569,603, *ibid.*, protein expression being induced by switching the fermentation temperature from 32° C. to 42° C. SDS-PAGE and Commassie blue staining analysis indicated that a band of about 11 kD was only produced by induced BL21-pλcro-nCaIL-13₃₃₆ recombinant cells. The 11-kD band showed a positive reaction with a rabbit polyclonal antibody against human IL-13 (available from PeproTech Inc, Rocky Hill, N.J.), indicating expression of canine IL-13 in E. coli.

Example 7

This example describes the isolation and sequencing of feline interferon alpha nucleic acid molecules and proteins of the present invention.

Feline IFN-alpha nucleic acid molecules were PCR amplified from a feline cDNA library as follows. Total RNA was isolated from cat (kitten) mesenteric lymph node cells stimulated with PMA (phorbol myristate acetate) for 48 hours using Tri Reagent™ (available from Molecular Research Center, Cincinnati, Ohio). cDNA was made from the RNA using the cDNA synthesis kit containing Ready to Go -You Prime First-Strand Beads™ (available from Amersham Pharmacia Biotech, Piscataway, N.J.). An aliquot of this cDNA was used as a template to isolate a feline IFN-alpha nucleic acid molecule by PCR amplification using Amplitaq DNA polymerase™ (available from PE Applied Biosystems Inc, Foster City, Calif.) and the following primers and conditions. The sequence of the forward primer was 5' ATGGCGCTGC CCTCTTCCTT CTTG 3' (SEQ ID NO:143), and that of the reverse primer was 5' TCATTCTCG CTCCTTAATC TTTTCTGC 3' (SEQ ID NO:148). The following PCR protocol was used: one initial

denaturation step at 95° C. for 5 minutes; then 43 cycles of the following: 94° C. for 45 seconds, then 47° C. for 45 seconds, then 72° C. for 120 seconds; followed by a final extension at 72° C. for 7 minutes. PCR products were cloned into the TA cloning vector (available from Invitrogen Corporation) and the clones were sequenced using an ABI Prism™ Model 377 Automatic DNA Sequencer (available from PE Applied Biosystems Inc.). DNA sequencing reactions were performed using Prism™ dRhodamine Terminator Cycle Sequencing Ready Reaction kits (available from PE Applied Biosystems Inc.).

Two PCR products were generated and sequenced. Both contained 570 nucleotides (including the termination codons), and are distinguished as Clone #2 and Clone #3 as there were differences in the sequences of the clones.

Clone #2 includes a feline IFN-alpha nucleic acid molecule that is represented herein as nFeIFN α_{567a} , the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:107. The complement of SEQ ID NO:107 is represented herein by SEQ ID NO:109. Translation of SEQ ID NO:107 suggests that nFeIFN α_{567a} encodes a protein containing 189 amino acids, referred to herein as PFeIFN α_{189a} , with an amino acid sequence denoted SEQ ID NO:108. The open reading frame of SEQ ID NO:107 is assumed to be the following: the first codon spans from nucleotide 1 through nucleotide 3 and the last codon before the stop codon spans from nucleotide 565 to nucleotide 567 of SEQ ID NO:107. The encoded protein has a predicted molecular weight of 21 kDa. The putative signal peptide cleavage site occurs between amino acid positions 23 and 24, based on homology with the human and canine interferon-alpha proteins. The proposed mature protein (i.e. feline IFN α protein from which the signal sequence has been cleaved), denoted herein as PFeIFN α_{166a} , contains about 166 amino acids, extending from residue 24 to residue 166 of SEQ ID NO:108; the amino acid sequence is denoted herein as SEQ ID NO:114. The nucleic acid molecule encoding PFeIFN α_{166a} is denoted herein as nFeIFN α_{498a} , which is represented by SEQ ID NO:113, with a complementary sequence represented by SEQ ID NO:115. A putative N-glycosylation site and an interferon alpha-beta-delta family signature motif are present at amino acid positions 102 and 145, respectively, of PFeIFN α_{189a} .

Clone #3 includes a feline IFN-alpha nucleic acid molecule that is represented herein as nFeIFN α_{567b} , the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:110. The complement of SEQ ID NO:110 is represented herein by SEQ ID NO:112. Translation of SEQ ID NO:110 suggests that nFeIFN α_{567b} encodes a protein containing 189 amino acids, referred to herein as PFeIFN α_{189b} , with an amino acid sequence denoted SEQ ID NO:111. The open reading frame of SEQ ID NO:110 is assumed to be the following: the first codon spans from nucleotide 1 through nucleotide 3 and the last codon before the stop codon spans from nucleotide 565 through nucleotide 567 of SEQ ID NO:110. The encoded protein has a predicted molecular weight of 21 kDa. The putative signal peptide cleavage site occurs between amino acid positions 23 and 24, based on homology with the human and canine interferon-alpha proteins. The proposed mature protein (i.e. feline IFN α protein from which the signal sequence has been cleaved), denoted herein as PFeIFN α_{166b} , contains about 166 amino acids, extending from residue 24 to residue 166 of SEQ ID NO:111, the amino acid sequence is denoted herein as SEQ ID NO:117. The nucleic acid molecule encoding PFeIFN α_{166b} is denoted herein as nFeIFN α_{498b} , which is represented by

SEQ ID NO:116, with a complementary sequence represented by SEQ ID NO:118. A putative N-glycosylation site and an interferon alpha-beta-delta family signature motif are present at amino acid positions 102 and 145, respectively, of PFeIFN α_{189b} .

The differences between the proteins encoded by SEQ ID NO:107 and SEQ ID NO:110 are detailed as follows: The amino acid residues at position 56 in SEQ ID NO:108 (i.e., the protein encoded by SEQ ID NO:107) and at position 56 in SEQ ID NO:111 (i.e., the protein encoded by SEQ ID NO:110) are both arginines, although the corresponding codons in SEQ ID NO:107 and SEQ ID NO:110 are AGA and AGG, respectively. The amino acid residues at position 74 in SEQ ID NO:108 and at position 74 in SEQ ID NO:111 are both alanines, although the corresponding codons in SEQ ID NO:107 and SEQ ID NO:110 are GCC and GCT, respectively. The amino acid residue at position 86 in SEQ ID NO:108 is lysine, encoded by AAG in SEQ ID NO:107, whereas the amino acid residue at position 86 in SEQ ID NO:111 is glutamic acid, encoded by GAG in SEQ ID NO:110. The amino acid residue at position 125 in SEQ ID NO:108 is methionine, encoded by CTG in SEQ ID NO:107, whereas the amino acid residue at position 125 in SEQ ID NO:111 is valine, encoded by GTG in SEQ ID NO:110. The amino acid residue at position 141 in SEQ ID NO:108 is isovaline, encoded by ATC in SEQ ID NO:107, whereas the amino acid residue at position 141 in SEQ ID NO:111 is leucine, encoded by CTC in SEQ ID NO:110.

Feline IFN-alpha proteins of the present invention PFeIFN α_{189a} and PFeIFN α_{189b} are five amino acids shorter than the GenBank entry for feline IFN-alpha, accession #E02521. In addition, there are 3 non-conservative and 2 conservative changes at the amino acid level between this GenBank entry and SEQ ID NO:108 (PFeIFN α_{189a}) as well as 4 non-conservative and 3 conservative changes at the amino acid level between this GenBank entry and SEQ ID NO:111 (PFeIFN α_{189b}). The lengths of SEQ ID NO:108 and SEQ ID NO:111, when compared with those of IFN-alpha proteins of other species, are two amino acids longer than published canine interferon-alpha subtype 1, 2 and 3 sequences, two amino acids longer than published human interferon-alpha type I,B,D, F, and J, sequences, three amino acids longer than the published human interferon-alpha sequence type A sequence and two amino acids longer than published murine interferon-alpha type B, 8, 7, 11, and 19 sequences.

Example 8

This example describes the isolation and sequencing of feline granulocyte-macrophage colony-stimulating factor (GMCSF) nucleic acid molecules and proteins of the present invention. This example also describes expression of a feline GMCSF protein of the present invention.

Nucleic acid molecules encoding feline GMCSF were isolated as follows. A cDNA library was prepared from feline PBMCs stimulated with Con A for 12 hours, as previously described in Example 2. An aliquot of this library was used as a template to amplify feline GMCSF nucleic acid molecules by PCR using Amplitaq DNA polymerase™ (PE Applied Biosystems Inc, Foster City, Calif.) and the following primers and conditions. The sequence of the forward primer was 5' CAGGATCCA CCATGTGGCT GCA-GAACCTG CTTTTC 3' (SEQ ID NO:149), and that of the reverse primer was 5' TTA CTTCTGG TCTGGTCCCC AGCAGTCAAA GGGGTTGTTA AACAGAAAAT 3' (SEQ ID NO:150). The following PCR protocol was used:

one initial denaturation step at 95° C. for 5 minutes; then 35 cycles of the following: 94° C. for 30 seconds, then 50° C. for 30 seconds, then 72° C. for 90 seconds; followed by a final extension at 72° C. for 7 minutes. PCR products were cloned into the CMV-Intron A vector and the clones were sequenced as described in Example 7.

A PCR product was isolated, referred to herein as nFeGMCSF₄₄₄, the coding strand of which is represented herein as SEQ ID NO:119, and its complement is denoted SEQ ID NO:121. Translation of the open reading frame in SEQ ID NO:119 suggests that nucleic acid molecule nFeGMCSF₄₄₄ encodes a protein containing 144 amino acids, referred to herein as PFeGMCSF₁₄₄, with an amino acid sequence denoted SEQ ID NO:120, assuming an open reading frame in which the first codon spans from nucleotide 10 through nucleotide 12 of SEQ ID NO:119, and the stop codon spans from nucleotide 442 through nucleotide 444 of SEQ ID NO:121. The encoded protein has a predicted molecular weight of 16 kDa. The coding region encoding PFeGMCSF₁₄₄ is presented herein as nFeGMCSF₄₃₂ which has the nucleotide sequence SEQ ID NO:122 (the coding strand) and SEQ ID NO:123 (the complementary strand). A putative signal peptide cleavage site is between amino acid positions 17 and 18, based on homology with human, mouse and ovine GMCSF proteins. The nucleic acid molecule encoding the proposed mature protein is denoted as nFeGMCSF₃₈₁ and has a nucleotide sequence represented herein as SEQ ID NO:124 and a complementary sequence represented herein as SEQ ID NO:126. The amino acid sequence

of the putative mature protein, referred to herein as PFeGMCSF₁₂₇, has an amino acid sequence represented herein as SEQ ID NO:125. The number of amino acids in the feline GMCSF protein is the same compared to human, porcine, ovine and canine GMCSF proteins. The feline GMCSF protein is one amino acid longer than bovine GMCSF and three amino acid longer than murine GMCSF.

The deduced amino acid sequence of the full-length feline GMCSF protein of the present invention has four non-conservative changes and one conservative change compared to a GenBank entry for feline GMCSF (accession #AF053007). Amino acids asparagine, methionine, threonine, and lysine at positions 10, 36, 56 and 126 of the GenBank entry have been changed to glycine, isoleucine, alanine and asparagine, respectively, in PFeGMCSF₁₄₄, containing the above-noted amino acid substitutions, appears to have GMCSF activity, as demonstrated by an experiment in which supernatant collected from Chinese Hamster Ovary (CHO) cells that were transiently transfected with a recombinant molecule encoding a feline GMCSF protein of the present invention was able to induce proliferation of TF-1 cells.

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 154

<210> SEQ ID NO 1

<211> LENGTH: 549

<212> TYPE: DNA

<213> ORGANISM: Canis familiaris

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (43)..(438)

<400> SEQUENCE: 1

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ggcacgaggt ctgctattgt cactgcaa at agagatctat ta atg ggt ctc acc      54
                                     Met Gly Leu Thr
                                     1

tcc caa ctg att cca act ctg gtc tgc tta cta gca ctc acc agc acc      102
Ser Gln Leu Ile Pro Thr Leu Val Cys Leu Leu Ala Leu Thr Ser Thr
  5                10                15                20

ttt gtc cac gga cat aac ttc aat att act att aaa gag atc atc aaa      150
Phe Val His Gly His Asn Phe Asn Ile Thr Ile Lys Glu Ile Ile Lys
  25                30                35

atg ttg aac atc ctc aca gcg aga aac gac tcg tgc atg gag ctg act      198
Met Leu Asn Ile Leu Thr Ala Arg Asn Asp Ser Cys Met Glu Leu Thr
  40                45                50

gtc aag gac gtc ttc act gct cca aag aac aca agc gat aag gaa atc      246
Val Lys Asp Val Phe Thr Ala Pro Lys Asn Thr Ser Asp Lys Glu Ile
  55                60                65

ttc tgc aga gct gct act gta ctg cgg cag atc tat aca cac aac tgc      294
Phe Cys Arg Ala Ala Thr Val Leu Arg Gln Ile Tyr Thr His Asn Cys
  70                75                80

tcc aac aga tat ctc aga gga ctc tac agg aac ctc agc agc atg gca      342
Ser Asn Arg Tyr Leu Arg Gly Leu Tyr Arg Asn Leu Ser Ser Met Ala

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85	90	95	100	
aac aag acc tgt tct atg aat gaa atc aag aag agt aca ctg aaa gac				390
Asn Lys Thr Cys Ser Met Asn Glu Ile Lys Lys Ser Thr Leu Lys Asp				
	105	110	115	
ttc ttg gaa agg cta aaa gtg atc atg cag aag aaa tac tac agg cat				438
Phe Leu Glu Arg Leu Lys Val Ile Met Gln Lys Lys Tyr Tyr Arg His				
	120	125	130	
tgaagctgaa tattttaatt tatgagtttt taaatagctt tattttaaaa atatttatat				498
atttataaca taataaaata aaatatatat agaaaaaaaa aaaaaaaaaa a				549

<210> SEQ ID NO 2
 <211> LENGTH: 132
 <212> TYPE: PRT
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 2

Met Gly Leu Thr Ser Gln Leu Ile Pro Thr Leu Val Cys Leu Leu Ala				
1	5	10	15	
Leu Thr Ser Thr Phe Val His Gly His Asn Phe Asn Ile Thr Ile Lys				
	20	25	30	
Glu Ile Ile Lys Met Leu Asn Ile Leu Thr Ala Arg Asn Asp Ser Cys				
	35	40	45	
Met Glu Leu Thr Val Lys Asp Val Phe Thr Ala Pro Lys Asn Thr Ser				
50	55	60		
Asp Lys Glu Ile Phe Cys Arg Ala Ala Thr Val Leu Arg Gln Ile Tyr				
65	70	75	80	
Thr His Asn Cys Ser Asn Arg Tyr Leu Arg Gly Leu Tyr Arg Asn Leu				
	85	90	95	
Ser Ser Met Ala Asn Lys Thr Cys Ser Met Asn Glu Ile Lys Lys Ser				
	100	105	110	
Thr Leu Lys Asp Phe Leu Glu Arg Leu Lys Val Ile Met Gln Lys Lys				
	115	120	125	
Tyr Tyr Arg His				
130				

<210> SEQ ID NO 3
 <211> LENGTH: 549
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 3

tttttttttt tttttttttc tatatatatt ttattttatt atgttataaa tatataaata	60
tttttaaaat aaagctattht aaaaactcat aaattaaaat attcagcttc aatgcctgta	120
gtattttcttc tgcatgatca ctttttagcct ttccaagaag tctttcagtg tactcttctt	180
gatttcattc atagaacagg tcttgtttgc catgctgctg aggttctctg agagtcctct	240
gagatatctg ttggagcagt tgtgtgtata gatctgccgc agtacagtag cagctctgca	300
gaagatttcc ttatcgcttg tgttctttgg agcagtgaag acgtccttga cagtcagctc	360
catgcacgag tcgtttctcg ctgtgaggat gttcaacatt ttgatgatct ctttaatagt	420
aatattgaag ttatgtccgt ggacaaaggt gctggtgagt gctagtaagc agaccagagt	480
tggaatcagt tgggaggtga gaccattaa tagatctcta tttgcagtga caatagcaga	540
cctcgtgcc	549

<210> SEQ ID NO 4

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<211> LENGTH: 396
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 4

atgggtctca cctcccaact gattccaact ctggtctgct tactagcact caccagcacc	60
tttgtccacg gacataactt caatattact attaaagaga tcatcaaaat gttgaacatc	120
ctcacagcga gaaacgactc gtgcatggag ctgactgtca aggacgtctt cactgctcca	180
aagaacacaa gcgataagga aatcttctgc agagctgcta ctgtactgcg gcagatctat	240
acacacaact gctccaacag atatctcaga ggactctaca ggaacctcag cagcatggca	300
aacaagacct gttctatgaa tgaatcaag aagagtacac tgaagactt cttggaaagg	360
ctaaaagtga tcatgcagaa gaaatactac aggcatt	396

<210> SEQ ID NO 5
 <211> LENGTH: 396
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 5

atgcctgtag tatttcttct gcatgatcac ttttagcctt tccaagaagt ctttcagtgt	60
actcttcttg atttcattca tagaacaggt cttgtttgcc atgctgctga ggttcctgta	120
gagtcctctg agatatctgt tggagcagtt gtgtgtatag atctgccgca gtacagtagc	180
agctctgcag aagatttctt tctcgttctg gttctttgga gcagtgaaga cgtccttgac	240
agtcagctcc atgcacgagt cgtttctcgc tgtgaggatg ttcaacattt tgatgatctc	300
tttaaatagta atattgaagt tatgtccgtg gacaaagggt ctggtgagtg ctagtaagca	360
gaccagagtt ggaatcagtt gggaggtgag acctat	396

<210> SEQ ID NO 6
 <211> LENGTH: 1013
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (35)..(916)

<400> SEQUENCE: 6

atctgacat aggcattgag ggcctccggc cgag atg ata gtg ctg gcg cca gcc	55
Met Ile Val Leu Ala Pro Ala	
1 5	
tgg agc cca act gcc tcc ctg ttg ctg ctg ctg ctg ctc agc ccc ggc	103
Trp Ser Pro Thr Ala Ser Leu Leu Leu Leu Leu Leu Ser Pro Gly	
10 15 20	
ctc cgc ggg acc ccc gac tgc tcc ttc agc cac agc ccc atc tcc tcc	151
Leu Arg Gly Thr Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser	
25 30 35	
acc ttc gcg gtc acc atc cgc aag ctg tct gat tac ctg ctt cag gac	199
Thr Phe Ala Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp	
40 45 50 55	
tat cca gtc act gtc gcc tcc aac ctg cag gac gac gag ctc tgc ggg	247
Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly	
60 65 70	
gcg ttc tgg cgc ctg gtc ctg gcc cag cgc tgg atg gtg cgg ctc cag	295
Ala Phe Trp Arg Leu Val Leu Ala Gln Arg Trp Met Val Arg Leu Gln	
75 80 85	
gct gtg gct gga tcc caa atg caa atc ctg ctg gag gct gtc aac acg	343
Ala Val Ala Gly Ser Gln Met Gln Ile Leu Leu Glu Ala Val Asn Thr	

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

<210> SEQ ID NO 8
 <211> LENGTH: 1013
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 8

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
 tttttttttt ttttttttgg tagaaaagga tgatttatat acaatttctt gggggcaagg 120
 actttgtaca gagggggaga ggtggggctg gggctggctt tgggggcgtt gggggcgggc 180
 gttgccttga tcctggggag ggagcagcgc gggctgcgtg gtcgaggaag ggaccagtct 240
 ctgctgact ccctccaggt cccagctctg tgcctcggg cagatggctc cgctcgtg 300
 gcctcagtgt cctctgctcc ccagggtagg gtgacctccg ccgccgcctc cttecgcaat 360
 gcaggcacca ggcagtggac atcagcagga gagccacggg cagcagcagc aggaggagca 420
 gccgaggtgc ctgaggggct ggcaaggcag tggcctccag ggccccgggg ctcccttgggg 480
 gcaccaatgt agaggagtgc ggctgacact gcagctccag gcacccggag aaattcctgc 540
 gggatgacca gggcttcagg gcgccagct gctgggaggt gtcctgcagg aggtgggaga 600
 tgttggtctg gacgaagcga agacagctgg ggaggggctg gaaggcacag aaggtgacaa 660
 agtgtatctc cgtggtgaca gcctccagca ggatttgcatt tgggatcca gccacagcct 720
 ggagccgcac catccagcgc tgggccagga ccaggcgcga gaacgccccg cagagctcgt 780
 cgtcctgcag gttggaggcg acagtgactg gatagtcctg aagcaggtaa tcagacagct 840
 tgcggatggt gaccgcgaag gtggaggaga tggggctgtg gctgaaggag cagtcggggg 900
 tcccgcggag gccggggctg agcagcagca gcagcaacag ggaggcagtt gggctccagg 960

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ctggcgccag cactatcatc tcggccggag gccctcatg cctatggtca gat 1013

<210> SEQ ID NO 9
 <211> LENGTH: 882
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 9

atgatagtgc tggcgccagc ctggagccca actgcctccc tgttgctgct gctgctgctc 60
 agccccggcc tccgcgggac ccccgactgc tccttcagcc acagccccat ctctccacc 120
 ttcgcggtca ccatccgcaa gctgtctgat tacctgcttc aggactatcc agtcaactgtc 180
 gcctccaacc tgcaggacga cgagctctgc gggcgcttct ggcgcctggt cctggccag 240
 cgctggatgg tgcggctcca ggctgtggct ggatcccaaa tgcaaatcct gctggaggct 300
 gtcaacacgg agatacactt tgtcaccttc tgtgccttcc agcccctccc cagctgtctt 360
 cgcttcgtcc agaccaacat ctcccacctc ctgcaggaca cctcccagca gctggccgcc 420
 ctgaagccct ggatcaccgg caggaatttc tccgggtgcc tggagctgca gtgtcagccc 480
 gactcctcta cattggtgcc cccaaggagc cccggggccc tggaggccac tgccttgcca 540
 gccctcagg cacctcggct gctcctcctg ctgctgctgc ccgtggctct cctgctgatg 600
 tccactgcct ggtgcctgca ttggcgaagg aggcggcggc ggaggtcacc ctaccctggg 660
 gagcagagga cactgaggcc cagcgagcgg agccatctgc ccgaggacac agagctggga 720
 cctggaggga gtcagctaga gactggctcc ttctctgacc acgcagcccc gctcgtctcc 780
 tccccaggat caaggcaacg cccgccccca acgccccaa agccagcccc agccccacct 840
 ctccccctct gtacaaagtc cttgccccca agaaattgta ta 882

<210> SEQ ID NO 10
 <211> LENGTH: 882
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 10

tatacaatth cttgggggca aggactttgt acagaggggg agaggtgggg ctggggctgg 60
 ctttgggggc gttgggggcg ggcgcttgcct tgatcctggg gagggagcga gcggggctgc 120
 gtggtcgagg aagggaccag tctctagctg actccctcca ggtcccagct ctgtgtcctc 180
 gggcagatgg ctccgctcgc tgggcctcag tgtcctctgc tccccagggt aggggtgacct 240
 ccgccgccgc ctcttcgcc aatgcaggca ccaggcagtg gacatcagca ggagagccac 300
 gggcagcagc agcaggagga gcagccgagg tgcctgaggg gctggcaagg cagtggcctc 360
 cagggccccg gggctccttg ggggcaccaa tgtagaggag tcgggctgac actgcagctc 420
 caggcaccgg gagaaattcc tgcgggtgat ccagggttcc agggcggcca gctgctggga 480
 ggtgtcctgc aggaggtggg agatggtggg ctggacgaag cgaagacagc tggggagggg 540
 ctggaaggca cagaaggatga caaagtgtat ctccgtgttg acagcctcca gcaggattg 600
 catttgggat ccagccacag cctggagccg caccatccag cgctgggcca ggaccaggcg 660
 ccagaacgcc ccgacagagc cgtcgtcctg cagggtggag gcgacagtga ctggatagtc 720
 ctgaagcagg taatcagaca gcttgccgat ggtgaccggc aaggtggagg agatggggct 780
 gtggctgaag gagcagtcgg gggctcccgcg gaggccgggg ctgagcagca gcagcagcaa 840
 cagggaggca gttgggctcc aggctggcgc cagcaactatc at 882

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<210> SEQ ID NO 11
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 11

ctattaatgg gtctcacctc ccaact 26

<210> SEQ ID NO 12
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 12

tcaactcggg gcacagagtc ttgg 24

<210> SEQ ID NO 13
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 13

ctggcgccag cctggagccc 20

<210> SEQ ID NO 14
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 14

gggagatggt ggtctggacg 20

<210> SEQ ID NO 15
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 15

gaccaggcgc cagaacgc 18

<210> SEQ ID NO 16
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 16

cggtcaccat ccgcaagc 18

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<210> SEQ ID NO 17
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 17

tggcaaggca gtggcctc 18

<210> SEQ ID NO 18
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 18

gccgagatga tagtgctggc 20

<210> SEQ ID NO 19
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(324)

<400> SEQUENCE: 19

cat aac ttc aat att act att aaa gag atc atc aaa atg ttg aac atc 48
 His Asn Phe Asn Ile Thr Ile Lys Glu Ile Ile Lys Met Leu Asn Ile
 1 5 10 15

ctc aca gcg aga aac gac tcg tgc atg gag ctg act gtc aag gac gtc 96
 Leu Thr Ala Arg Asn Asp Ser Cys Met Glu Leu Thr Val Lys Asp Val
 20 25 30

ttc act gct cca aag aac aca agc gat aag gaa atc ttc tgc aga gct 144
 Phe Thr Ala Pro Lys Asn Thr Ser Asp Lys Glu Ile Phe Cys Arg Ala
 35 40 45

gct act gta ctg cgg cag atc tat aca cac aac tgc tcc aac aga tat 192
 Ala Thr Val Leu Arg Gln Ile Tyr Thr His Asn Cys Ser Asn Arg Tyr
 50 55 60

ctc aga gga ctc tac agg aac ctc agc agc atg gca aac aag acc tgt 240
 Leu Arg Gly Leu Tyr Arg Asn Leu Ser Ser Met Ala Asn Lys Thr Cys
 65 70 75 80

tct atg aat gaa atc aag aag agt aca ctg aaa gac ttc ttg gaa agg 288
 Ser Met Asn Glu Ile Lys Lys Ser Thr Leu Lys Asp Phe Leu Glu Arg
 85 90 95

cta aaa gtg atc atg cag aag aaa tac tac agg cat 324
 Leu Lys Val Ile Met Gln Lys Lys Tyr Tyr Arg His
 100 105

<210> SEQ ID NO 20
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 20

His Asn Phe Asn Ile Thr Ile Lys Glu Ile Ile Lys Met Leu Asn Ile
 1 5 10 15

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

Phe Thr Ala Pro Lys Asn Thr Ser Asp Lys Glu Ile Phe Cys Arg Ala

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35	40	45	
Ala Thr Val Leu Arg Gln Ile Tyr Thr His Asn Cys Ser Asn Arg Tyr			
50	55	60	
Leu Arg Gly Leu Tyr Arg Asn Leu Ser Ser Met Ala Asn Lys Thr Cys			
65	70	75	80
Ser Met Asn Glu Ile Lys Lys Ser Thr Leu Lys Asp Phe Leu Glu Arg			
85	90	95	
Leu Lys Val Ile Met Gln Lys Lys Tyr Tyr Arg His			
100	105		

<210> SEQ ID NO 21
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 21

atgcctgtag tatttcttct gcatgatcac ttttagcctt tccaagaagt ctttcagtgt	60
actcttcttg atttcattca tagaacaggt cttgtttgcc atgctgctga ggttcctgta	120
gagtcctctg agatatctgt tggagcagtt gtgtgtatag atctgccgca gtacagtagc	180
agctctgcag aagatttcct tatcgcttgt gttctttgga gcagtgaaga cgtccttgac	240
agtcagctcc atgcacgagt cgtttctcgc tgtgaggatg ttcaacattt tgatgatctc	300
tttaaatagta atattgaagt tatg	324

<210> SEQ ID NO 22
 <211> LENGTH: 804
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(804)

<400> SEQUENCE: 22

acc ccc gac tgc tcc ttc agc cac agc ccc atc tcc tcc acc ttc gcg	48
Thr Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Ala	
1 5 10 15	
gtc acc atc cgc aag ctg tct gat tac ctg ctt cag gac tat cca gtc	96
Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val	
20 25 30	
act gtc gcc tcc aac ctg cag gac gac gag ctc tgc ggg gcg ttc tgg	144
Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Ala Phe Trp	
35 40 45	
cgc ctg gtc ctg gcc cag cgc tgg atg gtg cgg ctc cag gct gtg gct	192
Arg Leu Val Leu Ala Gln Arg Trp Met Val Arg Leu Gln Ala Val Ala	
50 55 60	
gga tcc caa atg caa atc ctg ctg gag gct gtc aac acg gag ata cac	240
Gly Ser Gln Met Gln Ile Leu Leu Glu Ala Val Asn Thr Glu Ile His	
65 70 75 80	
ttt gtc acc ttc tgt gcc ttc cag ccc ctc ccc agc tgt ctt cgc ttc	288
Phe Val Thr Phe Cys Ala Phe Gln Pro Leu Pro Ser Cys Leu Arg Phe	
85 90 95	
gtc cag acc aac atc tcc cac ctc ctg cag gac acc tcc cag cag ctg	336
Val Gln Thr Asn Ile Ser His Leu Leu Gln Asp Thr Ser Gln Gln Leu	
100 105 110	
gcc gcc ctg aag ccc tgg atc acc cgc agg aat ttc tcc ggg tgc ctg	384
Ala Ala Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu	
115 120 125	
gag ctg cag tgt cag ccc gac tcc tct aca ttg gtg ccc cca agg agc	432
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Val Pro Pro Arg Ser	

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195	200	205
Glu Asp Thr Glu Leu Gly Pro Gly Gly Ser Gln Leu Glu Thr Gly Pro 210 215 220		
Phe Leu Asp His Ala Ala Pro Leu Ala Pro Ser Pro Gly Ser Arg Gln 225 230 235 240		
Arg Pro Pro Pro Thr Pro Pro Lys Pro Ala Pro Ala Pro Pro Leu Pro 245 250 255		
Leu Cys Thr Lys Ser Leu Pro Pro Arg Asn Cys Ile 260 265		

<210> SEQ ID NO 24
 <211> LENGTH: 804
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 24

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tatacaattt cttgggggca aggactttgt acagaggggg agaggtgggg ctggggctgg 60
ctttgggggc gttgggggcg ggcgttgccct tgatcctggg gagggagcga gcggggctgc 120
gtggtcgagg aaggaccag tctctagctg actccctcca ggtcccagct ctgtgtcctc 180
gggcagatgg ctccgctcgc tgggcctcag tgcctctgc tcccagggt agggtgacct 240
ccgccccgc ctccttcgcc aatgcaggca ccaggcagtg gacatcagca ggagagccac 300
gggcagcagc agcaggagga gcagccgagg tgcctgaggg gctggcaagg cagtggcctc 360
cagggccccg gggctccttg ggggcaccaa tgtagaggag tcgggctgac actgcagctc 420
caggcaccgc gagaaattcc tgcgggtgat ccagggcttc agggcggcca gctgctggga 480
ggtgtcctgc aggaggtggg agatggtggg ctggacgaag cgaagacagc tggggagggg 540
ctggaaggca cagaaggta caaagtgtat ctccgtgttg acagcctcca gcaggatttg 600
catttgggat ccagccacag cctggagccg caccatccag cgctgggcca ggaccaggcg 660
ccagaacgcc ccgacagagct cgtcgtcctg caggttgag ggcacagtga ctggatagtc 720
ctgaagcagg taatcagaca gcttgccgat ggtgaccgag aaggtggagg agatggggct 780
gtggctgaag gagcagtcgg gggg 804
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<210> SEQ ID NO 25
 <211> LENGTH: 985
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (74)..(901)

<400> SEQUENCE: 25

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ccggcctggc cccttcacg cccagctggg gcaagcctga tctgaccata ggcagtaggg 60
gcctccggcc gag atg ata gtg ctg gcg cca gcc tgg agc cca act gcc 109
Met Ile Val Leu Ala Pro Ala Trp Ser Pro Thr Ala
1 5 10
tcc ctg ttg ctg ctg ctg ctg ctc agc ccc ggc ctc cgc ggg acc ccc 157
Ser Leu Leu Leu Leu Leu Leu Ser Pro Gly Leu Arg Gly Thr Pro
15 20 25
gac tgc tcc ttc agc cac agc ccc atc tcc tcc acc ttc gcg gtc acc 205
Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Ala Val Thr
30 35 40
atc cgc aag ctg tct gat tac ctg ctt cag gac tat cca gtc act gtc 253
Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val
45 50 55 60
```


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gcc tcc aac ctg cag gac gac gag ctc tgc ggg gcg ttc tgg cgc ctg Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Ala Phe Trp Arg Leu	301
65 70 75	
gtc ctg gcc cag cgc tgg atg gtg cgg ctc cag gct gtg gct gga tcc Val Leu Ala Gln Arg Trp Met Val Arg Leu Gln Ala Val Ala Gly Ser	349
80 85 90	
caa atg caa atc ctg ctg gag gct gtc aac acg gag ata cac ttt gtc Gln Met Gln Ile Leu Leu Glu Ala Val Asn Thr Glu Ile His Phe Val	397
95 100 105	
acc ttc tgt gcc ttc cag gac acc tcc cag cag ctg gcc gcc ctg aag Thr Phe Cys Ala Phe Gln Asp Thr Ser Gln Gln Leu Ala Ala Leu Lys	445
110 115 120	
ccc tgg atc acc cgc agg aat ttc tcc ggg tgc ctg gag ctg cag tgt Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu Glu Leu Gln Cys	493
125 130 135 140	
cag ccc gac tcc tct aca ttg gtg ccc cca agg agc ccc ggg gcc ctg Gln Pro Asp Ser Ser Thr Leu Val Pro Pro Arg Ser Pro Gly Ala Leu	541
145 150 155	
gag gcc act gcc ttg cca gcc cct cag gca cct cgg ctg ctc ctc ctg Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala Pro Arg Leu Leu Leu Leu	589
160 165 170	
ctg ctg ctg ccc gtg gct ctc ctg ctg atg tcc act gcc tgg tgc ctg Leu Leu Leu Pro Val Ala Leu Leu Leu Met Ser Thr Ala Trp Cys Leu	637
175 180 185	
cat tgg cga agg agg cgg cgg cgg agg tca ccc tac cct ggg gag cag His Trp Arg Arg Arg Arg Arg Arg Arg Ser Pro Tyr Pro Gly Glu Gln	685
190 195 200	
agg aca ctg agg ccc agc gag cgg agc cat ctg ccc gag gac aca gag Arg Thr Leu Arg Pro Ser Glu Arg Ser His Leu Pro Glu Asp Thr Glu	733
205 210 215 220	
ctg gga cct gga ggg agt cag cta gag act ggt ccc ttc ctc gac cac Leu Gly Pro Gly Gly Ser Gln Leu Glu Thr Gly Pro Phe Leu Asp His	781
225 230 235	
gca gcc ccg ctc gct ccc tcc cca gga tca agg caa cgc ccg ccc cca Ala Ala Pro Leu Ala Pro Ser Pro Gly Ser Arg Gln Arg Pro Pro Pro	829
240 245 250	
acg ccc cca aag cca gcc cca gcc cca cct ctc ccc ctc tgt aca aag Thr Pro Pro Lys Pro Ala Pro Ala Pro Pro Leu Pro Leu Cys Thr Lys	877
255 260 265	
tcc ttg ccc cca aga aat tgt ata taaatcatcc ttttctacca gcaaaaaaaaa Ser Leu Pro Pro Arg Asn Cys Ile	931
270 275	
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa	985

<210> SEQ ID NO 26

<211> LENGTH: 276

<212> TYPE: PRT

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 26

Met Ile Val Leu Ala Pro Ala Trp Ser Pro Thr Ala Ser Leu Leu Leu 1 5 10 15
Leu Leu Leu Leu Ser Pro Gly Leu Arg Gly Thr Pro Asp Cys Ser Phe 20 25 30
Ser His Ser Pro Ile Ser Ser Thr Phe Ala Val Thr Ile Arg Lys Leu 35 40 45
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu 50 55 60
Gln Asp Asp Glu Leu Cys Gly Ala Phe Trp Arg Leu Val Leu Ala Gln

-continued

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

<210> SEQ ID NO 27

<211> LENGTH: 985

<212> TYPE: DNA

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 27

```

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt      60
ttgctggtag aaaaggatga tttatataca atttcttggg ggcaaggact ttgtacagag      120
ggggagaggt ggggctgggg ctggctttgg ggcggttggg ggcgggcgtt gccttgatcc      180
tggggagggg gcgagcgggg ctgctgtgtc gaggaaggga ccagtctcta gctgactccc      240
tccaggcccc agctctgtgt cctcgggcag atggctccgc tcgctgggcc tcagtgtcct      300
ctgctcccca gggtagggtg acctccgccg ccgcctcctt cgccaatgca ggcaccaggc      360
agtggacatc agcaggagag ccacgggcag cagcagcagg aggagcagcc gaggtgcctg      420
aggggctggc aaggcagtgg cctccagggc cccggggctc cttgggggca ccaatgtaga      480
ggagtcgggc tgacactgca gctccaggca cccggagaaa ttcctgcggg tgatccaggg      540
cttcagggcg gccagctgct gggaggtgtc ctggaaggca cagaaggtga caaagtgtat      600
ctccgtgttg acagcctcca gcaggatttg catttgggat ccagccacag cctggagccg      660
caccatccag cgctgggcca ggaccaggcg ccagaacgcc ccgcagagct cgctgtcctg      720
caggttgag gcgacagtga ctggatagtc ctgaagcagg taatcagaca gcttgccgat      780
ggtgaccgcg aaggtggagg agatggggct gtggctgaag gagcagtcgg gggccccgcg      840
gaggccgggg ctgagcagca gcagcagcaa cagggaggca gttgggctcc aggctggcgc      900

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-continued

cagcactatc atctcggccg gagggccctc atgcctatgg tcagatcagg cttgccccag 960
 ctgggcgtgg aaggggccaag gccgg 985

<210> SEQ ID NO 28
 <211> LENGTH: 828
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 28

atgatagtgc tggcgccagc ctggagccca actgcctccc tgttgctgct gctgctgctc 60
 agccccggcc tccgcgggac ccccgactgc tccttcagcc acagccccat ctccctccacc 120
 ttcgcgggtca ccatccgcaa gctgtctgat tacctgcttc aggactatcc agtcaactgtc 180
 gcctccaacc tgcaggacga cgagctctgc gggcgcttct ggcgcctggt cctggccccag 240
 cgctggatgg tgcggctcca ggctgtggct ggatcccaaa tgcaaatcct gctggaggct 300
 gtcaaacacgg agatacactt tgtcaccttc tgtgccttcc aggacacctc ccagcagctg 360
 gccgcctga agccctggat caccgcgagg aatttctccg ggtgcctgga gctgcagtgt 420
 cagccccgact cctctacatt ggtgccccca aggagccccg gggccctgga ggccactgcc 480
 ttgccagccc ctccagccacc tcggctgctc ctccctgctc tgctgcccgt ggctctcctg 540
 ctgatgtcca ctgcctggtg cctgcattgg cgaaggaggc ggcggcgag gtcaccctac 600
 cctggggagc agaggacact gagggccagc gagcggagcc atctgcccga ggacacagag 660
 ctgggacctg gagggagtca gctagagact ggtcccttcc tcgaccacgc agccccgctc 720
 gctccctccc caggatcaag gcaacgcccc ccccaaacgc ccccaagcc agccccagcc 780
 ccacctctcc ccctctgtac aaagtccttg ccccaagaa attgtata 828

<210> SEQ ID NO 29
 <211> LENGTH: 828
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 29

tatacaattt cttgggggca aggactttgt acagaggggg agaggtgggg ctggggctgg 60
 ctttgggggc gttgggggag ggcggtgcct tgatcctggg gagggagcga gcggggctgc 120
 gtggtcgagg aaggaccag tctctagctg actccctcca ggtcccagct ctgtgtcctc 180
 gggcagatgg ctccgctcgc tgggcctcag tgcctctgct tccccaggtt aggggtgacct 240
 ccgccgccgc ctccctcggc aatgcaggca ccaggcagtg gacatcagca ggagagccac 300
 gggcagcagc agcaggagga gcagccgagg tgcctgaggg gctggcaagg cagtggcctc 360
 cagggccccg gggctccttg ggggcaccaa tgtagaggag tcgggctgac actgcagctc 420
 caggcaccgc gagaaattcc tgcgggtgat ccagggcttc agggcgcca gctgctggga 480
 ggtgtcctgg aaggcacaga aggtgacaaa gtgtatctcc gtgttgacag cctccagcag 540
 gatttgattt tgggatccag ccacagcctg gagccgcacc atccagcgt gggccaggac 600
 caggcgccag aacgccccgc agagctcgtc gtccctgcagg ttggaggcga cagtgactgg 660
 atagtcctga agcaggaat cagacagctt gcggatggtg accgcgaagg tggaggagat 720
 ggggctgtgg ctgaaggagc agtcgggggt cccgcggagg ccggggctga gcagcagcag 780
 cagcaacagg gaggcagttg ggctccaggc tggcggcagc actatcat 828

<210> SEQ ID NO 30
 <211> LENGTH: 750

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<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(750)

<400> SEQUENCE: 30

acc ccc gac tgc tcc ttc agc cac agc ccc atc tcc tcc acc ttc gcg      48
Thr Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Ala
  1                               5                               10                               15

gtc acc atc cgc aag ctg tct gat tac ctg ctt cag gac tat cca gtc      96
Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
                               20                               25                               30

act gtc gcc tcc aac ctg cag gac gac gag ctc tgc ggg gcg ttc tgg     144
Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Ala Phe Trp
                               35                               40                               45

cgc ctg gtc ctg gcc cag cgc tgg atg gtg cgg ctc cag gct gtg gct     192
Arg Leu Val Leu Ala Gln Arg Trp Met Val Arg Leu Gln Ala Val Ala
  50                               55                               60

gga tcc caa atg caa atc ctg ctg gag gct gtc aac acg gag ata cac     240
Gly Ser Gln Met Gln Ile Leu Leu Glu Ala Val Asn Thr Glu Ile His
  65                               70                               75                               80

ttt gtc acc ttc tgt gcc ttc cag gac acc tcc cag cag ctg gcc gcc     288
Phe Val Thr Phe Cys Ala Phe Gln Asp Thr Ser Gln Gln Leu Ala Ala
                               85                               90                               95

ctg aag ccc tgg atc acc cgc agg aat ttc tcc ggg tgc ctg gag ctg     336
Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu Glu Leu
                               100                              105                              110

cag tgt cag ccc gac tcc tct aca ttg gtg ccc cca agg agc ccc ggg     384
Gln Cys Gln Pro Asp Ser Ser Thr Leu Val Pro Pro Arg Ser Pro Gly
                               115                              120                              125

gcc ctg gag gcc act gcc ttg cca gcc cct cag gca cct cgg ctg ctc     432
Ala Leu Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala Pro Arg Leu Leu
                               130                              135                              140

ctc ctg ctg ctg ctg ccc gtg gct ctc ctg ctg atg tcc act gcc tgg     480
Leu Leu Leu Leu Leu Pro Val Ala Leu Leu Leu Met Ser Thr Ala Trp
                               145                              150                              155                              160

tgc ctg cat tgg cga agg agg cgg cgg cgg agg tca ccc tac cct ggg     528
Cys Leu His Trp Arg Arg Arg Arg Arg Arg Ser Pro Tyr Pro Gly
                               165                              170                              175

gag cag agg aca ctg agg ccc agc gag cgg agc cat ctg ccc gag gac     576
Glu Gln Arg Thr Leu Arg Pro Ser Glu Arg Ser His Leu Pro Glu Asp
                               180                              185                              190

aca gag ctg gga cct gga ggg agt cag cta gag act ggt ccc ttc ctc     624
Thr Glu Leu Gly Pro Gly Gly Ser Gln Leu Glu Thr Gly Pro Phe Leu
                               195                              200                              205

gac cac gca gcc ccg ctc gct ccc tcc cca gga tca agg caa cgc ccg     672
Asp His Ala Ala Pro Leu Ala Pro Ser Pro Gly Ser Arg Gln Arg Pro
                               210                              215                              220

ccc cca acg ccc cca aag cca gcc cca gcc cca cct ctc ccc ctc tgt     720
Pro Pro Thr Pro Pro Lys Pro Ala Pro Ala Pro Pro Leu Pro Leu Cys
                               225                              230                              235                              240

aca aag tcc ttg ccc cca aga aat tgt ata                               750
Thr Lys Ser Leu Pro Pro Arg Asn Cys Ile
                               245                              250

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<210> SEQ ID NO 31
<211> LENGTH: 250
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 31

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-continued

Thr Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Ala
 1 5 10 15
 Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
 20 25 30
 Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Ala Phe Trp
 35 40 45
 Arg Leu Val Leu Ala Gln Arg Trp Met Val Arg Leu Gln Ala Val Ala
 50 55 60
 Gly Ser Gln Met Gln Ile Leu Leu Glu Ala Val Asn Thr Glu Ile His
 65 70 75 80
 Phe Val Thr Phe Cys Ala Phe Gln Asp Thr Ser Gln Gln Leu Ala Ala
 85 90 95
 Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu Glu Leu
 100 105 110
 Gln Cys Gln Pro Asp Ser Ser Thr Leu Val Pro Pro Arg Ser Pro Gly
 115 120 125
 Ala Leu Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala Pro Arg Leu Leu
 130 135 140
 Leu Leu Leu Leu Leu Pro Val Ala Leu Leu Leu Met Ser Thr Ala Trp
 145 150 155 160
 Cys Leu His Trp Arg Arg Arg Arg Arg Arg Ser Pro Tyr Pro Gly
 165 170 175
 Glu Gln Arg Thr Leu Arg Pro Ser Glu Arg Ser His Leu Pro Glu Asp
 180 185 190
 Thr Glu Leu Gly Pro Gly Gly Ser Gln Leu Glu Thr Gly Pro Phe Leu
 195 200 205
 Asp His Ala Ala Pro Leu Ala Pro Ser Pro Gly Ser Arg Gln Arg Pro
 210 215 220
 Pro Pro Thr Pro Pro Lys Pro Ala Pro Ala Pro Pro Leu Pro Leu Cys
 225 230 235 240
 Thr Lys Ser Leu Pro Pro Arg Asn Cys Ile
 245 250

<210> SEQ ID NO 32

<211> LENGTH: 750

<212> TYPE: DNA

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 32

tatacaattt cttgggggca aggactttgt acagaggggg agaggtgggg ctggggctgg 60
 ctttgggggc gttgggggcg ggcgttgcct tgatcctggg gagggagcga gcggggctgc 120
 gtggtcgagg aagggaccag tctctagctg actccctcca ggtcccagct ctgtgtcctc 180
 gggcagatgg ctccgctcgc tgggcctcag tgtcctctgc tccccagggt agggtgacct 240
 ccgccgccgc ctcttcgcc aatgcaggca ccaggcagtg gacatcagca ggagagccac 300
 gggcagcagc agcaggagga gcagccgagg tgcctgaggg gctggcaagg cagtggcctc 360
 cagggccccg gggctccttg ggggcaccaa thtagaggag tcgggctgac actgcagctc 420
 caggcaccgc gagaaattcc tgcgggtgat ccagggcttc agggcgcca gctgctggga 480
 ggtgtcctgg aaggcacaga aggtgacaaa gtgtatctcc gtgttgacag cctccagcag 540
 gatttgatt tgggatccag ccacagcctg gagccgcacc atccagcgt gggccaggac 600
 caggcgcag aacgccccgc agagctcgtc gtcctgcagg ttggaggcga cagtgactgg 660

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atagtcttga agcaggtaat cagacagctt gcggatggtg accgcgaagg tggaggagat 720
ggggctgtgg ctgaaggagc agtcgggggt 750

```

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<210> SEQ ID NO 33
<211> LENGTH: 1019
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (74)..(166)

```

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<400> SEQUENCE: 33

```

```

ccggcctggc cccttccacg cccagctggg gcaagcctga tctgaccata ggcattgaggg 60
gcctccggcc gag atg ata gtg ctg gcg cca gcc tgg agc cca act gtg 109
      Met Ile Val Leu Ala Pro Ala Trp Ser Pro Thr Val
      1             5             10
cgt ata ccc ggg gga caa ggc ggg gga cag gca gag cgc tac cga gct 157
Arg Ile Pro Gly Gly Gln Gly Gly Gln Ala Glu Arg Tyr Arg Ala
      15             20             25
ggg cag agc tgagagagca gacggacaga ggcctccctg ttgctgctgc 206
Gly Gln Ser
      30
tgctgctcag ccccgccctc cgcgggaccc ccgactgctc cttcagccac agccccatct 266
cctccacctt cgcggtcacc atccgcaagc tgtctgatta cctgcttcag gactatccag 326
tcaactgtgc ctccaacctg caggacgacg agctctgctg ggcgttcttg cgctgggtcc 386
tggcccagcg ctggatggtg cggctccagg ctgtggctgg atcccaaagt caaatcctgc 446
tggaggctgt caacacggag atacactttg tcaccttctg tgccttccag gacacctccc 506
agcagctggc cgcctgaag ccctggatca cccgcaggaa tttctccggg tgcttgagc 566
tgcagtgtca gcccgaactc tctacattgg tgcccccaag gagccccggg gccctggagg 626
ccactgcctt gccagcccct caggcacctc ggctgctcct cctgctgctg ctgcccgtgg 686
ctctcctgct gatgtccact gcctggtgcc tgcaattggc aaggaggcgg cggcggagggt 746
caccctaccc tggggagcag aggacactga ggcccagcga gcggagccat ctgcccgagg 806
acacagagct gggacctgga gggagtcagc tagagactgg tcccttctc gaccacgcag 866
ccccgctcgc tccctcccca ggatcaaggc aacgcccgcc cccaacgccc ccaaagccag 926
ccccagcccc acctctcccc ctctgtacaa agtccttgcc cccaagaaat tgtatataaa 986
tcatcctttt ctaccaaaaa aaaaaaaaaa aaa 1019

```

```

<210> SEQ ID NO 34
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

```

```

<400> SEQUENCE: 34

```

```

Met Ile Val Leu Ala Pro Ala Trp Ser Pro Thr Val Arg Ile Pro Gly
  1             5             10             15
Gly Gln Gly Gly Gly Gln Ala Glu Arg Tyr Arg Ala Gly Gln Ser
      20             25             30

```

```

<210> SEQ ID NO 35
<211> LENGTH: 1019
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

```

```

<400> SEQUENCE: 35

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```

tttttttttt ttttttttgg tagaaaagga tgatttatat acaatttctt gggggcaagg    60
actttgtaca gagggggaga ggtggggctg gggctggctt tgggggcgtt gggggcgggc    120
gttgccttga tcctggggag ggagcgagcg gggctgcgtg gtcgaggaag ggaccagtct    180
ctagctgact ccctccaggt cccagctctg tgcctcggg cagatggctc cgctcgtgg    240
gcctcagtgt cctctgctcc ccagggtagg gtgacctccg ccgccgcctc cttegccaat    300
gcaggcacca ggcagtggac atcagcagga gagccacggg cagcagcagc aggaggagca    360
gccgaggtgc ctgaggggct ggcaaggcag tggcctccag ggccccgggg ctccctgggg    420
gcaccaatgt agaggagtcg ggctgacact gcagctccag gcaccggag aaattcctgc    480
gggtgatcca gggcttcagg gcggccagct gctgggaggt gtcctggaag gcacagaagg    540
tgacaaagtg tatctccgtg ttgacagcct ccagcaggat ttgcatttgg gatccagcca    600
cagcctggag ccgcaccatc cagcgtggg ccaggaccag gcgccagaac gccccgcaga    660
gctcgtcgtc ctgcaggttg gaggcgacag tgactggata gtcctgaagc aggtaatcag    720
acagcttgcg gatggtgacc gcgaagggtg aggagatggg gctgtggctg aaggagcagt    780
cgggggtccc gcggaggccg gggctgagca gcagcagcag caacaggag gcctctgtcc    840
gtctgtcttc tcagctctgc ccagctcggg agcgtctctg ctgtcccccg ccttgtcccc    900
cgggtatacg cacagttggg ctccaggctg gcgccagcac tatcatctcg gccggaggcc    960
cctcatgcct atggtcagat caggcttgcc ccagctgggc gtggaagggg ccaggccgg    1019

```

```

<210> SEQ ID NO 36
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

```

```

<400> SEQUENCE: 36

```

```

atgatagtgc tggcgccagc ctggagccca actgtgcgta taccggggg acaaggcggg    60
ggacaggcag agcgtaccg agctgggcag agc                                93

```

```

<210> SEQ ID NO 37
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

```

```

<400> SEQUENCE: 37

```

```

gctctgccc gctcggtagc gctctgctg tccccgcct tgtcccccg gtatacgcac    60
agttgggctc caggctggcg ccagcactat cat                                93

```

```

<210> SEQ ID NO 38
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

```

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<400> SEQUENCE: 38

```

```

tgaattcgga cataacttca atattac                                27

```

```

<210> SEQ ID NO 39
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

```


-continued

<400> SEQUENCE: 39

tctcgagatt cagcttcaat gcctgta 27

<210> SEQ ID NO 40

<211> LENGTH: 28

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 40

cccaagctta tgggtctcac ctcccaac 28

<210> SEQ ID NO 41

<211> LENGTH: 395

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 41

ggccatagggc atgaagggcc tccggccgag atgatagtgc tggcgccagc ctggagccca 60

actacctccc tgctgctgct gctactgctc agccctggcc tccgcgggtc ccccgactgt 120

tccttcagcc acagcccat ctcctccacc ttcaaggctca ccatccgaaa gctgtctgat 180

tacctgcttc aggattacc agtcaccgtc gcctccaacc tacaggacga cgagctctgt 240

gggccattct ggcacctggt cctggcccag cgctggatgg gtcggctcaa ggctgtggct 300

gggtcccaga tgcaaagcct gctggaggcg gtcaacaccg agatacattt tgtcaccttg 360

tgtgccttcc agcccctccc cagctgtctt cgatt 395

<210> SEQ ID NO 42

<211> LENGTH: 793

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 42

cttcaaggtc accatccgaa agctgtctga ttacctgctt caggattacc cagtcaccgt 60

cgcctccaac ctacaggacg acgagctctg tgggccattc tggcacctgg tccctggccca 120

gcgctggatg ggtcggctca aggctgtggc tgggtcccag atgcaaagcc tgctggaggc 180

ggcaacacc gagatacatt ttgtcacctt gtgtgccttc cagcccctcc ccagctgtct 240

tcgattcgtc cagaccaaca tctcccacct cctgcaggac acctccgagc agctggcggc 300

cttgaagccc tggatcacc gcaggaattt ctcgggggtgc ctggagctac agtgtcagcc 360

cgactcctcc acccactgc cccaaggag cccagggcc ttggaggcca cagccctgcc 420

agcccctcag gcccctctgc tgctcctcct gctgctgttg cctgtggctc tcttgctgat 480

gtccgcccgc tgggtgcctgc actggcgaag aaggagatgg agaacgccct accccagggc 540

gcagaggaag aactgaggc ccagagagag gaatcacctg cccgaggaca cagagccggg 600

actcggagaa agtcagctag agactgggtc cttcctogac cacgctgccc cgctcactct 660

ccccccggga tggaggcaac gccagcccc aacgccagcc ccagaccac ctatccccct 720

ctgtacaaag tccttgtcct caggaaattg tatataaatc atccttttct accaaaaaaa 780

aaaaaaaaaaa aaa 793

<210> SEQ ID NO 43

<211> LENGTH: 942

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<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (31)..(903)

<400> SEQUENCE: 43

ggccatagggc atgaagggcc tccggccgag atg ata gtg ctg gcg cca gcc tgg      54
                               Met Ile Val Leu Ala Pro Ala Trp
                               1           5

agc cca act acc tcc ctg ctg ctg ctg cta ctg ctc agc cct ggc ctc      102
Ser Pro Thr Thr Ser Leu Leu Leu Leu Leu Leu Leu Ser Pro Gly Leu
   10           15           20

cgc ggg tcc ccc gac tgt tcc ttc agc cac agc ccc atc tcc tcc acc      150
Arg Gly Ser Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr
   25           30           35           40

ttc aag gtc acc atc cga aag ctg tct gat tac ctg ctt cag gat tac      198
Phe Lys Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
           45           50           55

cca gtc acc gtc gcc tcc aac cta cag gac gac gag ctc tgt ggg cca      246
Pro Val Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Pro
           60           65           70

ttc tgg cac ctg gtc ctg gcc cag cgc tgg atg ggt cgg ctc aag gct      294
Phe Trp His Leu Val Leu Ala Gln Arg Trp Met Gly Arg Leu Lys Ala
           75           80           85

gtg gct ggg tcc cag atg caa agc ctg ctg gag gcg gtc aac acc gag      342
Val Ala Gly Ser Gln Met Gln Ser Leu Leu Glu Ala Val Asn Thr Glu
           90           95           100

ata cat ttt gtc acc ttg tgt gcc ttc cag ccc ctc ccc agc tgt ctt      390
Ile His Phe Val Thr Leu Cys Ala Phe Gln Pro Leu Pro Ser Cys Leu
 105           110           115           120

cga ttc gtc cag acc aac atc tcc cac ctc ctg cag gac acc tcc gag      438
Arg Phe Val Gln Thr Asn Ile Ser His Leu Leu Gln Asp Thr Ser Glu
           125           130           135

cag ctg gcg gcc ttg aag ccc tgg atc acc cgc agg aat ttc tcg ggg      486
Gln Leu Ala Ala Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly
           140           145           150

tgc ctg gag cta cag tgt cag ccc gac tcc tcc acc cca ctg ccc cca      534
Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Pro Leu Pro Pro
           155           160           165

agg agc ccc agg gcc ttg gag gcc aca gcc ctg cca gcc cct cag gcc      582
Arg Ser Pro Arg Ala Leu Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala
           170           175           180

cct ctg ctg ctc ctc ctg ctg ctg ttg cct gtg gct ctc ttg ctg atg      630
Pro Leu Leu Leu Leu Leu Leu Leu Leu Pro Val Ala Leu Leu Leu Met
 185           190           195           200

tcc gcc gcc tgg tgc ctg cac tgg cga aga agg aga tgg aga acg ccc      678
Ser Ala Ala Trp Cys Leu His Trp Arg Arg Arg Arg Trp Arg Thr Pro
           205           210           215

tac ccc agg gag cag agg aag aca ctg agg ccc aga gag agg aat cac      726
Tyr Pro Arg Glu Gln Arg Lys Thr Leu Arg Pro Arg Glu Arg Asn His
           220           225           230

ctg ccc gag gac aca gag ccg gga ctc gga gaa agt cag cta gag act      774
Leu Pro Glu Asp Thr Glu Pro Gly Leu Gly Glu Ser Gln Leu Glu Thr
           235           240           245

ggg tcc ttc ctc gac cac gct gcc ccg ctc act ctc ccc ccg gga tgg      822
Gly Ser Phe Leu Asp His Ala Ala Pro Leu Thr Leu Pro Pro Gly Trp
           250           255           260

agg caa cgc cag ccc cca acg cca gcc cca gac cca cct atc ccc ctc      870
Arg Gln Arg Gln Pro Pro Thr Pro Ala Pro Asp Pro Pro Ile Pro Leu
 265           270           275           280

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tgt aca aag tcc ttg tcc tca gga aat tgt ata taaatcatcc ttttctacca 923
 Cys Thr Lys Ser Leu Ser Ser Gly Asn Cys Ile
 285 290

aaaaaaaaaa aaaaaaaaaa 942

<210> SEQ ID NO 44
 <211> LENGTH: 291
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 44

Met Ile Val Leu Ala Pro Ala Trp Ser Pro Thr Thr Ser Leu Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Ser Pro Gly Leu Arg Gly Ser Pro Asp Cys Ser Phe
 20 25 30
 Ser His Ser Pro Ile Ser Ser Thr Phe Lys Val Thr Ile Arg Lys Leu
 35 40 45
 Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
 50 55 60
 Gln Asp Asp Glu Leu Cys Gly Pro Phe Trp His Leu Val Leu Ala Gln
 65 70 75 80
 Arg Trp Met Gly Arg Leu Lys Ala Val Ala Gly Ser Gln Met Gln Ser
 85 90 95
 Leu Leu Glu Ala Val Asn Thr Glu Ile His Phe Val Thr Leu Cys Ala
 100 105 110
 Phe Gln Pro Leu Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 115 120 125
 His Leu Leu Gln Asp Thr Ser Glu Gln Leu Ala Ala Leu Lys Pro Trp
 130 135 140
 Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu Glu Leu Gln Cys Gln Pro
 145 150 155 160
 Asp Ser Ser Thr Pro Leu Pro Pro Arg Ser Pro Arg Ala Leu Glu Ala
 165 170 175
 Thr Ala Leu Pro Ala Pro Gln Ala Pro Leu Leu Leu Leu Leu Leu Leu
 180 185 190
 Leu Pro Val Ala Leu Leu Leu Met Ser Ala Ala Trp Cys Leu His Trp
 195 200 205
 Arg Arg Arg Arg Trp Arg Thr Pro Tyr Pro Arg Glu Gln Arg Lys Thr
 210 215 220
 Leu Arg Pro Arg Glu Arg Asn His Leu Pro Glu Asp Thr Glu Pro Gly
 225 230 235 240
 Leu Gly Glu Ser Gln Leu Glu Thr Gly Ser Phe Leu Asp His Ala Ala
 245 250 255
 Pro Leu Thr Leu Pro Pro Gly Trp Arg Gln Arg Gln Pro Pro Thr Pro
 260 265 270
 Ala Pro Asp Pro Pro Ile Pro Leu Cys Thr Lys Ser Leu Ser Ser Gly
 275 280 285
 Asn Cys Ile
 290

<210> SEQ ID NO 45
 <211> LENGTH: 942
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 45

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ttttttttt ttttttttt ggtagaaaag gatgatttat atacaatttc ctgaggacaa    60
ggactttgta cagaggggga taggtgggtc tggggctggc gttgggggct ggcgttgctt    120
ccatcccggg gggagagtga gcggggcagc gtggtcgagg aaggaaccag tctctagctg    180
actttctccg agtcccggct ctgtgtcctc gggcagggtga ttctctctc tgggcctcag    240
tgtcttctc tgctccctgg ggtagggcgt tctccatctc cttcttcgcc agtgcaggca    300
ccaggcggcg gacatcagca agagagccac aggaacagc agcaggagga gcagcagagg    360
ggcctgaggg gctggcaggg ctgtggcctc caaggccctg gggctccttg ggggcagtgg    420
ggtggaggag tcgggctgac actgtagctc caggcaccac gagaaattcc tgcgggtgat    480
ccaggccttc aaggccgcca gctgctcggg ggtgtcctgc aggaggtggg agatggtggg    540
ctggacgaat cgaagacagc tggggagggg ctggaaggca cacaagggtga caaatgtat    600
ctcgggtgtg accgcctcca gcaggctttg catctgggac ccagccacag ccttgagccg    660
acccatccag cgctgggcca ggaccagggt ccagaatggc ccacagagct cgtcgtcctg    720
taggttgag ggcacgggtga ctgggtaatc ctgaagcagg taatcagaca gctttcggat    780
ggtgaccttg aagggtggag agatggggct gtggctgaag gaacagtcgg gggaccgcg    840
gaggccaggg ctgagcagta gcagcagcag cagggaggta gttgggctcc aggctggcgc    900
cagcactatc atctcggccg gaggccttc atgcctatgg cc                                942

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<210> SEQ ID NO 46

<211> LENGTH: 873

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 46

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atgatagtgc tggcgccagc ctggagccca actacctccc tgctgctgct gctactgctc    60
agccctggcc tccgcgggtc ccccgactgt tccttcagcc acagcccat ctcctccacc    120
ttcaaggta ccatccgaaa gctgtctgat tacctgcttc aggattacc agtcaccgctc    180
gcctccaacc tacaggacga cgagctctgt gggccattct ggcacctggt cctggccag    240
cgctggatgg gtcggctcaa ggctgtggct gggcccaga tgcaaagcct gctggaggcg    300
gtcaacaccg agatacattt tgtcaccttg tgtgccttcc agcccctccc cagctgtctt    360
cgattcgtcc agaccaacat ctcccacctc ctgcaggaca cctccgagca gctggcggcc    420
ttgaagccct ggatcaccgg caggaatttc tcgggggtgc tggagctaca gtgtcagccc    480
gactcctcca cccactgcc cccaaggagc cccaggcctc tggaggccac agccctgcca    540
gcccctcagg cccctctgct gctcctcctg ctgctgttgc ctgtggctct cttgctgatg    600
tccgccgctt ggtgcctgca ctggcgaaga aggagatgga gaacgcccta cccagggag    660
cagaggaaga cactgaggcc cagagagagg aatcacctgc ccgaggacac agagccggga    720
ctcggagaaa gtcagctaga gactggttcc ttctcagacc acgctgccc gctcactctc    780
ccccgggat ggaggcaacg ccagcccca acgccagccc cagaccacc tatccccctc    840
tgtacaaagt ccttgcctc aggaaattgt ata                                873

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<210> SEQ ID NO 47

<211> LENGTH: 873

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 47

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tatacaatth cctgaggaca aggactttgt acagaggggg ataggtgggt ctggggctgg      60
cgttgggggc tggcgttgcc tccatcccgg ggggagagtg agcggggcag cgtggtcgag      120
gaaggaacca gtctctagct gactttctcc gagtcccggc tctgtgtcct cgggcaggtg      180
attcctctct ctgggcctca gtgtcttctt ctgctccctg gggtagggcg ttctccatct      240
ccttcttcgc cagtgcaggc accaggcggc ggacatcagc aagagagcca caggcaacag      300
cagcaggagg agcagcagag gggcctgagg ggcctggcagg gctgtggcct ccaaggccct      360
ggggctcctt gggggcagtg ggggtggagga gtcgggctga cactgtagct ccaggcaccg      420
cgagaaattc ctgagggtga tccagggtt caaggccgcc agctgctcgg aggtgtcctg      480
caggaggtgg gagatggttg tctggacgaa tcgaagacag ctggggaggg gctggaaggg      540
acacaaggtg acaaaatgta tctcgggtgt gaccgcctcc agcaggcttt gcatctggga      600
cccagccaca gccttgagcc gaccatcca gcgctggggc aggaccaggt gccagaatgg      660
cccacagagc tcgtcgtcct gtaggttggg ggcgacgggt actgggtaat cctgaagcag      720
gtaatcagac agctttcggg tgggtgacct gaaggtggag gagatggggc tgtggctgaa      780
ggaacagtcg ggggaccgc ggaggccagg gctgagcagt agcagcagca gcaggaggt      840
agttgggctc caggctggcg ccagcactat cat                                     873

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<210> SEQ ID NO 48
<211> LENGTH: 795
<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(795)

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<400> SEQUENCE: 48

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tcc ccc gac tgt tcc ttc agc cac agc ccc atc tcc tcc acc ttc aag      48
Ser Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Lys
  1             5             10            15

gtc acc atc cga aag ctg tct gat tac ctg ctt cag gat tac cca gtc      96
Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
             20             25             30

acc gtc gcc tcc aac cta cag gac gac gag ctc tgt ggg cca ttc tgg      144
Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Pro Phe Trp
             35             40             45

cac ctg gtc ctg gcc cag cgc tgg atg ggt cgg ctc aag gct gtg gct      192
His Leu Val Leu Ala Gln Arg Trp Met Gly Arg Leu Lys Ala Val Ala
             50             55             60

ggg tcc cag atg caa agc ctg ctg gag gcg gtc aac acc gag ata cat      240
Gly Ser Gln Met Gln Ser Leu Leu Glu Ala Val Asn Thr Glu Ile His
             65             70             75            80

ttt gtc acc ttg tgt gcc ttc cag ccc ctc ccc agc tgt ctt cga ttc      288
Phe Val Thr Leu Cys Ala Phe Gln Pro Leu Pro Ser Cys Leu Arg Phe
             85             90             95

gtc cag acc aac atc tcc cac ctc ctg cag gac acc tcc gag cag ctg      336
Val Gln Thr Asn Ile Ser His Leu Leu Gln Asp Thr Ser Glu Gln Leu
             100            105            110

gcg gcc ttg aag ccc tgg atc acc cgc agg aat ttc tcg ggg tgc ctg      384
Ala Ala Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu
             115            120            125

gag cta cag tgt cag ccc gac tcc tcc acc cca ctg ccc cca agg agc      432
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Pro Leu Pro Pro Arg Ser
             130            135            140

ccc agg gcc ttg gag gcc aca gcc ctg cca gcc cct cag gcc cct ctg      480
Pro Arg Ala Leu Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala Pro Leu

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145	150	155	160	
ctg ctg ctg ctg ctg ctg ttg cct gtg gct ctc ttg ctg atg tcc gcc				528
Leu Leu Leu Leu Leu Leu Leu Pro Val Ala Leu Leu Leu Met Ser Ala				
	165	170	175	
gcc tgg tgc ctg cac tgg cga aga agg aga tgg aga acg ccc tac ccc				576
Ala Trp Cys Leu His Trp Arg Arg Arg Arg Trp Arg Thr Pro Tyr Pro				
	180	185	190	
agg gag cag agg aag aca ctg agg ccc aga gag agg aat cac ctg ccc				624
Arg Glu Gln Arg Lys Thr Leu Arg Pro Arg Glu Arg Asn His Leu Pro				
	195	200	205	
gag gac aca gag ccg gga ctc gga gaa agt cag cta gag act ggt tcc				672
Glu Asp Thr Glu Pro Gly Leu Gly Glu Ser Gln Leu Glu Thr Gly Ser				
	210	215	220	
ttc ctc gac cac gct gcc ccg ctc act ctc ccc ccg gga tgg agg caa				720
Phe Leu Asp His Ala Ala Pro Leu Thr Leu Pro Pro Gly Trp Arg Gln				
	225	230	235	240
cgc cag ccc cca acg cca gcc cca gac cca cct atc ccc ctc tgt aca				768
Arg Gln Pro Pro Thr Pro Ala Pro Asp Pro Pro Ile Pro Leu Cys Thr				
	245	250	255	
aag tcc ttg tcc tca gga aat tgt ata				795
Lys Ser Leu Ser Ser Gly Asn Cys Ile				
	260	265		

<210> SEQ ID NO 49
 <211> LENGTH: 265
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 49

Ser Pro Asp Cys Ser Phe Ser His Ser Pro Ile Ser Ser Thr Phe Lys				
1	5	10	15	
Val Thr Ile Arg Lys Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val				
	20	25	30	
Thr Val Ala Ser Asn Leu Gln Asp Asp Glu Leu Cys Gly Pro Phe Trp				
	35	40	45	
His Leu Val Leu Ala Gln Arg Trp Met Gly Arg Leu Lys Ala Val Ala				
	50	55	60	
Gly Ser Gln Met Gln Ser Leu Leu Glu Ala Val Asn Thr Glu Ile His				
	65	70	75	80
Phe Val Thr Leu Cys Ala Phe Gln Pro Leu Pro Ser Cys Leu Arg Phe				
	85	90	95	
Val Gln Thr Asn Ile Ser His Leu Leu Gln Asp Thr Ser Glu Gln Leu				
	100	105	110	
Ala Ala Leu Lys Pro Trp Ile Thr Arg Arg Asn Phe Ser Gly Cys Leu				
	115	120	125	
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Pro Leu Pro Pro Arg Ser				
	130	135	140	
Pro Arg Ala Leu Glu Ala Thr Ala Leu Pro Ala Pro Gln Ala Pro Leu				
	145	150	155	160
Leu Leu Leu Leu Leu Leu Leu Pro Val Ala Leu Leu Leu Met Ser Ala				
	165	170	175	
Ala Trp Cys Leu His Trp Arg Arg Arg Arg Trp Arg Thr Pro Tyr Pro				
	180	185	190	
Arg Glu Gln Arg Lys Thr Leu Arg Pro Arg Glu Arg Asn His Leu Pro				
	195	200	205	
Glu Asp Thr Glu Pro Gly Leu Gly Glu Ser Gln Leu Glu Thr Gly Ser				
	210	215	220	

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Phe Leu Asp His Ala Ala Pro Leu Thr Leu Pro Pro Gly Trp Arg Gln
 225 230 235 240

Arg Gln Pro Pro Thr Pro Ala Pro Asp Pro Pro Ile Pro Leu Cys Thr
 245 250 255

Lys Ser Leu Ser Ser Gly Asn Cys Ile
 260 265

<210> SEQ ID NO 50
 <211> LENGTH: 795
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 50

tatacaatth cctgaggaca aggactttgt acagaggggg ataggtgggt ctggggctgg 60
 cgttgggggc tggcgttgcc tccatcccgg ggggagagtg agcggggcag cgtggctcag 120
 gaaggaacca gtctctagct gactttctcc gagtcccggc tctgtgtcct cgggcaggtg 180
 attcctctct ctgggcctca gtgtcttctt ctgctccctg gggtagggcg ttctccatct 240
 ctttcttcgc cagtgcaggc accaggcggc ggacatcagc aagagagcca caggcaacag 300
 cagcaggagg agcagcagag gggcctgagg ggctggcagg gctgtggcct ccaaggccct 360
 ggggctcctt gggggcagtg ggggtggagga gtcgggctga cactgtagct ccaggcacc 420
 cgagaaattc ctgcggtgga tccagggtt caaggccgcc agctgctcgg aggtgtcctg 480
 caggaggtgg gagatgttg tctggacgaa tcgaagacag ctggggaggg gctggaaggc 540
 acacaagggtg acaaaatgta tctcggtgtt gaccgcctcc agcaggcttt gcatctggga 600
 cccagccaca gccttgagcc gaccatcca gcgctgggcc aggaccaggt gccagaatgg 660
 cccacagagc tcgtcgtcct gtaggttga ggcgacggtg actgggtaat cctgaagcag 720
 gtaatcagac agctttcggg tgggtgacct gaaggtggag gagatggggc tgtggctgaa 780
 ggaacagtcg gggga 795

<210> SEQ ID NO 51
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 51

aatgtgtctt ctgctttgga aaagtgtcac ccttgacaa gctgtgaaac caaaggcctg 60
 gtgaaggttc aggcgggaac taacaagact gatgttatct gtggccccca gcctcgggta 120
 agagccctag tgggtgtccc catcattatg gggatcctgc ttgttgcct gttgggtgtct 180
 gcctgcatcc gaaaggtggt caagaagcca gagaataagg ttatgtatca ggaccctgtg 240
 gaggacttgg aggaatttcc tatgcccccg cactccattg ctccgggtgca agagacctta 300
 catgggtgcc agcccgtcac c 321

<210> SEQ ID NO 52
 <211> LENGTH: 1425
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (196)..(1017)

<400> SEQUENCE: 52

tagactccc ggaatattca ggggaactcc cggcgctaag ggtctccagg agctccgccc 60

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tgcccaacga agccggccac gattggtccc cgaagacccc gcccatctcc tgggcggggc	120
gggcgggggc aagggctggg gagttactaa agacatcccc gcgcccctac tccgctgcct	180
gctattcacc tcgcc atg gtt ctc ctg cct ctg cgc tgt ctc ttc tgg ggc	231
Met Val Leu Leu Pro Leu Arg Cys Leu Phe Trp Gly	
1 5 10	
tcc ttg ttg acc acc gtc tac cca gaa cca cgc act gca tgc aga gaa	279
Ser Leu Leu Thr Thr Val Tyr Pro Glu Pro Arg Thr Ala Cys Arg Glu	
15 20 25	
aag caa tac cta gta gac agt cag tgc tgt aat atg tgc cca cca gga	327
Lys Gln Tyr Leu Val Asp Ser Gln Cys Cys Asn Met Cys Pro Pro Gly	
30 35 40	
gag aaa ctg gtg aat gac tgc cta cat acc att gac acg gaa tgc act	375
Glu Lys Leu Val Asn Asp Cys Leu His Thr Ile Asp Thr Glu Cys Thr	
45 50 55 60	
cgt tgc caa aca ggc gaa ttc cta gac act tgg aac gca gag aga cac	423
Arg Cys Gln Thr Gly Glu Phe Leu Asp Thr Trp Asn Ala Glu Arg His	
65 70 75	
tgt cac cag cac aaa tac tgc gac ccc aac cta ggg ctc cat gtc gag	471
Cys His Gln His Lys Tyr Cys Asp Pro Asn Leu Gly Leu His Val Glu	
80 85 90	
aag gag ggc acg tca gaa aca gac acc act tgc aca tgc gat gaa ggt	519
Lys Glu Gly Thr Ser Glu Thr Asp Thr Thr Cys Thr Cys Asp Glu Gly	
95 100 105	
ctg cat tgt acc aac gct gcc tgt gag agc tgc acc atg cac agc ctg	567
Leu His Cys Thr Asn Ala Ala Cys Glu Ser Cys Thr Met His Ser Leu	
110 115 120	
tgc ccc cct ggc ctg gga gtc aaa cag atc gct aca ggg att tct gat	615
Cys Pro Pro Gly Leu Gly Val Lys Gln Ile Ala Thr Gly Ile Ser Asp	
125 130 135 140	
acc atc tgc gat ccc tgc ccc atc ggc ttc ttc tcc aat gtg tct tct	663
Thr Ile Cys Asp Pro Cys Pro Ile Gly Phe Phe Ser Asn Val Ser Ser	
145 150 155	
gct ttg gaa aag tgt cac cct tgg aca agc tgt gaa acc aaa ggc ctg	711
Ala Leu Glu Lys Cys His Pro Trp Thr Ser Cys Glu Thr Lys Gly Leu	
160 165 170	
gtg aag gtt cag gcg gga act aac aag act gat gtt atc tgt ggt ccc	759
Val Lys Val Gln Ala Gly Thr Asn Lys Thr Asp Val Ile Cys Gly Pro	
175 180 185	
cag cct cgg tta aga gcc cta gtg gtg gtc ccc atc att atg ggg atc	807
Gln Pro Arg Leu Arg Ala Leu Val Val Val Pro Ile Ile Met Gly Ile	
190 195 200	
ctg ctt gtt gtc ctg ttg gtg tct gcc tgc atc cga aag gtg gtc aag	855
Leu Leu Val Val Leu Leu Val Ser Ala Cys Ile Arg Lys Val Val Lys	
205 210 215 220	
aag cca gag aat aag gtt atg tat cag gac cct gtg gag gac ttg gag	903
Lys Pro Glu Asn Lys Val Met Tyr Gln Asp Pro Val Glu Asp Leu Glu	
225 230 235	
gaa ttt cct atg ccc ccg cac tcc att gct ccg gtg caa gag acc tta	951
Glu Phe Pro Met Pro Pro His Ser Ile Ala Pro Val Gln Glu Thr Leu	
240 245 250	
cat ggg tgc cag ccc gtc acc cag gag gac ggc aaa gag agc cgc atc	999
His Gly Cys Gln Pro Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile	
255 260 265	
tcc gtg cag gag aga gtg tgaggcagcg tgtgccagg agtgtgacag	1047
Ser Val Gln Glu Arg Val	
270	
cgtgggagag tgggcgcgtg gctggagagc ctggagctgc tggaggggca tgaaggggcg	1107
gtgctcccct gcctgcacc ctgtgctgca gaaacagaga accttcacc ccaccctgg	1167

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agccattcc acctccaac ttgcttttaa agatggagat gaaacttttg gggggccaga 1227
tagtaatatc caccaacca gcatttcagg gccctgaggt gtatatcacg gtggtttcta 1287
cgagcccagg aagaccacg aagagccatt gtggcattgt ttgtgacagt ggacaactgg 1347
aggccactta gctgttcagc agcaggggac tggctaaata aaatttgtaa tatatttata 1407
aaaaaaaaa aaaaaaaaa 1425

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<210> SEQ ID NO 53
<211> LENGTH: 274
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 53

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Met Val Leu Leu Pro Leu Arg Cys Leu Phe Trp Gly Ser Leu Leu Thr
  1           5           10           15
Thr Val Tyr Pro Glu Pro Arg Thr Ala Cys Arg Glu Lys Gln Tyr Leu
          20           25           30
Val Asp Ser Gln Cys Cys Asn Met Cys Pro Pro Gly Glu Lys Leu Val
          35           40           45
Asn Asp Cys Leu His Thr Ile Asp Thr Glu Cys Thr Arg Cys Gln Thr
          50           55           60
Gly Glu Phe Leu Asp Thr Trp Asn Ala Glu Arg His Cys His Gln His
          65           70           75           80
Lys Tyr Cys Asp Pro Asn Leu Gly Leu His Val Glu Lys Glu Gly Thr
          85           90           95
Ser Glu Thr Asp Thr Thr Cys Thr Cys Asp Glu Gly Leu His Cys Thr
          100          105          110
Asn Ala Ala Cys Glu Ser Cys Thr Met His Ser Leu Cys Pro Pro Gly
          115          120          125
Leu Gly Val Lys Gln Ile Ala Thr Gly Ile Ser Asp Thr Ile Cys Asp
          130          135          140
Pro Cys Pro Ile Gly Phe Phe Ser Asn Val Ser Ser Ala Leu Glu Lys
          145          150          155          160
Cys His Pro Trp Thr Ser Cys Glu Thr Lys Gly Leu Val Lys Val Gln
          165          170          175
Ala Gly Thr Asn Lys Thr Asp Val Ile Cys Gly Pro Gln Pro Arg Leu
          180          185          190
Arg Ala Leu Val Val Val Pro Ile Ile Met Gly Ile Leu Leu Val Val
          195          200          205
Leu Leu Val Ser Ala Cys Ile Arg Lys Val Val Lys Lys Pro Glu Asn
          210          215          220
Lys Val Met Tyr Gln Asp Pro Val Glu Asp Leu Glu Glu Phe Pro Met
          225          230          235          240
Pro Pro His Ser Ile Ala Pro Val Gln Glu Thr Leu His Gly Cys Gln
          245          250          255
Pro Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser Val Gln Glu
          260          265          270
Arg Val

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<210> SEQ ID NO 54
<211> LENGTH: 1425
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 54

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ttttttttt tttttttta taaatatatt acaaatttta tttagccagt cccctgctgc 60
tgaacagcta agtggcctcc agttgtccac tgtcacaac aatgccaca tggctcttcg 120
tgggtcttcc tgggctcgta gaaaccaccg tgatatacac ctgagggcc tgaatgctg 180
ggttgggtgga tattactatc tggcccccca aaagtttcat ctccatcttt aaaagcaagt 240
tgggaggtgg aatgggctcc aggggtgggg tggaaaggtc tctgtttctg cagcacaggg 300
gtgcaggcag gggagcaccg ccccttcatg cccctccagc agctccaggc tctccagcca 360
cgcgcccact ctcccacgct gtcacactcc tgggcacacg ctgcctcaca ctctctctg 420
cacggagatg cggctctctt tgccgtcctc ctgggtgacg ggctggcacc catgtaaggt 480
ctcttgacc ggagcaatgg agtgcggggg cataggaaat tcctccaagt cctccacagg 540
gtcctgatac ataacctat tctctggctt cttgaccacc tttcggatgc aggagacac 600
caacaggaca acaagcagga tcccataat gatggggacc accactaggg ctcttaaccg 660
aggctgggga ccacagataa catcagtctt gttagttccc gcctgaacct tcaccaggcc 720
tttggtttca cagcttgtcc aagggtgaca cttttccaaa gcagaagaca cattggagaa 780
gaagccgatg gggcagggat cgcagatgg atcagaaatc cctgtagcga tctgtttgac 840
tcccaggcca ggggggcaca ggctgtgcat ggtgcagctc tcacaggcag cgttggtaca 900
atgcagacct tcacgcatg tgcaagtgg gtctgtttct gacgtgccct ccttctcgac 960
atggagccct aggttggggg cgcagtattt gtgctggtga cagtgtctct ctgcgttcca 1020
agtgtctagg aattcgcctg tttggcaacg agtgcattcc gtgtcaatgg tatgtaggca 1080
gtcattcacc agtttctctc ctgggtgggca catattacag cactgactgt ctactaggta 1140
ttgcttttct ctgcatgcag tgcgtggttc tgggtagacg gtggtcaaca aggagcccca 1200
gaagagacag cgcagaggca ggagaacct ggcgaggtga atagcaggca gcggagtagg 1260
ggcgcgggga tgtctttagt aactccccag cccttgcccc cgcccccccc gccagggaga 1320
tgggcggggg cttcggggac caatcgtggc cggcttcggt gggcagggcg gagctcctgg 1380
agacccttag cgccgggagt tcccctgaat attcccggga gtcta 1425

```

<210> SEQ ID NO 55

<211> LENGTH: 822

<212> TYPE: DNA

<213> ORGANISM: *Canis familiaris*

<400> SEQUENCE: 55

```

atggttctcc tgcctctgcg ctgtctcttc tgggctcct tgttgaccac cgtctacca 60
gaaccacgca ctgcatgcag agaaaagcaa tacctagtag acagtcagtg ctgtaatatg 120
tgcccaccag gagagaaact ggtgaatgac tgcctacata ccattgacac ggaatgcact 180
cgttgccaaa caggcgaatt cctagacact tggaaacgag agagacactg tcaccagcac 240
aaatactgcg accccaacct agggctccat gtcgagaagg agggcacgtc agaaacagac 300
accacttgca catgcgatga aggtctgcat tgtaccaacg ctgcctgtga gagctgcacc 360
atgcacagcc tgtgcccccc tggcctggga gtcaaacaga tcgctacagg gatttctgat 420
accatctgcg atccctgcc catcggcttc ttctccaatg tgtcttctgc tttggaaaag 480
tgtcacccct ggacaagctg tgaaaccaa ggctggtga aggttcaggc gggaactaac 540
aagactgatg ttatctgtgg tcccagcct cggttaagag ccctagtggg ggtccccatc 600
attatgggga tcctgcttgt tgtcctggtg gtgtctgcct gcatccgaaa ggtggtcaag 660

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aagccagaga ataaggttat gtatcaggac cctgtggagg acttgaggga atttcctatg 720
ccccgcact ccattgctcc ggtgcaagag accttacatg ggtgccagcc cgtcaccag 780
gaggacggca aagagagccg catctccgtg caggagagag tg 822

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<210> SEQ ID NO 56
<211> LENGTH: 822
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 56

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cactctctcc tgcacggaga tgcggctctc tttgccgtcc tcctgggtga cgggctggca 60
cccatgtaag gtctcttgca cgggagcaat ggagtgcggg ggcataggaa attcctccaa 120
gtcctccaca gggctctgat acataacctt attctctggc ttcttgacca cctttcggat 180
gcaggcagac accaacagga caacaagcag gatccccata atgatgggga ccaccactag 240
ggctcttaac cgaggctggg gaccacagat aacatcagtc ttgttagttc ccgcctgaac 300
cttcaccagg cctttggttt cacagcttgt ccaagggtga cacttttcca aagcagaaga 360
cacattggag aagaagccga tggggcaggg atcgcagatg gtatcagaaa tccctgtagc 420
gatctgtttg actcccaggc caggggggca caggctgtgc atgggtgcagc tctcacaggc 480
agcgttggtg caatgcagac cttcatcgca tgtgcaagtg gtgtctgttt ctgacgtgcc 540
ctccttctcg acatggagcc ctaggttggg gtcgcagtat ttgtgctggt gacagtgtct 600
ctctgcgttc caagtgtcta ggaattcgcc tgtttgcaa cgagtgcatt ccgtgtcaat 660
ggtatgtagg cagtcattca ccagtttctc tcctgggtgg cacaattac agcactgact 720
gtctactagg tattgctttt ctctgcatgc agtgcgtggt tctgggtaga cggtggtcaa 780
caaggagccc cagaagagac agcgcagagg caggagaacc at 822

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<210> SEQ ID NO 57
<211> LENGTH: 765
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(765)

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<400> SEQUENCE: 57

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```

cca gaa cca cgc act gca tgc aga gaa aag caa tac cta gta gac agt 48
Pro Glu Pro Arg Thr Ala Cys Arg Glu Lys Gln Tyr Leu Val Asp Ser
  1             5             10
cag tgc tgt aat atg tgc cca cca gga gag aaa ctg gtg aat gac tgc 96
Gln Cys Cys Asn Met Cys Pro Pro Gly Glu Lys Leu Val Asn Asp Cys
          20             25             30
cta cat acc att gac acg gaa tgc act cgt tgc caa aca ggc gaa ttc 144
Leu His Thr Ile Asp Thr Glu Cys Thr Arg Cys Gln Thr Gly Glu Phe
          35             40             45
cta gac act tgg aac gca gag aga cac tgt cac cag cac aaa tac tgc 192
Leu Asp Thr Trp Asn Ala Glu Arg His Cys His Gln His Lys Tyr Cys
          50             55             60
gac ccc aac cta ggg ctc cat gtc gag aag gag ggc acg tca gaa aca 240
Asp Pro Asn Leu Gly Leu His Val Glu Lys Glu Gly Thr Ser Glu Thr
          65             70             75             80
gac acc act tgc aca tgc gat gaa ggt ctg cat tgt acc aac gct gcc 288
Asp Thr Thr Cys Thr Cys Asp Glu Gly Leu His Cys Thr Asn Ala Ala
          85             90             95
tgt gag agc tgc acc atg cac agc ctg tgc ccc cct ggc ctg gga gtc 336
Cys Glu Ser Cys Thr Met His Ser Leu Cys Pro Pro Gly Leu Gly Val

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100	105	110	
aaa cag atc gct aca ggg att tct gat acc atc tgc gat ccc tgc ccc			384
Lys Gln Ile Ala Thr Gly Ile Ser Asp Thr Ile Cys Asp Pro Cys Pro			
115	120	125	
atc ggc ttc ttc tcc aat gtg tct tct gct ttg gaa aag tgt cac cct			432
Ile Gly Phe Phe Ser Asn Val Ser Ser Ala Leu Glu Lys Cys His Pro			
130	135	140	
tgg aca agc tgt gaa acc aaa ggc ctg gtg aag gtt cag gcg gga act			480
Trp Thr Ser Cys Glu Thr Lys Gly Leu Val Lys Val Gln Ala Gly Thr			
145	150	155	160
aac aag act gat gtt atc tgt ggt ccc cag cct cgg tta aga gcc cta			528
Asn Lys Thr Asp Val Ile Cys Gly Pro Gln Pro Arg Leu Arg Ala Leu			
165	170	175	
gtg gtg gtc ccc atc att atg ggg atc ctg ctt gtt gtc ctg ttg gtg			576
Val Val Val Pro Ile Ile Met Gly Ile Leu Leu Val Val Leu Leu Val			
180	185	190	
tct gcc tgc atc cga aag gtg gtc aag aag cca gag aat aag gtt atg			624
Ser Ala Cys Ile Arg Lys Val Val Lys Lys Pro Glu Asn Lys Val Met			
195	200	205	
tat cag gac cct gtg gag gac ttg gag gaa ttt cct atg ccc ccg cac			672
Tyr Gln Asp Pro Val Glu Asp Leu Glu Glu Phe Pro Met Pro Pro His			
210	215	220	
tcc att gct ccg gtg caa gag acc tta cat ggg tgc cag ccc gtc acc			720
Ser Ile Ala Pro Val Gln Glu Thr Leu His Gly Cys Gln Pro Val Thr			
225	230	235	240
cag gag gac ggc aaa gag agc cgc atc tcc gtg cag gag aga gtg			765
Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser Val Gln Glu Arg Val			
245	250	255	

<210> SEQ ID NO 58

<211> LENGTH: 255

<212> TYPE: PRT

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 58

Pro	Glu	Pro	Arg	Thr	Ala	Cys	Arg	Glu	Lys	Gln	Tyr	Leu	Val	Asp	Ser
1				5					10					15	
Gln	Cys	Cys	Asn	Met	Cys	Pro	Pro	Gly	Glu	Lys	Leu	Val	Asn	Asp	Cys
			20					25					30		
Leu	His	Thr	Ile	Asp	Thr	Glu	Cys	Thr	Arg	Cys	Gln	Thr	Gly	Glu	Phe
		35					40					45			
Leu	Asp	Thr	Trp	Asn	Ala	Glu	Arg	His	Cys	His	Gln	His	Lys	Tyr	Cys
	50					55					60				
Asp	Pro	Asn	Leu	Gly	Leu	His	Val	Glu	Lys	Glu	Gly	Thr	Ser	Glu	Thr
65					70					75				80	
Asp	Thr	Thr	Cys	Thr	Cys	Asp	Glu	Gly	Leu	His	Cys	Thr	Asn	Ala	Ala
			85						90					95	
Cys	Glu	Ser	Cys	Thr	Met	His	Ser	Leu	Cys	Pro	Pro	Gly	Leu	Gly	Val
			100					105					110		
Lys	Gln	Ile	Ala	Thr	Gly	Ile	Ser	Asp	Thr	Ile	Cys	Asp	Pro	Cys	Pro
	115						120					125			
Ile	Gly	Phe	Phe	Ser	Asn	Val	Ser	Ser	Ala	Leu	Glu	Lys	Cys	His	Pro
130						135						140			
Trp	Thr	Ser	Cys	Glu	Thr	Lys	Gly	Leu	Val	Lys	Val	Gln	Ala	Gly	Thr
145						150				155				160	
Asn	Lys	Thr	Asp	Val	Ile	Cys	Gly	Pro	Gln	Pro	Arg	Leu	Arg	Ala	Leu
				165					170					175	

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Val	Val	Val	Pro	Ile	Ile	Met	Gly	Ile	Leu	Leu	Val	Val	Leu	Leu	Val
			180					185					190		
Ser	Ala	Cys	Ile	Arg	Lys	Val	Val	Lys	Lys	Pro	Glu	Asn	Lys	Val	Met
		195					200					205			
Tyr	Gln	Asp	Pro	Val	Glu	Asp	Leu	Glu	Glu	Phe	Pro	Met	Pro	Pro	His
	210					215					220				
Ser	Ile	Ala	Pro	Val	Gln	Glu	Thr	Leu	His	Gly	Cys	Gln	Pro	Val	Thr
225					230					235					240
Gln	Glu	Asp	Gly	Lys	Glu	Ser	Arg	Ile	Ser	Val	Gln	Glu	Arg	Val	
				245					250					255	

<210> SEQ ID NO 59
 <211> LENGTH: 765
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 59

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cactctctcc tgcacggaga tgggctctc tttgccgtcc tcctgggtga cgggctggca    60
cccatgtaag gtctcttgca ccggagcaat ggagtgcggg ggcataggaa attcctccaa    120
gtcctccaca gggctctgat acataacctt attctctggc ttcttgacca cctttcggat    180
gcaggcagac accaacagga caacaagcag gatccccata atgatgggga ccaccactag    240
ggctcttaac cgaggctggg gaccacagat aacatcagtc ttgttagttc ccgcctgaac    300
cttcaccagg cctttggttt cacagcttgt ccaagggtga cacttttcca aagcagaaga    360
cacattggag aagaagccga tggggcaggg atcgcagatg gtatcagaaa tccctgtagc    420
gatctgtttg actcccaggc caggggggca caggctgtgc atgggtgcagc tctcacaggc    480
agcgttggtg caatgcagac cttcatcgca tgtgcaagtg gtgtctgttt ctgacgtgcc    540
ctccttctcg acatggagcc ctaggttggg gtcgcagtat ttgtgctggt gacagtgtct    600
ctctgcgttc caagtgtcta ggaattcgcc tgtttgcaa cgagtgcatt ccgtgtcaat    660
ggtatgtagg cagtcattca ccagtttctc tcctgggtgg cacatattac agcactgact    720
gtctactagg tattgctttt ctctgcatgc agtgcgtggt tctgg                    765
    
```

<210> SEQ ID NO 60
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(336)

<400> SEQUENCE: 60

aat	gtg	tca	tct	gct	tcg	gaa	aag	tgt	cac	cct	tgg	acg	agg	tgt	gag
Asn	Val	Ser	Ser	Ala	Ser	Glu	Lys	Cys	His	Pro	Trp	Thr	Arg	Cys	Glu
1				5					10					15	
acc	aaa	ggc	ctg	gtg	gag	ctt	cag	gcg	ggg	acc	aac	aag	acg	gat	gcc
Thr	Lys	Gly	Leu	Val	Glu	Leu	Gln	Ala	Gly	Thr	Asn	Lys	Thr	Asp	Ala
			20					25					30		
gtc	tgc	ggg	ttc	cag	gat	cgg	ata	aga	gcc	ctg	gtg	gtg	atc	ccc	atc
Val	Cys	Gly	Phe	Gln	Asp	Arg	Ile	Arg	Ala	Leu	Val	Val	Ile	Pro	Ile
			35				40					45			
acg	atg	gtg	gtc	ctg	ctt	gct	gtc	ttg	ttg	gtg	tct	gcg	tat	atc	aga
Thr	Met	Val	Val	Leu	Leu	Ala	Val	Leu	Leu	Val	Ser	Ala	Tyr	Ile	Arg
			50			55					60				
aag	gtg	acc	aag	aag	cca	gag	aat	aag	gtc	ctc	cag	cct	aag	gct	gtg
Lys	Val	Thr	Lys	Lys	Pro	Glu	Asn	Lys	Val	Leu	Gln	Pro	Lys	Ala	Val
			65			70				75					80

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tcg cag gac cct gtg gag gac ttg gag gtc ctt cct gtc ccc ctc cac 288
 Ser Gln Asp Pro Val Glu Asp Leu Glu Val Leu Pro Val Pro Leu His
 85 90 95

ccc att gct ccg gtg cag gag acc tta cac ggg tgc cag ccg gtc acc 336
 Pro Ile Ala Pro Val Gln Glu Thr Leu His Gly Cys Gln Pro Val Thr
 100 105 110

<210> SEQ ID NO 61
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 61

Asn Val Ser Ser Ala Ser Glu Lys Cys His Pro Trp Thr Arg Cys Glu
 1 5 10 15

Thr Lys Gly Leu Val Glu Leu Gln Ala Gly Thr Asn Lys Thr Asp Ala
 20 25 30

Val Cys Gly Phe Gln Asp Arg Ile Arg Ala Leu Val Val Ile Pro Ile
 35 40 45

Thr Met Val Val Leu Leu Ala Val Leu Leu Val Ser Ala Tyr Ile Arg
 50 55 60

Lys Val Thr Lys Lys Pro Glu Asn Lys Val Leu Gln Pro Lys Ala Val
 65 70 75 80

Ser Gln Asp Pro Val Glu Asp Leu Glu Val Leu Pro Val Pro Leu His
 85 90 95

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

<210> SEQ ID NO 62
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 62

ggtgaccggc tggcaccctg gtaaggtctc ctgcaccgga gcaatggggg ggagggggac 60

aggaaggacc tccaagtcct ccacagggtc ctgcgacaca gccttaggct ggaggacctt 120

attctctggc ttcttggcca cctttctgat atacgcagac accaacaaga cagcaagcag 180

gaccaccatc gtgatgggga tcaccaccag ggctcttata cgatcctgga aaccgcagac 240

ggcatccgtc ttgttggccc ccgcctgaag ctccaccagg cctttggtct cacacctcgt 300

ccaaggggta cacttttccg aagcagatga cacatt 336

<210> SEQ ID NO 63
 <211> LENGTH: 390
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 63

ataagtgagg ctagttagta cccagcgtcc gttctgcggg gggcgccaaa aggggtactac 60

accataagca gcaacctggt gagcctcgag aatgggaaac agttggccgt gaaaagacaa 120

ggactctatt acgtctatgc ccaagtcacc ttctgctcca atcgggcagc ttcgagtcaa 180

gtcccgttcg tcgccagcct atgcctccat tccccgagtg gaacggagag agtcttactc 240

cgcgccgcga gctcccgcgg ctctgcaaaa ccttgcggcc aacagtccat ccacttggga 300

ggagtatttg aattgcatcc aggtgcttcg gtgttcgcca acgtgactga tccaagccaa 360

gtgagccacg ggaccggctt cacgtctttt 390

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<210> SEQ ID NO 64
<211> LENGTH: 1878
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (284)..(1063)

<400> SEQUENCE: 64

aatgtatgga agaagaaact tgtttcttct ttactaaca aagggaaagc ctggaagtga      60
atgatatggg tataattaaa aaaaaaaaaa aaaaaaaaaa aaaaccttta cgtaactttt      120
tttgctggga gagaagacta cgaagcacat tttccaggaa gtgtgggctg caacgattgt      180
gcgctcttaa ctaatcctga gtaaggtggc cactttgaca gtgttttcat gctgcctctg      240
ccaccttctc ggtctgaaga tatcatttca actctaacac agc atg atc gaa aca      295
                                         Met Ile Glu Thr
                                         1

tat agc caa act gct ccc cga tct gtg gcc act gga cca ccc gtc agt      343
Tyr Ser Gln Thr Ala Pro Arg Ser Val Ala Thr Gly Pro Pro Val Ser
  5              10              15              20

atg aaa att ttt atg tat ttg ctt act gtt ttt ctc atc acc cag atg      391
Met Lys Ile Phe Met Tyr Leu Leu Thr Val Phe Leu Ile Thr Gln Met
              25              30              35

att gga tcg gca ctc ttt gct gta tat ctt cac aga aga ttg gac aag      439
Ile Gly Ser Ala Leu Phe Ala Val Tyr Leu His Arg Arg Leu Asp Lys
              40              45              50

ata gaa gat gaa agg aat ctt tat gaa gat ttt gtg ttc atg aaa acg      487
Ile Glu Asp Glu Arg Asn Leu Tyr Glu Asp Phe Val Phe Met Lys Thr
              55              60              65

tta cag aaa tgc aac aaa ggg gag ggg tcc ttg tcc tta ctg aac tgt      535
Leu Gln Lys Cys Asn Lys Gly Glu Gly Ser Leu Ser Leu Leu Asn Cys
              70              75              80

gag gaa att aaa agc caa ttt gaa gcc ttt ctc aag gag ata atg cta      583
Glu Glu Ile Lys Ser Gln Phe Glu Ala Phe Leu Lys Glu Ile Met Leu
              85              90              95              100

aac aac gaa atg aag aaa gaa gaa aac att gca atg caa aaa ggt gat      631
Asn Asn Glu Met Lys Lys Glu Glu Asn Ile Ala Met Gln Lys Gly Asp
              105              110              115

cag gat cct cga att gca gcc cat gtc ata agt gag gct agt agt aac      679
Gln Asp Pro Arg Ile Ala Ala His Val Ile Ser Glu Ala Ser Ser Asn
              120              125              130

cca gcg tcc gtt ctg cgg tgg gcg cca aaa ggg tac tac acc ata agc      727
Pro Ala Ser Val Leu Arg Trp Ala Pro Lys Gly Tyr Tyr Thr Ile Ser
              135              140              145

agc aac ctg gtg agc ctc gag aat ggg aaa cag ttg gcc gtg aaa aga      775
Ser Asn Leu Val Ser Leu Glu Asn Gly Lys Gln Leu Ala Val Lys Arg
              150              155              160

caa gga ctc tat tac gtc tat gcc caa gtc acc ttc tgc tcc aat cgg      823
Gln Gly Leu Tyr Tyr Val Tyr Ala Gln Val Thr Phe Cys Ser Asn Arg
              165              170              175              180

gca gct tcg agt caa gct ccg ttc gtc gcc agc cta tgc ctc cat tcc      871
Ala Ala Ser Ser Gln Ala Pro Phe Val Ala Ser Leu Cys Leu His Ser
              185              190              195

ccg agt gga acg gag aga gtc tta ctc cgc gcc gcg agc tcc cgc ggc      919
Pro Ser Gly Thr Glu Arg Val Leu Leu Arg Ala Ala Ser Ser Arg Gly
              200              205              210

tcg tcc aaa cct tgc ggc caa cag tcc atc cac ttg gga gga gta ttt      967
Ser Ser Lys Pro Cys Gly Gln Gln Ser Ile His Leu Gly Gly Val Phe
              215              220              225

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gaa ttg cat cca ggt gct tcg gtg ttc gtc aac gtg act gat cca agc 1015
Glu Leu His Pro Gly Ala Ser Val Phe Val Asn Val Thr Asp Pro Ser
    230                235                240

caa gtg agc cac ggg acc ggc ttc acg tct ttt ggc tta ctc aaa ctc 1063
Gln Val Ser His Gly Thr Gly Phe Thr Ser Phe Gly Leu Leu Lys Leu
    245                250                255                260

tgagtgtctgg cacctcacag gctgcagctc agctcctggt ggtggctctc gtaatacggc 1123

cgagcagtta agaccaccac ccctgttgaa ctgcctatatt ataaccctag gatcctcctc 1183

gtggagaact atttattata cacccccagg cgtggaggggc tgcaagaagg gaatgacagg 1243

gcggggggcag cgccaacagg ccccggtcgg taagagttga tattctggaa gcagccgccc 1303

cactgatgca gacatccaga gagtcccatg aaaaagacga gactattatg cacagattga 1363

atcctcagta aacggcagat aattagtcca gtttcgtttt gtttctttgc atgcagtgtc 1423

tttactgga gaatgtactc gatttccccg cgaagatgct gaagggcaac agggagcctc 1483

agctcacagt cagttacggt tgaccggggg tccccggggc cccgatggag gggacaggct 1543

ccagaaagtc tgatggcgcg gagaactgga aaaccctgcc cccaccagcc accctgacac 1603

tcattctctc cctcctccgc ccccctcccc ccacagtcag gctgttgcta atcggttatc 1663

ttatttcaac cctgttgctc ctccaccagt gtaggcggga ggagagagca gaggctgccc 1723

actcctcctc ctgaaatgac tgtattttaa gaaatctct cctacctacc tgcagtctcc 1783

attgtttcca gagtgaactt gtgattatct tgttatttat tttttgaata ataaagcgcc 1843

cttaacgtta aaaaaaaaaa aaaaaaaaaa aaaaa 1878

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<210> SEQ ID NO 65

<211> LENGTH: 260

<212> TYPE: PRT

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 65

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Met Ile Glu Thr Tyr Ser Gln Thr Ala Pro Arg Ser Val Ala Thr Gly
  1             5             10             15

Pro Pro Val Ser Met Lys Ile Phe Met Tyr Leu Leu Thr Val Phe Leu
    20             25             30

Ile Thr Gln Met Ile Gly Ser Ala Leu Phe Ala Val Tyr Leu His Arg
    35             40             45

Arg Leu Asp Lys Ile Glu Asp Glu Arg Asn Leu Tyr Glu Asp Phe Val
    50             55             60

Phe Met Lys Thr Leu Gln Lys Cys Asn Lys Gly Glu Gly Ser Leu Ser
    65             70             75             80

Leu Leu Asn Cys Glu Glu Ile Lys Ser Gln Phe Glu Ala Phe Leu Lys
    85             90             95

Glu Ile Met Leu Asn Asn Glu Met Lys Lys Glu Glu Asn Ile Ala Met
    100            105            110

Gln Lys Gly Asp Gln Asp Pro Arg Ile Ala Ala His Val Ile Ser Glu
    115            120            125

Ala Ser Ser Asn Pro Ala Ser Val Leu Arg Trp Ala Pro Lys Gly Tyr
    130            135            140

Tyr Thr Ile Ser Ser Asn Leu Val Ser Leu Glu Asn Gly Lys Gln Leu
    145            150            155            160

Ala Val Lys Arg Gln Gly Leu Tyr Tyr Val Tyr Ala Gln Val Thr Phe
    165            170            175

Cys Ser Asn Arg Ala Ala Ser Ser Gln Ala Pro Phe Val Ala Ser Leu

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ttcagaccga gaaggtggca gaggcagcat gaaaacactg tcaaagtggc caccttactc 1680
aggattagtt aagagcgcac aatcgttgca gccacactt cctggaaaat gtgcttcgta 1740
gtcttctctc ccagcaaaaa aagttacgta aagggtttttt tttttttttt tttttttttt 1800
taattatacc catatcattc acttccaggc tttccctttt gttagtaaag aagaaacaag 1860
tttcttcttc catacatt 1878

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<210> SEQ ID NO 67
<211> LENGTH: 780
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 67

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atgatcgaaa catatagcca aactgctccc cgatctgtgg ccaactggacc acccgtcagt 60
atgaaaattt ttatgtattt gcttactgtt tttctcatca cccagatgat tggatcggca 120
ctctttgctg tatacttca cagaagattg gacaagatag aagatgaaag gaatctttat 180
gaagattttg tgttcatgaa aacgttacag aaatgcaaca aaggggaggg gtccttgtcc 240
ttactgaact gtgaggaaat taaaagccaa tttgaagcct ttctcaagga gataatgcta 300
aacaacgaaa tgaagaaaga agaaaacatt gcaatgcaaa aaggtgatca ggatcctcga 360
attgcagccc atgtcataag tgaggctagt agtaaccag cgtccgttct gcggtgggcg 420
ccaaaagggg actacacat aagcagcaac ctggtgagcc tcgagaatgg gaaacagttg 480
gccgtgaaaa gacaaggact ctattacgtc tatgccaag tcaccttctg ctccaatcgg 540
gcagcttcga gtcaagctcc gttcgtcgcc agcctatgcc tccattcccc gagtggaacg 600
gagagagtct tactccgctc cgcgagctcc cgcggtcgt ccaaacctg cggccaacag 660
tccatccact tgggaggagt atttgaattg catccagggt cttcgggtgt cgtcaacgtg 720
actgatccaa gccaaagtgag ccacgggacc ggcttcacgt cttttggctt actcaaactc 780

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<210> SEQ ID NO 68
<211> LENGTH: 780
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 68

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gagtttgagt aagccaaaag acgtgaagcc ggtcccgtgg ctcaactggc ttggatcagt 60
cacgttgacg aacaccgaag cacctggatg caattcaaat actcctccca agtggatgga 120
ctggtggccg caaggtttg acgagccgcg ggagctcgcg gcgaggagta agactctctc 180
cgttccactc ggggaatgga ggcataggct ggcgacgaac ggagcttgac tcgaagctgc 240
ccgattggag cagaaggtga cttgggcata gacgtaatag agtccttgtc ttttcacggc 300
caactgtttc ccattctcga ggctcaccag gttgctgctt atggtgtagt acccttttgg 360
cgcccaccgc agaacggacg ctgggttact actagcctca cttatgacat gggctgcaat 420
tcgaggatcc tgatcacctt tttgcattgc aatgttttct tctttcttca tttcgttgtt 480
tagcattatc tccttgagaa aggcttcaaa ttggctttta atttcctcac agttcagtaa 540
ggacaaggac ccctcccctt tgttgcatth ctgtaacgth ttcataaaca caaaatcttc 600
ataaagattc ctttcatctt ctatcttctc caatcttctg tgaagatata cagcaaagag 660
tgccgatcca atcatctggg tgatgagaaa aacagtaagc aaatacataa aaattttcat 720
actgacgggt ggtccagtgg ccacagatcg gggagcagtt tggctatatg tttcgtatcat 780

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Leu Asn Cys Glu Glu Ile Lys Ser Gln Phe Glu Ala Phe Leu Lys Glu
 35 40 45
 Ile Met Leu Asn Asn Glu Met Lys Lys Glu Glu Asn Ile Ala Met Gln
 50 55 60
 Lys Gly Asp Gln Asp Pro Arg Ile Ala Ala His Val Ile Ser Glu Ala
 65 70 75 80
 Ser Ser Asn Pro Ala Ser Val Leu Arg Trp Ala Pro Lys Gly Tyr Tyr
 85 90 95
 Thr Ile Ser Ser Asn Leu Val Ser Leu Glu Asn Gly Lys Gln Leu Ala
 100 105 110
 Val Lys Arg Gln Gly Leu Tyr Tyr Val Tyr Ala Gln Val Thr Phe Cys
 115 120 125
 Ser Asn Arg Ala Ala Ser Ser Gln Ala Pro Phe Val Ala Ser Leu Cys
 130 135 140
 Leu His Ser Pro Ser Gly Thr Glu Arg Val Leu Leu Arg Ala Ala Ser
 145 150 155 160
 Ser Arg Gly Ser Ser Lys Pro Cys Gly Gln Gln Ser Ile His Leu Gly
 165 170 175
 Gly Val Phe Glu Leu His Pro Gly Ala Ser Val Phe Val Asn Val Thr
 180 185 190
 Asp Pro Ser Gln Val Ser His Gly Thr Gly Phe Thr Ser Phe Gly Leu
 195 200 205
 Leu Lys Leu
 210

<210> SEQ ID NO 71
 <211> LENGTH: 633
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 71

gagtttgagt aagcctaaag acgtgaagcc ggtcccgtgg ctcaactggc ttggatcagt 60
 cacgttgacg aacaccgaag cacctggatg caattcaaact actcctccca agtggatgga 120
 ctgttgcccg caaggtttgg acgagccgcg ggagctcgcg gcgcggagta agactctctc 180
 cgttccactc ggggaatgga ggcataggct ggcgacgaac ggagcttgac tcgaagctgc 240
 ccgattggag cagaaggtga cttgggcata gacgtaatag agtccttgtc ttttcacggc 300
 caactgtttc ccattctcga ggctcaccag gttgctgctt atgggtgtagt acccttttgg 360
 cgcccaccgc agaacggacg ctgggttact actagcctca cttatgacat gggctgcaat 420
 tcgaggatcc tgatcacctt tttgcattgc aatgttttct tctttcttca tttcgttggt 480
 tagcattatc tccttgagaa aggcttcaaa ttggctttta atttcctcac agttcagtaa 540
 ggacaaggac ccctcccctt tgttgcattt ctgtaacggt ttcatgaaca caaaatcttc 600
 ataaagattc ctttcatctt ctatcttgtc caa 633

<210> SEQ ID NO 72
 <211> LENGTH: 885
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (29)..(808)

<400> SEQUENCE: 72

gaagatacca tttcaacttt aacacagc atg atc gaa aca tat agc caa act 52

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	Met	Ile	Glu	Thr	Tyr	Ser	Gln	Thr		
	1				5					
gct ccc cgc tcc gtg gcc cct gga cca ccc gtc agt atg aaa att ttt										100
Ala Pro Arg Ser Val Ala Pro Gly Pro Pro Val Ser Met Lys Ile Phe										
10 15 20										
atg tat tta ctt act gtg ttt ctc atc acc cag atg att ggg tca gca										148
Met Tyr Leu Leu Thr Val Phe Leu Ile Thr Gln Met Ile Gly Ser Ala										
25 30 35 40										
ctc ttt gct gtg tat ctt cac aga aga ctg gac aag ata gaa gat gaa										196
Leu Phe Ala Val Tyr Leu His Arg Arg Leu Asp Lys Ile Glu Asp Glu										
45 50 55										
agg aat ctt tat gaa gat ttt gtg ttc atg aaa aca tta cag aaa tgc										244
Arg Asn Leu Tyr Glu Asp Phe Val Phe Met Lys Thr Leu Gln Lys Cys										
60 65 70										
aac aaa gga gag ggg gcc tta tcc tta ctg aac tgt gag gaa att aaa										292
Asn Lys Gly Glu Gly Ala Leu Ser Leu Leu Asn Cys Glu Glu Ile Lys										
75 80 85										
agc cgg ttt gaa gcc ttt ctc aag gag ata atg cta aac aaa gaa acg										340
Ser Arg Phe Glu Ala Phe Leu Lys Glu Ile Met Leu Asn Lys Glu Thr										
90 95 100										
aag aaa gaa aaa aat gtt gca atg caa aaa ggc gac cag gat cct cga										388
Lys Lys Glu Lys Asn Val Ala Met Gln Lys Gly Asp Gln Asp Pro Arg										
105 110 115 120										
gtt gca gca cat gtc ata agt gag gcc agc agt agc aca gcg tct gtt										436
Val Ala Ala His Val Ile Ser Glu Ala Ser Ser Ser Thr Ala Ser Val										
125 130 135										
ctc cag tgg gcc ccc aaa ggc tac tac acc ata agc agc aac ttg gtg										484
Leu Gln Trp Ala Pro Lys Gly Tyr Tyr Thr Ile Ser Ser Asn Leu Val										
140 145 150										
acc ctc gag aac ggg aag cag ctg gcc gtt aaa aga caa gga ctc tat										532
Thr Leu Glu Asn Gly Lys Gln Leu Ala Val Lys Arg Gln Gly Leu Tyr										
155 160 165										
tat atc tac gcc caa gtc acc ttc tgt tcc aat cgg gaa gct tcg agt										580
Tyr Ile Tyr Ala Gln Val Thr Phe Cys Ser Asn Arg Glu Ala Ser Ser										
170 175 180										
caa gct ccg ttc ata gcc agc ctc tgc ctg cat tcc ccg agt gga tcc										628
Gln Ala Pro Phe Ile Ala Ser Leu Cys Leu His Ser Pro Ser Gly Ser										
185 190 195 200										
gag aga gtc tta ctc aga gct gca aat gcc cgc agt tcc tcc aaa ccc										676
Glu Arg Val Leu Leu Arg Ala Ala Asn Ala Arg Ser Ser Ser Lys Pro										
205 210 215										
tgt ggg cag caa tcc att cac ttg gga gga gtc ttc gaa ctg cat cca										724
Cys Gly Gln Gln Ser Ile His Leu Gly Gly Val Phe Glu Leu His Pro										
220 225 230										
ggt gct tcg gtg ttc gtg aac gtg act gat ccg agc caa gtg agc cac										772
Gly Ala Ser Val Phe Val Asn Val Thr Asp Pro Ser Gln Val Ser His										
235 240 245										
ggg acg ggc ttc acg tct ttt ggc ttg ctc aaa ctc tgaacactgg										818
Gly Thr Gly Phe Thr Ser Phe Gly Leu Leu Lys Leu										
250 255 260										
cacctcgcag gccgcgaggc ctgcaggccg cggctgagct cacgctggga gtcttcacaa										878
tacagca										885

<210> SEQ ID NO 73

<211> LENGTH: 260

<212> TYPE: PRT

<213> ORGANISM: Felis catus

<400> SEQUENCE: 73

-continued

Met Ile Glu Thr Tyr Ser Gln Thr Ala Pro Arg Ser Val Ala Pro Gly
 1 5 10 15
 Pro Pro Val Ser Met Lys Ile Phe Met Tyr Leu Leu Thr Val Phe Leu
 20 25 30
 Ile Thr Gln Met Ile Gly Ser Ala Leu Phe Ala Val Tyr Leu His Arg
 35 40 45
 Arg Leu Asp Lys Ile Glu Asp Glu Arg Asn Leu Tyr Glu Asp Phe Val
 50 55 60
 Phe Met Lys Thr Leu Gln Lys Cys Asn Lys Gly Glu Gly Ala Leu Ser
 65 70 75 80
 Leu Leu Asn Cys Glu Glu Ile Lys Ser Arg Phe Glu Ala Phe Leu Lys
 85 90 95
 Glu Ile Met Leu Asn Lys Glu Thr Lys Lys Glu Lys Asn Val Ala Met
 100 105 110
 Gln Lys Gly Asp Gln Asp Pro Arg Val Ala Ala His Val Ile Ser Glu
 115 120 125
 Ala Ser Ser Ser Thr Ala Ser Val Leu Gln Trp Ala Pro Lys Gly Tyr
 130 135 140
 Tyr Thr Ile Ser Ser Asn Leu Val Thr Leu Glu Asn Gly Lys Gln Leu
 145 150 155 160
 Ala Val Lys Arg Gln Gly Leu Tyr Tyr Ile Tyr Ala Gln Val Thr Phe
 165 170 175
 Cys Ser Asn Arg Glu Ala Ser Ser Gln Ala Pro Phe Ile Ala Ser Leu
 180 185 190
 Cys Leu His Ser Pro Ser Gly Ser Glu Arg Val Leu Leu Arg Ala Ala
 195 200 205
 Asn Ala Arg Ser Ser Ser Lys Pro Cys Gly Gln Gln Ser Ile His Leu
 210 215 220
 Gly Gly Val Phe Glu Leu His Pro Gly Ala Ser Val Phe Val Asn Val
 225 230 235 240
 Thr Asp Pro Ser Gln Val Ser His Gly Thr Gly Phe Thr Ser Phe Gly
 245 250 255
 Leu Leu Lys Leu
 260

<210> SEQ ID NO 74

<211> LENGTH: 885

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 74

tgctgtatta tgaagactcc cagcgtgagc tcagccgcgg cctgcaggcc tcgcggcctg 60
 cgaggtgcc a gtgttcagag tttgagcaag ccaaagacg tgaagcccgt cccgtggctc 120
 acttggtcgc gatcagtcac gttcacgaac accgaagcac ctggatgcag ttccaagact 180
 cctccaagt gaatggattg ctgcccacag ggtttgagg aactgcgggc atttcagct 240
 ctgagtaaga ctctctcga tccactcggg gaatgcaggc agaggctggc tatgaacgga 300
 gcttgactcg aagcttccc attggaacag aaggtgactt gggcgtagat ataatagagt 360
 ccttgcttt taacggccag ctgcttccc ttctcgagg tcaccaagt gctgcttatg 420
 gtgtagtagc ctttggggc cactggaga acagacgctg tgctactgct ggctcactt 480
 atgacatgtg ctgcaactcg aggatcctgg tcgccttttt gcattgcaac attttttct 540
 ttcttcgttt cttgttttag cattatctcc ttgagaaagg cttcaaccg gcttttaatt 600

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tcctcacagt tcagtaagga taaggccccc tctcctttgt tgcatttctg taatgttttc	660
atgaaacaaa aatcttcata aagattcctt tcatcttcta tcttgtccag tcttctgtga	720
agatacacag caaagagtgc tgacccaatc atctgggtga tgagaaacac agtaagtaaa	780
tacataaaaa ttttcatact gacgggtggt ccaggggcca cggagcgggg agcagtttgg	840
ctatatgttt cgatcatgct gtgttaaagt tgaaatggta tcttc	885

<210> SEQ ID NO 75
 <211> LENGTH: 780
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 75

atgatcgaaa catatagcca aactgctccc cgctccgtgg cccctggacc acccgtcagt	60
atgaaaattt ttatgtattt acttactgtg tttctcatca cccagatgat tgggtcagca	120
ctctttgctg tgtatcttca cagaagactg gacaagatag aagatgaaag gaatctttat	180
gaagattttg tgttcatgaa aacattacag aaatgcaaca aaggagaggg ggccttatcc	240
ttactgaact gtgaggaaat taaaagccgg tttgaagcct ttctcaagga gataatgcta	300
aacaaagaaa cgaagaaaga aaaaaatggt gcaatgcaaa aaggcgacca ggatcctcga	360
gttgcagcac atgtcataag tgaggccagc agtagcacag cgtctgttct ccagtggggc	420
cccaaaggct actacacat aagcagcaac ttggtgacct tcgagaacgg gaagcagctg	480
gccgttaaaa gacaaggact ctattatata tacgccaag tcaccttctg ttccaatcgg	540
gaagcttcga gtcaagctcc gttcatagcc agcctctgcc tgcattcccc gagtggatcc	600
gagagagtct tactcagagc tgcaaatgcc cgcagttcct ccaaaccctg tgggcagcaa	660
tccattcact tgggaggagt cttcgaactg catccagggtg cttcgggtgt cgtgaacgtg	720
actgatccga gccaaagtgag ccacgggacg ggcttcacgt cttttggctt gctcaaactc	780

<210> SEQ ID NO 76
 <211> LENGTH: 780
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 76

gagtttgagc aagccaaaag acgtgaagcc cgtcccgtgg ctcacttggc tcggatcagt	60
cacgttcacg aacaccgaag cacctggatg cagttcgaag actcctccca agtgaatgga	120
ttgctgcca cagggtttg aggaactgcg ggcatattgca gctctgagta agactctctc	180
ggatccactc ggggaatgca ggcagaggct ggctatgaac ggagcttgac tcgaagcttc	240
ccgattggaa cagaaggtga cttgggcgta gatataatag agtccttgtc ttttaacggc	300
cagctgcttc ccgttctcga gggtcaccaa gttgctgctt atgggtgtagt agcctttggg	360
ggcccactgg agaacagacg ctgtgctact gctggcctca cttatgacat gtgctgcaac	420
tcgaggatcc tggctgcctt tttgcattgc aacatTTTTT tctttcttcg tttctttgtt	480
tagcattatc tccttgagaa aggcttcaaa ccggctttta atttcctcac agttcagtaa	540
ggataaggcc ccctctcctt tgttgcatth ctgtaatggt ttcatgaaca caaaatcttc	600
ataaagattc ctttcatctt ctatcttctc cagtcttctg tgaagataca cagcaaagag	660
tgctgaccca atcatctggg tgatgagaaa cacagtaagt aaatacataa aaattttcat	720
actgacgggt ggtccagggg ccacgggacg gggagcagtt tggctatatg tttcagatcat	780

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Leu Asn Cys Glu Glu Ile Lys Ser Arg Phe Glu Ala Phe Leu Lys Glu
 35 40 45
 Ile Met Leu Asn Lys Glu Thr Lys Lys Glu Lys Asn Val Ala Met Gln
 50 55 60
 Lys Gly Asp Gln Asp Pro Arg Val Ala Ala His Val Ile Ser Glu Ala
 65 70 75 80
 Ser Ser Ser Thr Ala Ser Val Leu Gln Trp Ala Pro Lys Gly Tyr Tyr
 85 90 95
 Thr Ile Ser Ser Asn Leu Val Thr Leu Glu Asn Gly Lys Gln Leu Ala
 100 105 110
 Val Lys Arg Gln Gly Leu Tyr Tyr Ile Tyr Ala Gln Val Thr Phe Cys
 115 120 125
 Ser Asn Arg Glu Ala Ser Ser Gln Ala Pro Phe Ile Ala Ser Leu Cys
 130 135 140
 Leu His Ser Pro Ser Gly Ser Glu Arg Val Leu Leu Arg Ala Ala Asn
 145 150 155 160
 Ala Arg Ser Ser Ser Lys Pro Cys Gly Gln Gln Ser Ile His Leu Gly
 165 170 175
 Gly Val Phe Glu Leu His Pro Gly Ala Ser Val Phe Val Asn Val Thr
 180 185 190
 Asp Pro Ser Gln Val Ser His Gly Thr Gly Phe Thr Ser Phe Gly Leu
 195 200 205
 Leu Lys Leu
 210

<210> SEQ ID NO 79
 <211> LENGTH: 633
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 79

gagtttgagc aagccaaaag acgtgaagcc cgtcccgtgg ctcaactggc tcggatcagt 60
 cacgttcacg aacaccgaag cacctggatg cagttcgaag actcctccca agtgaatgga 120
 ttgctgcca cagggtttgg aggaactgcg ggcatttgca gctctgagta agactctctc 180
 ggatccactc ggggaatgca ggcagaggct ggctatgaac ggagcttgac tcgaagcttc 240
 ccgattggaa cagaaggtga cttgggcgta gatataatag agtccttgtc ttttaacggc 300
 cagctgcttc ccgttctcga gggtcaccaa gttgctgctt atgggtgtagt agcctttggg 360
 ggcccactgg agaacagacg ctgtgctact gctggcctca cttatgacat gtgctgcaac 420
 tcgaggatcc tggctgcctt tttgcattgc aacatTTTTT tctttcttcg tttctttggt 480
 tagcattatc tccttgagaa aggcttcaaa ccggctttta atttcctcac agttcagtaa 540
 ggataaggcc ccctctcctt tgttgcattt ctgtaatggt ttcatgaaca caaaatcttc 600
 ataaagattc ctttcatctt ctatcttgtc cag 633

<210> SEQ ID NO 80
 <211> LENGTH: 610
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (29)..(430)

<400> SEQUENCE: 80

caaggcaaac actgaacatt tcagagct atg aga atg ctt ctg aat ttg agt 52

-continued

	Met	Arg	Met	Leu	Leu	Asn	Leu	Ser									
	1				5												
ttg cta gct ctt ggg gct gcc tat gtt tct gcc ttt gct gta gaa aat																	100
Leu Leu Ala Leu Gly Ala Ala Tyr Val Ser Ala Phe Ala Val Glu Asn																	
10					15					20							
ccc atg aat aga ctg gtg gca gag acc ttg aca ctg ctc tcc act cat																	148
Pro Met Asn Arg Leu Val Ala Glu Thr Leu Thr Leu Leu Ser Thr His																	
25					30					35						40	
cga act tgg ctg ata ggc gat ggg aac ctg atg att cct act cct gaa																	196
Arg Thr Trp Leu Ile Gly Asp Gly Asn Leu Met Ile Pro Thr Pro Glu																	
45										50						55	
aat aaa aat cac caa ctg tgc att aaa gaa gtt ttt cag ggt ata gac																	244
Asn Lys Asn His Gln Leu Cys Ile Lys Glu Val Phe Gln Gly Ile Asp																	
60										65						70	
aca ttg aag aac caa act gcc cac ggg gag gct gtg gat aaa cta ttc																	292
Thr Leu Lys Asn Gln Thr Ala His Gly Glu Ala Val Asp Lys Leu Phe																	
75										80						85	
caa aac ttg tct tta ata aaa gaa cac ata gag cgc caa aaa aaa agg																	340
Gln Asn Leu Ser Leu Ile Lys Glu His Ile Glu Arg Gln Lys Lys Arg																	
90										95						100	
tgt gca gga gaa aga tgg aga gtg aca aag ttc cta gac tac ctg caa																	388
Cys Ala Gly Glu Arg Trp Arg Val Thr Lys Phe Leu Asp Tyr Leu Gln																	
105										110						115	120
gta ttt ctt ggt gta ata aac acc gag tgg aca ccg gaa agt																	430
Val Phe Leu Gly Val Ile Asn Thr Glu Trp Thr Pro Glu Ser																	
125										130							
tgagaacaaa ccggcttatt gtagtgaag attttgaga agaatggttt tttggcgatg																	490
agaatgaggg ccaaccaaca gtagggactt aatggccagt ataactaagc ttcagagaca																	550
aagtaaatat ttcagcatc ctactacttt atcacttcac acagatgaaa tatatttgag																	610

<210> SEQ ID NO 81

<211> LENGTH: 134

<212> TYPE: PRT

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 81

Met Arg Met Leu Leu Asn Leu Ser Leu Leu Ala Leu Gly Ala Ala Tyr																	
1					5					10						15	
Val Ser Ala Phe Ala Val Glu Asn Pro Met Asn Arg Leu Val Ala Glu																	
20										25						30	
Thr Leu Thr Leu Leu Ser Thr His Arg Thr Trp Leu Ile Gly Asp Gly																	
35										40						45	
Asn Leu Met Ile Pro Thr Pro Glu Asn Lys Asn His Gln Leu Cys Ile																	
50										55						60	
Lys Glu Val Phe Gln Gly Ile Asp Thr Leu Lys Asn Gln Thr Ala His																	
65										70						75	80
Gly Glu Ala Val Asp Lys Leu Phe Gln Asn Leu Ser Leu Ile Lys Glu																	
85										90						95	
His Ile Glu Arg Gln Lys Lys Arg Cys Ala Gly Glu Arg Trp Arg Val																	
100										105						110	
Thr Lys Phe Leu Asp Tyr Leu Gln Val Phe Leu Gly Val Ile Asn Thr																	
115										120						125	
Glu Trp Thr Pro Glu Ser																	
130																	

<210> SEQ ID NO 82

<211> LENGTH: 610

-continued

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<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 82

ctcaaatata tttcatctgt gtgaagtgat aaagtagtag gatgcctgaa atatttactt    60
tgtctctgaa gcttagttat actggccatt aagtccttac tgttggttg ccctcattct    120
catcgccaaa aaaccattct tctccaaaat cttccactac aataagccgg tttgttctca    180
actttccggg gtccactcgg tgtttattac accaagaaat acttgcaggt agtctaggaa    240
ctttgtcact ctccatcttt ctctgcaca cctttttttt tggcgctcta tgtgttcttt    300
tattaaagac aagttttgga atagtttatc cacagcctcc ccgtgggcag tttggttctt    360
caatgtgtct ataccctgaa aaacttcttt aatgcacagt tggtgatttt tattttcagg    420
agtaggaatc atcaggttcc catcgcctat cagccaagtt cgatgagtgg agagcagtgt    480
caaggtctct gccaccagtc tattcatggg attttctaca gcaaaggcag aaacataggg    540
agccccaaga gctagcaaac tcaaattcag aagcattctc atagctctga aatgttcagt    600
gtttgccttg                                     610

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<210> SEQ ID NO 83
<211> LENGTH: 402
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 83

atgagaatgc ttctgaatth gagtttgcta gctcttgggg ctgcctatgt ttctgccttt    60
gctgtagaaa atcccatgaa tagactgggtg gcagagacct tgacactgct ctccactcat    120
cgaacttggc tgataggcga tgggaacctg atgattccta ctctgaaaa taaaaatcac    180
caactgtgca ttaaagaagt ttttcagggt atagacacat tgaagaacca aactgcccac    240
ggggaggctg tggataaact attccaaaac ttgtctttaa taaaagaaca catagagcgc    300
caaaaaaaaaa ggtgtgcagg agaaagatgg agagtgacaa agttcctaga ctacctgcaa    360
gtatttcttg gtgtaataaa caccgagtgg acaccggaaa gt                                     402

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<210> SEQ ID NO 84
<211> LENGTH: 402
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 84

actttccggg gtccactcgg tgtttattac accaagaaat acttgcaggt agtctaggaa    60
ctttgtcact ctccatcttt ctctgcaca cctttttttt tggcgctcta tgtgttcttt    120
tattaaagac aagttttgga atagtttatc cacagcctcc ccgtgggcag tttggttctt    180
caatgtgtct ataccctgaa aaacttcttt aatgcacagt tggtgatttt tattttcagg    240
agtaggaatc atcaggttcc catcgcctat cagccaagtt cgatgagtgg agagcagtgt    300
caaggtctct gccaccagtc tattcatggg attttctaca gcaaaggcag aaacataggg    360
agccccaaga gctagcaaac tcaaattcag aagcattctc at                                     402

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<210> SEQ ID NO 85
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(345)

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<400> SEQUENCE: 85

```

ttt gct gta gaa aat ccc atg aat aga ctg gtg gca gag acc ttg aca      48
Phe Ala Val Glu Asn Pro Met Asn Arg Leu Val Ala Glu Thr Leu Thr
  1                    5                      10                15

ctg ctc tcc act cat cga act tgg ctg ata ggc gat ggg aac ctg atg      96
Leu Leu Ser Thr His Arg Thr Trp Leu Ile Gly Asp Gly Asn Leu Met
                20                      25                30

att cct act cct gaa aat aaa aat cac caa ctg tgc att aaa gaa gtt     144
Ile Pro Thr Pro Glu Asn Lys Asn His Gln Leu Cys Ile Lys Glu Val
                35                      40                45

ttt cag ggt ata gac aca ttg aag aac caa act gcc cac ggg gag gct     192
Phe Gln Gly Ile Asp Thr Leu Lys Asn Gln Thr Ala His Gly Glu Ala
                50                      55                60

gtg gat aaa cta ttc caa aac ttg tct tta ata aaa gaa cac ata gag     240
Val Asp Lys Leu Phe Gln Asn Leu Ser Leu Ile Lys Glu His Ile Glu
                65                      70                75                80

cgc caa aaa aaa agg tgt gca gga gaa aga tgg aga gtg aca aag ttc     288
Arg Gln Lys Lys Arg Cys Ala Gly Glu Arg Trp Arg Val Thr Lys Phe
                85                      90                95

cta gac tac ctg caa gta ttt ctt ggt gta ata aac acc gag tgg aca     336
Leu Asp Tyr Leu Gln Val Phe Leu Gly Val Ile Asn Thr Glu Trp Thr
                100                   105                110

ccg gaa agt
Pro Glu Ser
                115

```

<210> SEQ ID NO 86

<211> LENGTH: 115

<212> TYPE: PRT

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 86

```

Phe Ala Val Glu Asn Pro Met Asn Arg Leu Val Ala Glu Thr Leu Thr
  1                    5                      10                15

Leu Leu Ser Thr His Arg Thr Trp Leu Ile Gly Asp Gly Asn Leu Met
                20                      25                30

Ile Pro Thr Pro Glu Asn Lys Asn His Gln Leu Cys Ile Lys Glu Val
                35                      40                45

Phe Gln Gly Ile Asp Thr Leu Lys Asn Gln Thr Ala His Gly Glu Ala
                50                      55                60

Val Asp Lys Leu Phe Gln Asn Leu Ser Leu Ile Lys Glu His Ile Glu
                65                      70                75                80

Arg Gln Lys Lys Arg Cys Ala Gly Glu Arg Trp Arg Val Thr Lys Phe
                85                      90                95

Leu Asp Tyr Leu Gln Val Phe Leu Gly Val Ile Asn Thr Glu Trp Thr
                100                   105                110

Pro Glu Ser
                115

```

<210> SEQ ID NO 87

<211> LENGTH: 345

<212> TYPE: DNA

<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 87

```

actttccggt gtccactcgg tgtttattac accaagaaat acttgcaggt agtctaggaa      60
ctttgtcact ctccatcttt ctctgcaca cctttttttt tggcgcctcta tgtgttcttt     120

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tattaaagac aagttttgga atagtttatc cacagcctcc ccgtgggcag tttggttcct	180
caatgtgtct ataccctgaa aaacttcttt aatgcacagt tggatgattt tattttcagg	240
agtaggaatc atcaggttcc catcgcctat cagccaagtt cgatgagtgg agagcagtgt	300
caaggtctct gccaccagtc tattcatggg attttctaca gcaaa	345

<210> SEQ ID NO 88
 <211> LENGTH: 166
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 88

ctcagcttag gccagcctac gacctgcctg ctcttccctc gctcctcctg cattggctct	60
gggctccatg gcgctctggt tgactgtggt cattgctctc acctgcctcg gtggccttgc	120
ctccccgagc cctgtgactc cctccccaac cctcaaggag ctcat	166

<210> SEQ ID NO 89
 <211> LENGTH: 272
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 89

tggccttgcc tccccgagcc ctgtgactcc ctccccaac ctcaaggagc tcattgagga	60
gctggtcaac atcaccaga atcaggcatc cctctgcaac ggcagcatgg tgtggagcgt	120
caacctgacc gccggcatgt actgcgagc tctagaatct ctgatcaatg tctccgactg	180
cagcgccatc caaaggacc agaggatgct gaaagcactg tgctctcaa agcccgcggc	240
agggcagatt tccagtgaac gcagccgaga ca	272

<210> SEQ ID NO 90
 <211> LENGTH: 278
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 90

atggcgctct ggttgactgt ggtcattgct ctcacctgcc tcggtggcct tgctccccg	60
agccctgtga ctccctccc aacctcaag gagctcattg aggagctggt caacatcacc	120
cagaatcagg catccctctg caacggcagc atggtgtgga gcgtcaacct gaccgcccgc	180
atgtactgag cagctctaga atctctgatc aatgtctccg actgcagcgc catccaaagg	240
accagagga tgctgaaagc actgtgctct caaaagcc	278

<210> SEQ ID NO 91
 <211> LENGTH: 1302
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (52)..(444)

<400> SEQUENCE: 91

ctacgacctg cctgctctc cctcgtcct cctgcattgg ctctgggctc c atg gcg	57
	Met Ala
	1
ctc tgg ttg act gtg gtc att gct ctc acc tgc ctc ggt ggc ctt gcc	105
Leu Trp Leu Thr Val Val Ile Ala Leu Thr Cys Leu Gly Gly Leu Ala	
5 10 15	
tcc ccg agc cct gtg act ccc tcc cca acc ctc aag gag ctc att gag	153
Ser Pro Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile Glu	

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20	25	30	
gag ctg gtc aac atc acc cag aat cag gca tcc ctc tgc aac ggc agc			201
Glu Leu Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly Ser			
35	40	45	50
atg gtg tgg agc gtc aac ctg acc gcc ggc atg tac tgc gca gct cta			249
Met Val Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu			
	55	60	65
gaa tct ctg atc aat gtc tcc gac tgc agc gcc atc caa agg acc cag			297
Glu Ser Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr Gln			
	70	75	80
agg atg ctg aaa gca ctg tgc tct caa aag ccc gcg gca ggg cag att			345
Arg Met Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Gln Ile			
	85	90	95
tcc agt gaa cgc agc cga gac acc aaa att gaa gtg atc cag ttg gtg			393
Ser Ser Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val			
100	105	110	
aaa aac ctg ctc acc tat gta agg gga gtt tat cgc cat gga aat ttc			441
Lys Asn Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe			
115	120	125	130
aga tgaagcatga aaacttagca tccttatctg tagaccaga cctgaccact			494
Arg			
taagttccag attcattttt ctttccgacg tcacaaattt cttagggagg tggggggggg			554
ggagaacat ttcctcagct gggacctcag cctgcaccgc ctgcctccat ggagctgagc			614
ccagccaccc ctgccttggg gcatggggcc cagccgggtg gccctcctcc gtctgcactt			674
catcaacgct gagggaaagc actgcatccc atgactgtcc cctcctcaga gcaaagtgca			734
gcattacagt ggaggcagat atgtgtggga gggggtcttg ctgtacctgg gagtggcaca			794
gacatgtttc ttcttagcct tatttattat tgtgtgttat ttaaacaagt gtctttgttt			854
gtgctgggga cagggagtgg cttggagctg ggggccagc gactcgggtt tagagagtcc			914
ctgggaataa gcactgtgtg taaaattctg ctacctcact gggatccttg ggccgacaca			974
ggggacagga gaaagggtca gagatgctgc tctgtctgca cactcagcag ctggccctca			1034
gccaagcagt aatttattgt ttttccttgt atttaaagtt aagaaataaa atatgttatc			1094
aaagagttaa taatatatag aagagtagcc taaaaggctg catttggtgt gtgtggccag			1154
gccggggcgg gtggggggga ggggtgtgtc actgaatgtg ctctttcact gactttgtca			1214
aactggaagc cagaaataaa gatggtgaca agagaaaaaa aaaaaaaaaa aaaaaaaaaa			1274
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa			1302
<210> SEQ ID NO 92			
<211> LENGTH: 131			
<212> TYPE: PRT			
<213> ORGANISM: Canis familiaris			
<400> SEQUENCE: 92			
Met Ala Leu Trp Leu Thr Val Val Ile Ala Leu Thr Cys Leu Gly Gly			
1	5	10	15
Leu Ala Ser Pro Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu			
	20	25	30
Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn			
	35	40	45
Gly Ser Met Val Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala			
	50	55	60
Ala Leu Glu Ser Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg			
	65	70	75
			80

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Thr Gln Arg Met Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly
 85 90 95
 Gln Ile Ser Ser Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln
 100 105 110
 Leu Val Lys Asn Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly
 115 120 125
 Asn Phe Arg
 130

<210> SEQ ID NO 93
 <211> LENGTH: 1302
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 93

```

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt ttttctcttg      60
tcaccatcct tatttctggc ttccagtttg acaaagtcag tgaaagagca cattcagtga      120
caacaccctc cccccaccc gccccggcct ggccacacac accaaatgca gccttttagg      180
ctactcttct atatattatt aactctttga taacatattt tatttcttaa ctttaaatac      240
aaggaaaaac aataaattac tgcttggctg agggccagct gctgagtggc agacaagagc      300
agcatctctg accctttctc ctgtcccctg tgtcggcccc aggatcccag tgaggtagca      360
gaattttaca cacagtgctt attcccaggg actctctaaa cccgagtcac tgggccccca      420
gtccaagcc actccctgtc cccagcacia acaaagacac ttgtttaaat aacacacaat      480
aataaataag gctaagaaga aacatgtctg tgccactccc aggtacagca agaccccctc      540
ccacacatat ctgcctccac tgtaatgctg cactttgctc tgaggagggg acagtcatgg      600
gatgcagtgc tttccctcag cgttgatgaa gtgcagacgg aggagggcca cccggctggg      660
ccccatgcac caaggcaggg gtggctgggc tcagctccat ggaggcaggc ggtgcaggct      720
gaggtcccag ctgaggaaat ggttctcccc cccccacc tccctaagaa atttgtgacg      780
tcggaagaa aatgaatct ggaacttaag tggtcaggtc tgggtctaca gataaggatg      840
ctaagttttc atgcttcctc tgaaatttcc atggcgataa actcccctta cataggtgag      900
caggtttttc accaactgga tcaactcaat tttggtgtct cggctgcgct cactggaaat      960
ctgccctgcc gcgggctttt gagagcacag tgctttcagc atcctctggg tcctttggat     1020
ggcgtgcag tcggagacat tgatcagaga ttctagagct gcgcagtaca tgccggcggt     1080
caggttgacg ctccacacca tgctgccgtt gcagagggat gcctgattct gggatgatgt     1140
gaccagctcc tcaatgagct ccttgagggg tggggagggg gtcacagggc tcggggaggg     1200
aagccaccg aggcaggtga gagcaatgac cacagtcaac cagagcgcca tggagcccag     1260
agccaatgca ggaggagcga gggaagagca ggcaggtcgt ag                               1302
  
```

<210> SEQ ID NO 94
 <211> LENGTH: 393
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 94

```

atggcgctct ggttgactgt ggtcattgct ctcacctgcc tcggtggcct tgctccccg      60
agccctgtga ctccctccc aaccctcaag gagctcattg aggagctggt caacatcacc     120
cagaatcagg catccctctg caacggcagc atggtgtgga gcgtcaacct gaccgcccgg     180
  
```

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atgtactgcg cagctctaga atctctgac aatgtctccg actgcagcgc catccaaagg 240
accagagga tgctgaaagc actgtgctct caaaagcccg cggcagggca gatttccagt 300
gaacgcagcc gagacaccaa aattgaagtg atccagttgg tgaaaaacct gctcacctat 360
gtaaggggag tttatcgcca tggaaatttc aga 393

```

```

<210> SEQ ID NO 95
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 95

```

```

tctgaaatth ccatggcgat aaactcccct tacataggtg agcaggthtt tcaccaactg 60
gatcacttca atthttggtg ctgggtgctg ttcactggaa atctgccttg ccgctgggctt 120
ttgagagcac agtgctttca gcatcctctg ggtcctttgg atggcgctgc agtcggagac 180
attgatcaga gattctagag ctgcgcagta catgccggcg gtcaggttga cgctccacac 240
catgctgccg ttgcagaggg atgcctgatt ctgggtgatg ttgaccagct cctcaatgag 300
ctccttgagg gttggggagg gagtcacagg gctcggggag gcaaggccac cgaggcaggt 360
gagagcaatg accacagtca accagagcgc cat 393

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<210> SEQ ID NO 96
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(333)

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<400> SEQUENCE: 96

```

```

agc cct gtg act ccc tcc cca acc ctc aag gag ctc att gag gag ctg 48
Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile Glu Glu Leu
1 5 10 15
gtc aac atc acc cag aat cag gca tcc ctc tgc aac ggc agc atg gtg 96
Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly Ser Met Val
20 25 30
tgg agc gtc aac ctg acc gcc ggc atg tac tgc gca gct cta gaa tct 144
Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu Ser
35 40 45
ctg atc aat gtc tcc gac tgc agc gcc atc caa agg acc cag agg atg 192
Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr Gln Arg Met
50 55 60
ctg aaa gca ctg tgc tct caa aag ccc gcg gca ggg cag att tcc agt 240
Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Gln Ile Ser Ser
65 70 75 80
gaa cgc agc cga gac acc aaa att gaa gtg atc cag ttg gtg aaa aac 288
Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val Lys Asn
85 90 95
ctg ctc acc tat gta agg gga gtt tat cgc cat gga aat ttc aga 333
Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe Arg
100 105 110

```

```

<210> SEQ ID NO 97
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 97

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```

Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile Glu Glu Leu
1 5 10 15

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Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly Ser Met Val
 20 25 30
 Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu Ser
 35 40 45
 Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr Gln Arg Met
 50 55 60
 Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Gln Ile Ser Ser
 65 70 75 80
 Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val Lys Asn
 85 90 95
 Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe Arg
 100 105 110

<210> SEQ ID NO 98
 <211> LENGTH: 333
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris

<400> SEQUENCE: 98

tctgaaattt ccatggcgat aaactcccct tacataggtg agcaggtttt tcaccaactg 60
 gatcaattca attttggtgt ctgggctgctg ttactggaa atctgccctg ccgogggctt 120
 ttgagagcac agtgctttca gcacccctctg gtccttttg atggcgctgc agtcggagac 180
 attgatcaga gattctagag ctgcgagta catgccggcg gtcaggttga cgctccacac 240
 catgctgccg ttgagaggg atgcctgatt ctgggtgatg ttgaccagct cctcaatgag 300
 ctccctgagg gttggggagg gagtcacagg gct 333

<210> SEQ ID NO 99
 <211> LENGTH: 1269
 <212> TYPE: DNA
 <213> ORGANISM: Canis familiaris
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (57)..(446)

<400> SEQUENCE: 99

ccagcctacg acctgcctgc tcttccctcg ctctcctgc attggctctg ggctcc atg 59
 Met
 1
 gcg ctc tgg ttg act gtg gtc att gct ctc acc tgc ctc ggt ggc ctt 107
 Ala Leu Trp Leu Thr Val Val Ile Ala Leu Thr Cys Leu Gly Gly Leu
 5 10 15
 gcc tcc ccg agc cct gtg act ccc tcc cca acc ctc aag gag ctc att 155
 Ala Ser Pro Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile
 20 25 30
 gag gag ctg gtc aac atc acc cag aat cag gca tcc ctc tgc aac ggc 203
 Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly
 35 40 45
 agc atg gtg tgg agc gtc aac ctg acc gcc ggc atg tac tgc gca gct 251
 Ser Met Val Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala
 50 55 60 65
 cta gaa tct ctg atc aat gtc tcc gac tgc agc gcc atc caa agg acc 299
 Leu Glu Ser Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr
 70 75 80
 cag agg atg ctg aaa gca ctg tgc tct caa aag ccc gcg gca ggg att 347
 Gln Arg Met Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Ile
 85 90 95
 tcc agt gaa cgc agc cga gac acc aaa att gaa gtg atc cag ttg gtg 395

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Ser Ser Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val
      100                               105                               110

aaa aac ctg ctc acc tat gta agg gga gtt tat cgc cat gga aat ttc      443
Lys Asn Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe
      115                               120                               125

aga tgaagcatga aaacttagca tccttatctg tagaccacaga cctgaccact      496
Arg
130

taagttccag attcattttt ctttccgacg tcacaaattht cttagggagg tggggggggg      556

ggagaacat ttcctcagct gggacctcag cctgcaccgc ctgcctccat ggagctgagc      616

ccagccaccc ctgccttggg gcatggggcc cagccgggtg gccctcctcc gtctgcactt      676

catcaacgct gagggaaagc actgcatccc atgactgtcc cctcctcaga gcaaagtgca      736

gcattacagt ggaggcagat atgtgtggga ggggtcttg ctgtacctgg gagtggcaca      796

gacatgtttc ttcttagcct tatttattat tgtgtgttat ttaaacaagt gtctttgttt      856

gtgctgggga cagggagtgg cttggagctg ggggccagc gactcgggtt tagagagtcc      916

ctgggaataa gcactgtgtg taaaattctg ctacctcact gggatcctgg ggccgacaca      976

ggggacagga gaaagggtca gagatgctgc tctgtctgca cactcagcag ctggccctca 1036

gccaaagcagt aatttattgt ttttccttgt atttaaagtt aagaaataaa atatgttatc 1096

aaagagttaa taatatatag aagagtagcc taaaaggctg catttggtgt gtgtggccag 1156

gccggggcgg gtggggggga ggggtgtgtc actgaatgtg ctctttcact gactttgtca 1216

aactggaagc cagaaataaa gatggtgaca agagaaaaaa aaaaaaaaaa aaa      1269

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<210> SEQ ID NO 100
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 100

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```

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

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

Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn
      35           40           45

Gly Ser Met Val Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala
      50           55           60

Ala Leu Glu Ser Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg
      65           70           75           80

Thr Gln Arg Met Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly
      85           90           95

Ile Ser Ser Glu Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu
      100          105          110

Val Lys Asn Leu Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn
      115          120          125

Phe Arg
      130

```

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<210> SEQ ID NO 101
<211> LENGTH: 1269
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 101

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ttttttttt ttttttttc tcttgcacc atctttatth ctggcttcca gtttgacaaa    60
gtcagtgaaa gagcacattc agtgacaaca ccctcccccc caccgcccc ggcttgcca    120
cacacaccaa atgcagcctt ttaggctact cttctatata ttattaactc tttgataaca    180
tattttatth ctttaacttta aatacaagga aaaacaataa attactgctt ggctgagggc    240
cagctgctga gtggcagaca agagcagcat ctctgaccct ttctcctgtc ccctgtgtcg    300
gccccaggat cccagtgagg tagcagaatt ttacacacag tgcttattcc cagggactct    360
ctaaaccoga gtcactgggc ccccagctcc aagccactcc ctgtccccag cacaaacaaa    420
gacacttggt taaataacac acaataataa ataaggctaa gaagaaacat gtctgtgcca    480
ctcccaggta cagcaagacc ccctcccaca catatctgcc tccactgtaa tgctgcactt    540
tgctctgagg aggggacagt catgggatgc agtgctttcc ctacagcgtt atgaagtgca    600
gacggaggag ggccaccggt ctgggccccca tgcaccaagg caggggtggc tgggctcagc    660
tccatggagg caggcgggtc aggctgaggt cccagctgag gaaatggttc tcccccccc    720
ccacctccct aagaaatttg tgacgtcggg aagaaaaatg aatctggaac ttaagtggtc    780
aggctcgggt ctacagataa ggatgctaag ttttcatgct tcatctgaaa tttccatggc    840
gataaactcc cttacatag gtgagcaggt ttttccacaa ctggatcact tcaattttgg    900
tgtctcggct gcgttactg gaaatccctg ccgcgggctt ttgagagcac agtgctttca    960
gcatcctctg ggtcctttgg atggcgctgc agtcggagac attgatcaga gattctagag   1020
ctgcgcagta catgccggcg gtcagggtga cgctccacac catgctgccg ttgcagaggg   1080
atgcctgatt ctgggtgatg ttgaccagct cctcaatgag ctctttgagg gttggggagg   1140
gagtcacagg gctcggggag gcaaggccac cgaggcaggt gagagcaatg accacagtca   1200
accagagcgc catggagccc agagccaatg caggaggagc gaggaagag caggcaggtc   1260
gtaggctgg                                     1269

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<210> SEQ ID NO 102
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 102

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atggcgctct ggttactgt ggtcattgct ctacactgcc tcggtggcct tgctccccg    60
agccctgtga ctccctcccc aaccctcaag gagctcattg aggagctggt caacatcacc   120
cagaatcagg catccctctg caacggcagc atggtgtgga gctcaacct gaccgcccgc   180
atgtactgag cagctctaga atctctgac aatgtctccg actgcagcgc catccaaagg   240
accagagga tgctgaaagc actgtgctct caaaagcccg cggcagggat ttccagtgaa   300
cgcagccgag acacaaaat tgaagtgatc cagttggtga aaaacctgct cacctatgta   360
aggggagttt atcgccatgg aaatttcaga                                     390

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<210> SEQ ID NO 103
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 103

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```

tctgaaatth ccatggcgat aaactcccct tacataggtg agcaggttth tcaccaactg    60
gatcacttca attttggtgt ctggctgagc ttcaactgaa atccctgccg cgggcttttg   120

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agagcacagt gctttcagca tcctctgggt cctttggatg gcgctgcagt cggagacatt 180
gatcagagat tctagagctg cgcagtacat gccggcggtc aggttgacgc tccacacat 240
gctgccgttg cagagggatg cctgattctg ggtgatggtg accagctcct caatgagctc 300
cttgaggggtt ggggagggag tcacagggct cggggaggca aggccaccga ggcaggtgag 360
agcaatgacc acagtcaacc agagcgccat 390

```

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<210> SEQ ID NO 104
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(330)

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<400> SEQUENCE: 104

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```

agc cct gtg act ccc tcc cca acc ctc aag gag ctc att gag gag ctg 48
Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile Glu Glu Leu
 1 5 10 15
gtc aac atc acc cag aat cag gca tcc ctc tgc aac ggc agc atg gtg 96
Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly Ser Met Val
 20 25 30
tgg agc gtc aac ctg acc gcc ggc atg tac tgc gca gct cta gaa tct 144
Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu Ser
 35 40 45
ctg atc aat gtc tcc gac tgc agc gcc atc caa agg acc cag agg atg 192
Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr Gln Arg Met
 50 55 60
ctg aaa gca ctg tgc tct caa aag ccc gcg gca ggg att tcc agt gaa 240
Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Ile Ser Ser Glu
 65 70 75 80
cgc agc cga gac acc aaa att gaa gtg atc cag ttg gtg aaa aac ctg 288
Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val Lys Asn Leu
 85 90 95
ctc acc tat gta agg gga gtt tat cgc cat gga aat ttc aga 330
Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe Arg
 100 105 110

```

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<210> SEQ ID NO 105
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 105

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```

Ser Pro Val Thr Pro Ser Pro Thr Leu Lys Glu Leu Ile Glu Glu Leu
 1 5 10 15
Val Asn Ile Thr Gln Asn Gln Ala Ser Leu Cys Asn Gly Ser Met Val
 20 25 30
Trp Ser Val Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu Ser
 35 40 45
Leu Ile Asn Val Ser Asp Cys Ser Ala Ile Gln Arg Thr Gln Arg Met
 50 55 60
Leu Lys Ala Leu Cys Ser Gln Lys Pro Ala Ala Gly Ile Ser Ser Glu
 65 70 75 80
Arg Ser Arg Asp Thr Lys Ile Glu Val Ile Gln Leu Val Lys Asn Leu
 85 90 95
Leu Thr Tyr Val Arg Gly Val Tyr Arg His Gly Asn Phe Arg
 100 105 110

```


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<210> SEQ ID NO 106
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 106

tctgaaatth ccatggcgat aaactcccct tacataggtg agcaggthtt tcaccaactg      60
gatcacttca atthttggtgt ctgggctgcg ttcactggaa atccctgccg cgggctthttg    120
agagcacagt gctthtcagca tcctctgggt cctthtggatg gcgctgcagt cggagacatt    180
gatcagagat tctagagctg cgcagttacat gccggcggtc aggttgacgc tccacacat      240
gctgccgtht cagagggatg cctgattctg ggtgatgtht accagctcct caatgagctc      300
cttgaggtht ggggaggag tcacagggt      330

```

```

<210> SEQ ID NO 107
<211> LENGTH: 567
<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(567)

<400> SEQUENCE: 107

atg gcg ctg ccc tct tcc ttc ttg gtg gcc ctg gtg gcg ctg ggc tgc      48
Met Ala Leu Pro Ser Ser Phe Leu Val Ala Leu Val Ala Leu Gly Cys
  1             5             10             15

aac tcc gtc tgc tct ctg ggc tgt gac ctg cct cag acc cac ggc ctg      96
Asn Ser Val Cys Ser Leu Gly Cys Asp Leu Pro Gln Thr His Gly Leu
             20             25             30

ctg aac agg agg gcc ttg acg ctc ctg gga caa atg agg aga ctc cct    144
Leu Asn Arg Arg Ala Leu Thr Leu Leu Gly Gln Met Arg Arg Leu Pro
             35             40             45

gcc agc tcc tgt cag aag gac aga aat gac ttc gcc ttc ccc cag gac    192
Ala Ser Ser Cys Gln Lys Asp Arg Asn Asp Phe Ala Phe Pro Gln Asp
             50             55             60

gtg ttt ggt gga gac cag tcc cac aag gcc caa gcc ctc tcg gtg gtg    240
Val Phe Gly Gly Asp Gln Ser His Lys Ala Gln Ala Leu Ser Val Val
             65             70             75             80

cac gtg acg aac cag aag atc ttc cac ttc ttc tgc aca gag gcg tcc    288
His Val Thr Asn Gln Lys Ile Phe His Phe Phe Cys Thr Glu Ala Ser
             85             90             95

tcg tct gct gct tgg aac acc acc ctc ctg gag gaa ttc tgc acg gga    336
Ser Ser Ala Ala Trp Asn Thr Thr Leu Leu Glu Glu Phe Cys Thr Gly
             100            105            110

ctt gat tgg cag ctg acc cgc ctg gaa gcc tgt gtc atg cag gag gtg    384
Leu Asp Trp Gln Leu Thr Arg Leu Glu Ala Cys Val Met Gln Glu Val
             115            120            125

ggg gag gga gag gct ccc ctc acg aac gag gac tcc atc ctg agg aac    432
Gly Glu Gly Glu Ala Pro Leu Thr Asn Glu Asp Ser Ile Leu Arg Asn
             130            135            140

tac ttc caa aga ctc tcc ctc tac ctg caa gag aag aaa tac agc cct    480
Tyr Phe Gln Arg Leu Ser Leu Tyr Leu Gln Glu Lys Lys Tyr Ser Pro
             145            150            155            160

tgt gcc tgg gag atc gtc aga gca gaa atc atg aga tcc ttg tat tat    528
Cys Ala Trp Glu Ile Val Arg Ala Glu Ile Met Arg Ser Leu Tyr Tyr
             165            170            175

tca tca aca gcc ttg cag aaa aga tta agg agc gag aaa      567
Ser Ser Thr Ala Leu Gln Lys Arg Leu Arg Ser Glu Lys
             180            185

```

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<210> SEQ ID NO 108
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Felis catus

<400> SEQUENCE: 108
Met Ala Leu Pro Ser Ser Phe Leu Val Ala Leu Val Ala Leu Gly Cys
 1             5             10            15
Asn Ser Val Cys Ser Leu Gly Cys Asp Leu Pro Gln Thr His Gly Leu
 20            25            30
Leu Asn Arg Arg Ala Leu Thr Leu Leu Gly Gln Met Arg Arg Leu Pro
 35            40            45
Ala Ser Ser Cys Gln Lys Asp Arg Asn Asp Phe Ala Phe Pro Gln Asp
 50            55            60
Val Phe Gly Gly Asp Gln Ser His Lys Ala Gln Ala Leu Ser Val Val
 65            70            75            80
His Val Thr Asn Gln Lys Ile Phe His Phe Phe Cys Thr Glu Ala Ser
 85            90            95
Ser Ser Ala Ala Trp Asn Thr Thr Leu Leu Glu Glu Phe Cys Thr Gly
 100           105           110
Leu Asp Trp Gln Leu Thr Arg Leu Glu Ala Cys Val Met Gln Glu Val
 115           120           125
Gly Glu Gly Glu Ala Pro Leu Thr Asn Glu Asp Ser Ile Leu Arg Asn
 130           135           140
Tyr Phe Gln Arg Leu Ser Leu Tyr Leu Gln Glu Lys Lys Tyr Ser Pro
 145           150           155           160
Cys Ala Trp Glu Ile Val Arg Ala Glu Ile Met Arg Ser Leu Tyr Tyr
 165           170           175
Ser Ser Thr Ala Leu Gln Lys Arg Leu Arg Ser Glu Lys
 180           185

```

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<210> SEQ ID NO 109
<211> LENGTH: 567
<212> TYPE: DNA
<213> ORGANISM: Felis catus

<400> SEQUENCE: 109
tttctcgctc cttaatcttt tctgcaaggc tgttgatgaa taatacaagg atctcatgat      60
ttctgctctg acgatctccc aggcacaagg gctgtatttc ttctcttgca ggtagaggga      120
gagtctttgg aagtagttcc tcaggatgga gtcctcgttc gtgagggggag cctctccctc      180
ccccacctcc tgcacgacac aggcttccag gcgggtcagc tgccaatcaa gtcccgtgca      240
gaattcctcc aggaggggtg tgttccaagc agcagacgag gacgcctctg tgcagaagaa      300
gtggaagatc ttctggttcg tcacgtgcac caccgagagg gcttgggcct tgtgggactg      360
gtctccacca aacacgtcct gggggaaggc gaagtcattt ctgtccttct gacaggagct      420
ggcagggagt ctcctcattt gtcccaggag cgtcaaggcc ctctgttca gcaggccgtg      480
ggtctgaggc aggtcacagc ccagagagca gacggagttg cagcccagcg ccaccagggc      540
caccaagaag gaagagggca gcgcat                                     567

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<210> SEQ ID NO 110
<211> LENGTH: 567
<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(567)

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<400> SEQUENCE: 110

```

atg gcg ctg ccc tct tcc ttc ttg gtg gcc ctg gtg gcg ctg ggc tgc      48
Met Ala Leu Pro Ser Ser Phe Leu Val Ala Leu Val Ala Leu Gly Cys
  1                    5                    10                    15

aac tcc gtc tgc tct ctg ggc tgt gac ctg cct cag acc cac ggc ctg      96
Asn Ser Val Cys Ser Leu Gly Cys Asp Leu Pro Gln Thr His Gly Leu
                20                    25                    30

ctg aac agg agg gcc ttg acg ctc ctg gga caa atg agg aga ctc cct     144
Leu Asn Arg Arg Ala Leu Thr Leu Leu Gly Gln Met Arg Arg Leu Pro
                35                    40                    45

gcc agc tcc tgt cag aag gac agg aat gac ttc gcc ttc ccc cag gac     192
Ala Ser Ser Cys Gln Lys Asp Arg Asn Asp Phe Ala Phe Pro Gln Asp
                50                    55                    60

gtg ttc ggt gga gac cag tcc cac aag gct caa gcc ctc tcg gtg gtg     240
Val Phe Gly Gly Asp Gln Ser His Lys Ala Gln Ala Leu Ser Val Val
                65                    70                    75                    80

cac gtg acg aac cag gag atc ttc cac ttc ttc tgc aca gag gcg tcc     288
His Val Thr Asn Gln Glu Ile Phe His Phe Phe Cys Thr Glu Ala Ser
                85                    90                    95

tcg tct gct gct tgg aac acc acc ctc ctg gag gaa ttc tgc acg gga     336
Ser Ser Ala Ala Trp Asn Thr Thr Leu Leu Glu Glu Phe Cys Thr Gly
                100                    105                    110

ctt gat cgg cag ctg acc cgc ctg gaa gcc tgt gtc gtg cag gag gtg     384
Leu Asp Arg Gln Leu Thr Arg Leu Glu Ala Cys Val Val Gln Glu Val
                115                    120                    125

ggg gag gga gag gct ccc ctc acg aac gag gac tcc ctc ctg agg aac     432
Gly Glu Gly Glu Ala Pro Leu Thr Asn Glu Asp Ser Leu Leu Arg Asn
                130                    135                    140

tac ttc caa aga ctc tcc ctc tac ctg caa gag aag aaa tac agc cct     480
Tyr Phe Gln Arg Leu Ser Leu Tyr Leu Gln Glu Lys Lys Tyr Ser Pro
                145                    150                    155                    160

tgt gcc tgg gag atc gtc aga gca gaa atc atg aga tcc ttg tat tat     528
Cys Ala Trp Glu Ile Val Arg Ala Glu Ile Met Arg Ser Leu Tyr Tyr
                165                    170                    175

tca tca aca gcc ttg caa aaa aga tta agg agc gag aaa                 567
Ser Ser Thr Ala Leu Gln Lys Arg Leu Arg Ser Glu Lys
                180                    185

```

<210> SEQ ID NO 111

<211> LENGTH: 189

<212> TYPE: PRT

<213> ORGANISM: Felis catus

<400> SEQUENCE: 111

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Met Ala Leu Pro Ser Ser Phe Leu Val Ala Leu Val Ala Leu Gly Cys
  1                    5                    10                    15

Asn Ser Val Cys Ser Leu Gly Cys Asp Leu Pro Gln Thr His Gly Leu
                20                    25                    30

Leu Asn Arg Arg Ala Leu Thr Leu Leu Gly Gln Met Arg Arg Leu Pro
                35                    40                    45

Ala Ser Ser Cys Gln Lys Asp Arg Asn Asp Phe Ala Phe Pro Gln Asp
                50                    55                    60

Val Phe Gly Gly Asp Gln Ser His Lys Ala Gln Ala Leu Ser Val Val
                65                    70                    75                    80

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

Ser Ser Ala Ala Trp Asn Thr Thr Leu Leu Glu Glu Phe Cys Thr Gly
                100                    105                    110

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Leu Asp Arg Gln Leu Thr Arg Leu Glu Ala Cys Val Val Gln Glu Val
 115 120 125

Gly Glu Gly Glu Ala Pro Leu Thr Asn Glu Asp Ser Leu Leu Arg Asn
 130 135 140

Tyr Phe Gln Arg Leu Ser Leu Tyr Leu Gln Glu Lys Lys Tyr Ser Pro
 145 150 155 160

Cys Ala Trp Glu Ile Val Arg Ala Glu Ile Met Arg Ser Leu Tyr Tyr
 165 170 175

Ser Ser Thr Ala Leu Gln Lys Arg Leu Arg Ser Glu Lys
 180 185

<210> SEQ ID NO 112
 <211> LENGTH: 567
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 112

tttctcgctc cttaatcttt ttgcaaggc tgttgatgaa taatacaagg atctcatgat 60
 ttctgctctg acgatctccc aggcacaagg gctgtatttc ttctcttgca ggtagaggga 120
 gagtctttgg aagtagttcc tcaggaggga gtctctgctc gtgaggggag cctctccctc 180
 cccacctcc tgcacgacac aggcttccag gcgggtcagc tgccgatcaa gtcccgtgca 240
 gaattcctcc aggaggggtg tgttccaagc agcagacgag gacgcctctg tgcagaagaa 300
 gtggaagatc tcctggttcg tcacgtgcac caccgagagg gcttgagcct tgtgggactg 360
 gtctccaccg aacacgtcct gggggaaggc gaagtcattc ctgtccttct gacaggagct 420
 ggacaggaggt ctctcattt gtcccaggag cgtcaaggcc ctctgttca gcaggccgtg 480
 ggtctgaggc aggtcacagc ccagagagca gacggagttg cagcccagcg ccaccagggc 540
 caccaagaag gaagagggca gcgcat 567

<210> SEQ ID NO 113
 <211> LENGTH: 498
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(498)

<400> SEQUENCE: 113

tgt gac ctg cct cag acc cac ggc ctg ctg aac agg agg gcc ttg acg 48
 Cys Asp Leu Pro Gln Thr His Gly Leu Leu Asn Arg Arg Ala Leu Thr
 1 5 10 15

ctc ctg gga caa atg agg aga ctc cct gcc agc tcc tgt cag aag gac 96
 Leu Leu Gly Gln Met Arg Arg Leu Pro Ala Ser Ser Cys Gln Lys Asp
 20 25 30

aga aat gac ttc gcc ttc ccc cag gac gtg ttt ggt gga gac cag tcc 144
 Arg Asn Asp Phe Ala Phe Pro Gln Asp Val Phe Gly Gly Asp Gln Ser
 35 40 45

cac aag gcc caa gcc ctc tcg gtg gtg cac gtg acg aac cag aag atc 192
 His Lys Ala Gln Ala Leu Ser Val Val His Val Thr Asn Gln Lys Ile
 50 55 60

ttc cac ttc ttc tgc aca gag gcg tcc tcg tct gct gct tgg aac acc 240
 Phe His Phe Phe Cys Thr Glu Ala Ser Ser Ser Ala Ala Trp Asn Thr
 65 70 75 80

acc ctc ctg gag gaa ttc tgc acg gga ctt gat tgg cag ctg acc cgc 288
 Thr Leu Leu Glu Glu Phe Cys Thr Gly Leu Asp Trp Gln Leu Thr Arg
 85 90 95

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ctg gaa gcc tgt gtc atg cag gag gtg ggg gag gga gag gct ccc ctc	336
Leu Glu Ala Cys Val Met Gln Glu Val Gly Glu Gly Glu Ala Pro Leu	
100 105 110	
acg aac gag gac tcc atc ctg agg aac tac ttc caa aga ctc tcc ctc	384
Thr Asn Glu Asp Ser Ile Leu Arg Asn Tyr Phe Gln Arg Leu Ser Leu	
115 120 125	
tac ctg caa gag aag aaa tac agc cct tgt gcc tgg gag atc gtc aga	432
Tyr Leu Gln Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Ile Val Arg	
130 135 140	
gca gaa atc atg aga tcc ttg tat tat tca tca aca gcc ttg cag aaa	480
Ala Glu Ile Met Arg Ser Leu Tyr Tyr Ser Ser Thr Ala Leu Gln Lys	
145 150 155 160	
aga tta agg agc gag aaa	498
Arg Leu Arg Ser Glu Lys	
165	

<210> SEQ ID NO 114
 <211> LENGTH: 166
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 114

Cys Asp Leu Pro Gln Thr His Gly Leu Leu Asn Arg Arg Ala Leu Thr	
1 5 10 15	
Leu Leu Gly Gln Met Arg Arg Leu Pro Ala Ser Ser Cys Gln Lys Asp	
20 25 30	
Arg Asn Asp Phe Ala Phe Pro Gln Asp Val Phe Gly Gly Asp Gln Ser	
35 40 45	
His Lys Ala Gln Ala Leu Ser Val Val His Val Thr Asn Gln Lys Ile	
50 55 60	
Phe His Phe Phe Cys Thr Glu Ala Ser Ser Ser Ala Ala Trp Asn Thr	
65 70 75 80	
Thr Leu Leu Glu Glu Phe Cys Thr Gly Leu Asp Trp Gln Leu Thr Arg	
85 90 95	
Leu Glu Ala Cys Val Met Gln Glu Val Gly Glu Gly Glu Ala Pro Leu	
100 105 110	
Thr Asn Glu Asp Ser Ile Leu Arg Asn Tyr Phe Gln Arg Leu Ser Leu	
115 120 125	
Tyr Leu Gln Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Ile Val Arg	
130 135 140	
Ala Glu Ile Met Arg Ser Leu Tyr Tyr Ser Ser Thr Ala Leu Gln Lys	
145 150 155 160	
Arg Leu Arg Ser Glu Lys	
165	

<210> SEQ ID NO 115
 <211> LENGTH: 498
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 115

tttctcgctc cttaatcttt tctgcaaggc tgttgatgaa taatacaagg atctcatgat	60
ttctgctctg acgatctccc aggcacaagg gctgtatttc ttctcttgca ggtagagggg	120
gagtctttgg aagtagttcc tcaggatgga gtcctcgttc gtgagggggag cctctccctc	180
ccccacctcc tgcatgacac aggcttccag gcgggtcagc tgccaatcaa gtcccgtgca	240
gaattcctcc aggaggggtg tgttccaagc agcagacgag gacgcctctg tgcagaagaa	300

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gtggaagatc ttctggttcg tcacgtgcac caccgagagg gcttgggcct tgtgggactg 360
gtctccacca aacacgtcct gggggaaggc gaagtcattt ctgtccttct gacaggagct 420
ggcagggagt ctctcattt gtcccaggag cgtcaaggcc ctctgttca gcaggccgtg 480
ggtctgaggc aggtcaca 498

```

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<210> SEQ ID NO 116
<211> LENGTH: 498
<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(498)

```

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<400> SEQUENCE: 116

```

```

tgt gac ctg cct cag acc cac ggc ctg ctg aac agg agg gcc ttg acg 48
Cys Asp Leu Pro Gln Thr His Gly Leu Leu Asn Arg Arg Ala Leu Thr
  1 5 10 15
ctc ctg gga caa atg agg aga ctc cct gcc agc tcc tgt cag aag gac 96
Leu Leu Gly Gln Met Arg Arg Leu Pro Ala Ser Ser Cys Gln Lys Asp
  20 25 30
agg aat gac ttc gcc ttc ccc cag gac gtg ttc ggt gga gac cag tcc 144
Arg Asn Asp Phe Ala Phe Pro Gln Asp Val Phe Gly Gly Asp Gln Ser
  35 40 45
cac aag gct caa gcc ctc tcg gtg gtg cac gtg acg aac cag gag atc 192
His Lys Ala Gln Ala Leu Ser Val Val His Val Thr Asn Gln Glu Ile
  50 55 60
ttc cac ttc ttc tgc aca gag gcg tcc tcg tct gct gct tgg aac acc 240
Phe His Phe Phe Cys Thr Glu Ala Ser Ser Ser Ala Ala Trp Asn Thr
  65 70 75 80
acc ctc ctg gag gaa ttc tgc acg gga ctt gat cgg cag ctg acc cgc 288
Thr Leu Leu Glu Glu Phe Cys Thr Gly Leu Asp Arg Gln Leu Thr Arg
  85 90 95
ctg gaa gcc tgt gtc gtg cag gag gtg ggg gag gga gag gct ccc ctc 336
Leu Glu Ala Cys Val Val Gln Glu Val Gly Glu Gly Glu Ala Pro Leu
  100 105 110
acg aac gag gac tcc ctc ctg agg aac tac ttc caa aga ctc tcc ctc 384
Thr Asn Glu Asp Ser Leu Leu Arg Asn Tyr Phe Gln Arg Leu Ser Leu
  115 120 125
tac ctg caa gag aag aaa tac agc cct tgt gcc tgg gag atc gtc aga 432
Tyr Leu Gln Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Ile Val Arg
  130 135 140
gca gaa atc atg aga tcc ttg tat tat tca tca aca gcc ttg caa aaa 480
Ala Glu Ile Met Arg Ser Leu Tyr Tyr Ser Ser Thr Ala Leu Gln Lys
  145 150 155 160
aga tta agg agc gag aaa 498
Arg Leu Arg Ser Glu Lys
  165

```

```

<210> SEQ ID NO 117
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Felis catus

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<400> SEQUENCE: 117

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```

Cys Asp Leu Pro Gln Thr His Gly Leu Leu Asn Arg Arg Ala Leu Thr
  1 5 10 15
Leu Leu Gly Gln Met Arg Arg Leu Pro Ala Ser Ser Cys Gln Lys Asp
  20 25 30
Arg Asn Asp Phe Ala Phe Pro Gln Asp Val Phe Gly Gly Asp Gln Ser
  35 40 45

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Met	Phe	Asp	Pro	Glu	Glu	Pro	Lys	Cys	Leu	Gln	Thr	His	Leu	Lys	Leu		
		65					70					75					
tac	gag	cag	ggc	cta	cgg	ggc	agc	ctc	atc	agc	ctc	aag	gag	cct	ctg		291
Tyr	Glu	Gln	Gly	Leu	Arg	Gly	Ser	Leu	Ile	Ser	Leu	Lys	Glu	Pro	Leu		
	80					85					90						
aga	atg	atg	gcc	aac	cat	tac	aag	cag	cac	tgc	ccc	ctt	act	ccg	gaa		339
Arg	Met	Met	Ala	Asn	His	Tyr	Lys	Gln	His	Cys	Pro	Leu	Thr	Pro	Glu		
	95				100					105					110		
acg	ccc	tgt	gaa	acc	cag	act	atc	acc	ttc	aaa	aat	ttc	aaa	gag	aat		387
Thr	Pro	Cys	Glu	Thr	Gln	Thr	Ile	Thr	Phe	Lys	Asn	Phe	Lys	Glu	Asn		
				115					120					125			
ctg	aag	gat	ttt	ctg	ttt	aac	aac	ccc	ttt	gac	tgc	tgg	gga	cca	gac		435
Leu	Lys	Asp	Phe	Leu	Phe	Asn	Asn	Pro	Phe	Asp	Cys	Trp	Gly	Pro	Asp		
			130					135					140				
cag	aag	taa															444
Gln	Lys																

<210> SEQ ID NO 120
 <211> LENGTH: 144
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 120

Met	Trp	Leu	Gln	Asn	Leu	Leu	Phe	Leu	Gly	Thr	Val	Val	Cys	Ser	Ile		
1				5					10					15			
Ser	Ala	Pro	Thr	Ser	Ser	Pro	Ser	Ser	Val	Thr	Arg	Pro	Trp	Gln	His		
			20					25					30				
Val	Asp	Ala	Ile	Lys	Glu	Ala	Leu	Ser	Leu	Leu	Asn	Asn	Ser	Ser	Glu		
		35					40					45					
Ile	Thr	Ala	Val	Met	Asn	Glu	Ala	Val	Glu	Val	Val	Ser	Glu	Met	Phe		
	50					55					60						
Asp	Pro	Glu	Glu	Pro	Lys	Cys	Leu	Gln	Thr	His	Leu	Lys	Leu	Tyr	Glu		
	65				70					75					80		
Gln	Gly	Leu	Arg	Gly	Ser	Leu	Ile	Ser	Leu	Lys	Glu	Pro	Leu	Arg	Met		
				85					90						95		
Met	Ala	Asn	His	Tyr	Lys	Gln	His	Cys	Pro	Leu	Thr	Pro	Glu	Thr	Pro		
			100					105					110				
Cys	Glu	Thr	Gln	Thr	Ile	Thr	Phe	Lys	Asn	Phe	Lys	Glu	Asn	Leu	Lys		
		115					120					125					
Asp	Phe	Leu	Phe	Asn	Asn	Pro	Phe	Asp	Cys	Trp	Gly	Pro	Asp	Gln	Lys		
	130					135					140						

<210> SEQ ID NO 121
 <211> LENGTH: 444
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 121

ttacttctgg	tctggtccc	agcagtcaaa	ggggttgta	aacagaaaat	ccttcagatt		60
ctctttgaaa	ttttgaagg	tgatagtctg	ggtttcacag	ggcgtttccg	gagtaagggg		120
gcagtgtgc	ttgtaatggt	tggccatcat	tctcagaggc	tccttgaggc	tgatgaggct		180
gccccgtagg	ccctgctcgt	acagcttttag	gtgagtctgc	aggcatttcg	gctcctcagg		240
gtcaaacatt	tcagagacga	cttctactgc	ttcattcatc	acagcagtta	tttactact		300
gttgttcaga	aggctcagg	cctccttgat	ggcatccacg	tgttgccagg	gccgagtgac		360
agagctgggt	gaactggtgg	gtgcagagat	gctgcagacc	acagtgccca	ggaaaagcag		420

-continued

 gttctgcagc cacatggtgg atcc 444

<210> SEQ ID NO 122
 <211> LENGTH: 432
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 122

atgtggctgc agaacctgct tttcctgggc actgtggtct gcagcatctc tgcaccacc 60
 agttcaccca gctctgtcac tcggccctgg caacacgtgg atgcatcaa ggaggccctg 120
 agccttctga acaacagtag tgaaataact gctgtgatga atgaagcagt agaagtcgtc 180
 tctgaaatgt ttgaccctga ggagccgaaa tgcctgcaga ctacctaata gctgtacgag 240
 cagggcctac ggggcagcct catcagcctc aaggagcctc tgagaatgat ggccaacat 300
 tacaagcagc actgccccct tactccgaa acgccctgtg aaaccagac tatcaccttc 360
 aaaaatttca aagagaatct gaaggatttt ctgtttaaca acccctttga ctgctgggga 420
 ccagaccaga ag 432

<210> SEQ ID NO 123
 <211> LENGTH: 432
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 123

cttctggtct ggtccccagc agtcaaagg gttgttaaac agaaaatcct tcagattctc 60
 ttgaaattt ttgaagggtga tagtctgggt ttcacagggc gtttccggag taagggggca 120
 gtgctgcttg taatggttg ccatcattct cagaggctcc ttgaggctga tgaggctgcc 180
 ccgtaggccc tgctcgtaca gctttagggt agtctgcagg catttcggct cctcagggtc 240
 aacatttca gagacgactt ctactgcttc attcatcaca gcagttattt cactactggt 300
 gttcagaagg ctgaggcct ccttgatggc atccacgtgt tgccagggcc gagtgacaga 360
 gctgggtgaa ctgggtgggtg cagagatgct gcagaccaca gtgcccagga aaagcagggt 420
 ctgcagccac at 432

<210> SEQ ID NO 124
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(381)

<400> SEQUENCE: 124

gca ccc acc agt tca ccc agc tct gtc act cgg ccc tgg caa cac gtg 48
 Ala Pro Thr Ser Ser Pro Ser Ser Val Thr Arg Pro Trp Gln His Val
 1 5 10 15
 gat gcc atc aag gag gcc ctg agc ctt ctg aac aac agt agt gaa ata 96
 Asp Ala Ile Lys Glu Ala Leu Ser Leu Leu Asn Asn Ser Ser Glu Ile
 20 25 30
 act gct gtg atg aat gaa gca gta gaa gtc gtc tct gaa atg ttt gac 144
 Thr Ala Val Met Asn Glu Ala Val Glu Val Val Ser Glu Met Phe Asp
 35 40 45
 cct gag gag ccg aaa tgc ctg cag act cac cta aag ctg tac gag cag 192
 Pro Glu Glu Pro Lys Cys Leu Gln Thr His Leu Lys Leu Tyr Glu Gln
 50 55 60
 ggc cta cgg ggc agc ctc atc agc ctc aag gag cct ctg aga atg atg 240
 Gly Leu Arg Gly Ser Leu Ile Ser Leu Lys Glu Pro Leu Arg Met Met

-continued

65	70	75	80	
gcc aac cat tac aag cag cac tgc ccc ctt act ccg gaa acg ccc tgt				288
Ala Asn His Tyr Lys Gln His Cys Pro Leu Thr Pro Glu Thr Pro Cys	85	90	95	
gaa acc cag act atc acc ttc aaa aat ttc aaa gag aat ctg aag gat				336
Glu Thr Gln Thr Ile Thr Phe Lys Asn Phe Lys Glu Asn Leu Lys Asp	100	105	110	
ttt ctg ttt aac aac ccc ttt gac tgc tgg gga cca gac cag aag				381
Phe Leu Phe Asn Asn Pro Phe Asp Cys Trp Gly Pro Asp Gln Lys	115	120	125	

<210> SEQ ID NO 125
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 125

Ala Pro Thr Ser Ser Pro Ser Ser Val Thr Arg Pro Trp Gln His Val	1	5	10	15
Asp Ala Ile Lys Glu Ala Leu Ser Leu Leu Asn Asn Ser Ser Glu Ile	20	25	30	
Thr Ala Val Met Asn Glu Ala Val Glu Val Val Ser Glu Met Phe Asp	35	40	45	
Pro Glu Glu Pro Lys Cys Leu Gln Thr His Leu Lys Leu Tyr Glu Gln	50	55	60	
Gly Leu Arg Gly Ser Leu Ile Ser Leu Lys Glu Pro Leu Arg Met Met	65	70	75	80
Ala Asn His Tyr Lys Gln His Cys Pro Leu Thr Pro Glu Thr Pro Cys	85	90	95	
Glu Thr Gln Thr Ile Thr Phe Lys Asn Phe Lys Glu Asn Leu Lys Asp	100	105	110	
Phe Leu Phe Asn Asn Pro Phe Asp Cys Trp Gly Pro Asp Gln Lys	115	120	125	

<210> SEQ ID NO 126
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Felis catus

<400> SEQUENCE: 126

cttctggtct ggtccccagc agtcaaaggg gttgttaaac agaaaatcct tcagattctc	60
tttgaatttt ttgaagtg tagtctgggt ttcacagggc gtttccggag taagggggca	120
gtgctgcttg taatggttg ccatcattct cagaggctcc ttgaggctga tgaggctgcc	180
ccgtaggccc tgctcgtaca gctttaggtg agtctgcagg catttcggct cctcagggtc	240
aaacatttca gagacgactt ctactgcttc attcatcaca gcagttattt cactactggt	300
gttcagaagg ctcaggcct ccttgatggc atccacgtgt tgccagggcc gaggtagaca	360
gctgggtgaa ctggtgggtg c	381

<210> SEQ ID NO 127
 <211> LENGTH: 28
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 127

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cctcgagatt cagctttcaa tgcttgta 28

<210> SEQ ID NO 128
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 128

tgcccrstcg gcttcttctc c 21

<210> SEQ ID NO 129
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 129

cgactctctt trcrtcctc ctg 23

<210> SEQ ID NO 130
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 130

cctcaaattg cggcacatgt c 21

<210> SEQ ID NO 131
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 131

ctgttcagag tttgagtaag cc 22

<210> SEQ ID NO 132
 <211> LENGTH: 28
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 132

gaagatacca tttcaacttt aacacagc 28

<210> SEQ ID NO 133
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

<400> SEQUENCE: 133

tgctgtattg tgaagactcc cagc 24

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<210> SEQ ID NO 134
 <211> LENGTH: 16
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 134

 atgcactttc tttgcc 16

<210> SEQ ID NO 135
 <211> LENGTH: 42
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 135

 ctggaggaaa akacttcrat gattctgata tctgaaatat at 42

<210> SEQ ID NO 136
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 136

 ctgacycttk sttgscctc attctca 27

<210> SEQ ID NO 137
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 137

 gggctcgaga aaagatttgc tgtagaaaat cccatg 36

<210> SEQ ID NO 138
 <211> LENGTH: 32
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 138

 cccgcggccg ctcaactttc cgggtgtccac tc 32

<210> SEQ ID NO 139
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 139

 gtcmtggctc tyrcttgctt tgg 23

-continued

<210> SEQ ID NO 140
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 140

aaastgggcy acytcgattt tgg 23

<210> SEQ ID NO 141
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 141

gtgatggtgm ycagctcctc 20

<210> SEQ ID NO 142
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 142

aattaaccct cactaaaggg 20

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 143

atggcgctct ggttgactgt 20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 144

ggcttttgag agcacagtgc 20

<210> SEQ ID NO 145
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Primer

<400> SEQUENCE: 145

ccccatatga gccctgtgac tccctcccc 29

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<210> SEQ ID NO 146
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 146

 ggggaattct catctgaaat ttccatggcg 30

<210> SEQ ID NO 147
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 147

 atggcgctgc cctcttcctt cttg 24

<210> SEQ ID NO 148
 <211> LENGTH: 28
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 148

 tcatttctcg ctccttaatc ttttctgc 28

<210> SEQ ID NO 149
 <211> LENGTH: 37
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 149

 cagggatcca ccatgtggct gcagaacctg cttttcc 37

<210> SEQ ID NO 150
 <211> LENGTH: 50
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 150

 ttactttctgg tctggtcccc agcagtcaaa ggggttgta aacagaaaat 50

<210> SEQ ID NO 151
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Primer

 <400> SEQUENCE: 151

 cacagyccca tctcctcc 18

<210> SEQ ID NO 152

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<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    Primer

<400> SEQUENCE: 152

gtaatacgac tcactatagg gc                                22

<210> SEQ ID NO 153
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    Primer

<400> SEQUENCE: 153

acggaattcg agatgatagt gctggc                            26

<210> SEQ ID NO 154
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    Primer

<400> SEQUENCE: 154

gtgtctagat ttggtagaaa aggatgat                          28

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What is claimed is:

1. An isolated protein selected from the group consisting of:

(a) an isolated protein of at least about 20 amino acids in length, wherein said 20 amino acids are encoded by a nucleic acid molecule that has at least 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, and SEQ ID NO:19; and

(b) an isolated protein of at least about 20 amino acids in length, wherein said protein has an at least 20 contiguous amino acid region identical in sequence to a 20 contiguous amino acid region selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:20,

wherein said isolated protein of (a) or (b) elicits an immune response against a canine IL-4 protein or has IL-4 activity.

2. The isolated protein of claim 1, wherein said protein has an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:20.

3. The isolated protein of claim 2, wherein the protein has the amino acid sequence of SEQ ID NO:2.

35 4. The isolated protein of claim 2, wherein the protein has the amino acid sequence of SEQ ID NO:20.

5. An isolated protein having an amino acid sequence that is at least about 85 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:20, wherein said isolated protein elicits and immune response against a canine IL-4 protein or has IL-4 activity.

40 6. A therapeutic composition comprising the isolated protein of claim 1.

7. The composition of claim 6, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.

50 8. A method to regulate an immune response in an animal comprising administering to the animal the therapeutic composition of claim 6.

9. The method of claim 8, wherein said animal is a canid.

55 10. The method of claim 8, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.

* * * * *