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(54) Title: TRANSGENIC MAMMALS AND METHODS OF USE

(57) Abstract: Transgenic mammals that express canine-based im-
munoglobulins are described herein, including transgenic rodents
that express canine-based immunoglobulins for the development of
canine therapeutic antibodies.

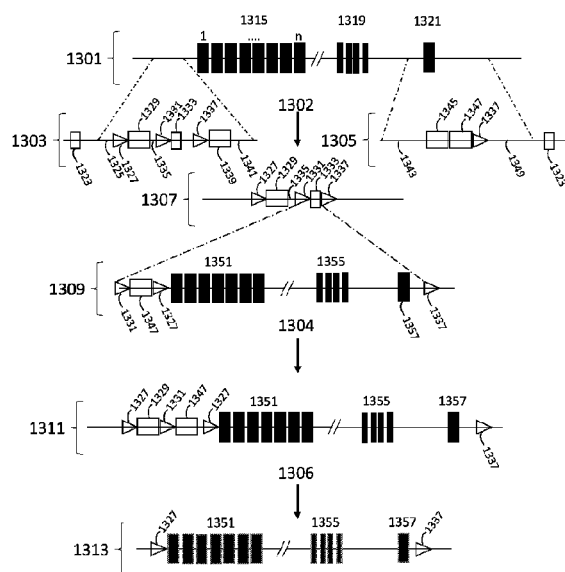


FIG. 13

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- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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TRANSGENIC MAMMALS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/869,435, filed July 1, 2019, the disclosure of which is incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 24, 2020, is named 0133-0006WO1_SL.txt and is 219,066 bytes in size.

FIELD OF THE INVENTION

[0003] This invention relates to production of immunoglobulin molecules, including methods for generating transgenic mammals capable of producing canine antigen-specific antibody-secreting cells for the generation of monoclonal antibodies.

BACKGROUND

[0004] In the following discussion certain articles and methods are described for background and introductory purposes. Nothing contained herein is to be construed as an “admission” of prior art. Applicant expressly reserves the right to demonstrate, where appropriate, that the articles and methods referenced herein do not constitute prior art under the applicable statutory provisions.

[0005] Antibodies have emerged as important biological pharmaceuticals because they (i) exhibit exquisite binding properties that can target antigens of diverse molecular forms, (ii) are physiological molecules with desirable pharmacokinetics that make them well tolerated in treated humans and animals, and (iii) are associated with powerful immunological properties that naturally ward off infectious agents. Furthermore, established technologies exist for the rapid isolation of antibodies from laboratory animals, which can readily mount a specific antibody response against virtually any foreign substance not present natively in the body.

- [0006] In their most elemental form, antibodies are composed of two identical heavy (H) chains that are each paired with an identical light (L) chain. The N-termini of both H and L chains includes a variable domain (V_H and V_L , respectively) that together provide the paired H-L chains with a unique antigen-binding specificity.
- [0007] The exons that encode the antibody V_H and V_L domains do not exist in the germ-line DNA. Instead, each V_H exon is generated by the recombination of randomly selected V_H , D, and J_H gene segments present in the immunoglobulin H chain locus (IGH); likewise, individual V_L exons are produced by the chromosomal rearrangements of randomly selected V_L and J_L gene segments in a light chain locus.
- [0008] The canine genome contains two alleles that can express the H chain (one allele from each parent), two alleles that can express the kappa (κ) L chain, and two alleles that can express the lambda (λ) L chain. There are multiple V_H , D, and J_H gene segments at the H chain locus as well as multiple V_L and J_L gene segments at both the immunoglobulin κ (IGK) and immunoglobulin λ (IGL) L chain loci (Collins and Watson (2018) Immunoglobulin Light Chain Gene Rearrangements, Receptor Editing and the Development of a Self-Tolerant Antibody Repertoire. *Front. Immunol.* 9:2249. (doi: 10.3389/fimmu.2018.02249)).
- [0009] In a typical immunoglobulin heavy chain variable region locus, V_H gene segments lie upstream (5') of J_H gene segments, with D gene segments located between the V_H and J_H gene segments. Downstream (3') of the J_H gene segments of the IGH locus are clusters of exons that encode the constant region (C_H) of the antibody. Each cluster of C_H exons encodes a different antibody class (isotype). Eight classes of antibody exist in mouse: IgM, IgD, IgG3, IgG1, IgG2a (or IgG2c), IgG2b, IgE, and IgA (at the nucleic acid level, they are respectively referred to as: μ , δ , $\gamma 3$, $\gamma 1$, $\gamma 2a/c$, $\gamma 2b$, ϵ , and α). In canine animals (e.g., the domestic dog and wolf), the putative isotypes are IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgE, and IgA (Fig. 12A).
- [00010] At the IGK locus of most mammalian species, a cluster of V_κ gene segments are located upstream of a small number of J_κ gene segments, with the J_κ gene segment cluster located upstream of a single C_κ gene. This organization of the κ locus can be represented as $(V_\kappa)_a \dots (J_\kappa)_b \dots C_\kappa$, wherein a and b, independently, are an integer of 1 or more. The dog κ locus is unusual in that half the V_κ genes are located upstream, and half are located

downstream of the J_{κ} and C_{κ} gene segments (see schematics of the mouse IGK locus in FIG. 1C and dog IGK locus in FIG. 12C).

[00011] The IGL locus of most species includes a set of V_{λ} gene segments that are located 5' to a variable number of J-C tandem cassettes, each made up of a J_{λ} gene segment and a C_{λ} gene segment (see schematic of the canine IGL locus in FIG. 12B). The organization of the λ locus can be represented as $(V_{\lambda})_a \dots (J_{\lambda}-C_{\lambda})_b$, wherein a and b are, independently, an integer of 1 or more. The mouse IGL locus is unusual in that it contains two units of $(V_{\lambda})_a \dots (J_{\lambda}-C_{\lambda})_b$.

[00012] During B cell development, gene rearrangements occur first on one of the two homologous chromosomes that contain the H chain variable gene segments. The resultant V_H exon is then spliced at the RNA level to the C_{μ} exons for IgM H chain expression. Subsequently, the V_L-J_L rearrangements occur on one L chain allele at a time until a functional L chain is produced, after which the L chain polypeptides can associate with the IgM H chain homodimers to form a fully functional B cell receptor (BCR) for antigen. In mouse and human, as B cells continue to mature, IgD is co-expressed with IgM as alternatively spliced forms, with IgD being expressed at a level 10 times higher than IgM in the main B cell population. This contrasts with B cell development in the dog, in which the C_{δ} exons are likely to be nonfunctional.

[00013] It is widely accepted by experts in the field that in mouse and human, V_L-J_L rearrangements first occur at the IGK locus on both chromosomes before the IGL light chain locus on either chromosome becomes receptive for V_L-J_L recombination. This is supported by the observation that in mouse B cells that express κ light chains, the λ locus on both chromosomes is usually inactivated by non-productive rearrangements. This may explain the predominant κ L chain usage in mouse, which is >90% κ and <10% λ .

[00014] However, immunoglobulins in the dog immune system are dominated by λ light chain usage, which has been estimated to be at least 90% λ to <10% κ . It is not known mechanistically whether $V_{\kappa}-J_{\kappa}$ rearrangements preferentially occur first over $V_{\lambda}-J_{\lambda}$ rearrangements in canines.

[00015] Upon encountering an antigen, the B cell may undergo another round of DNA recombination at the IGH locus to remove the C_{μ} and C_{δ} exons, effectively switching the

C_H region to one of the downstream isotypes (this process is called class switching). In the dog, although cDNA clones identified as encoding canine IgG1-IgG4 have been isolated (Tang, et al. (2001) Cloning and characterization of cDNAs encoding four different canine immunoglobulin γ chains. Vet. Immunol. and Immunopath. 80:259 PMID 11457479), only the IgG2 constant region gene has been physically mapped to the canine IGH locus on chromosome 8 (Martin, et al. (2018) Comprehensive annotation and evolutionary insights into the canine (*Canis lupus familiaris*) antigen receptor loci. Immunogenet. 70:223 doi: 10.1007/s00251-017-1028-0).

[00016] The genes encoding various canine and mouse immunoglobulins have been extensively characterized. Priat, et al., describe whole-genome radiation mapping of the dog genome in Genomics, 54:361-78 (1998), and Bao, et al., describe the molecular characterization of the V_H repertoire in *Canis familiaris* in Veterinary Immunology and Immunopathology, 137:64-75 (2010). Martin et al. provide an annotation of the canine (*Canis lupus familiaris*) immunoglobulin kappa and lambda (IGK, IGL) loci, and an update to the annotation of the IGH locus in Immunogenetics, 70(4):223-236 (2018).

[00017] Blankenstein and Krawinkel describe the mouse variable heavy chain region locus in Eur. J. Immunol., 17:1351-1357 (1987). Transgenic animals are routinely used in various research and development applications. For example, the generation of transgenic mice containing immunoglobulin genes is described in International Application WO 90/10077 and WO 90/04036. WO 90/04036 describes a transgenic mouse with an integrated human immunoglobulin "mini" locus. WO 90/10077 describes a vector containing the immunoglobulin dominant control region for use in generating transgenic animals.

[00018] Numerous methods have been developed for modifying the mouse endogenous immunoglobulin variable region gene locus with, e.g., human immunoglobulin sequences to create partly or fully human antibodies for drug discovery purposes. Examples of such mice include those described in, e.g., U.S. Pat. Nos. 7,145,056; 7,064,244; 7,041,871; 6,673,986; 6,596,541; 6,570,061; 6,162,963; 6,130,364; 6,091,001; 6,023,010; 5,593,598; 5,877,397; 5,874,299; 5,814,318; 5,789,650; 5,661,016; 5,612,205; and 5,591,669. However, many of the fully humanized immunoglobulin transgenic mice exhibit suboptimal antibody production because B cell development in these mice is severely

hampered by inefficient V(D)J recombination, and by inability of the fully human antibodies/BCRs to function optimally with mouse signaling proteins. Other humanized immunoglobulin transgenic mice, in which the mouse coding sequences have been "swapped" with human sequences, are very time consuming and expensive to create due to the approach of replacing individual mouse exons with the syntenic human counterpart.

[00019] The use of antibodies that function as drugs is not limited to the prevention or therapy of human disease. Companion animals such as dogs suffer from some of the same afflictions as humans, e.g., cancer, atopic dermatitis and chronic pain. Monoclonal antibodies targeting IL31, CD20, IgE and Nerve Growth Factor, respectively, are already in veterinary use as for treatment of these conditions. However, before clinical use these monoclonal antibodies, which were made in mice, had to be caninized, i.e., their amino acid sequence had to be changed from mouse to dog, in order to prevent an immune response in the recipient dogs. Importantly, due to immunological tolerance, canine antibodies to canine proteins cannot be easily raised in dogs. Based on the foregoing, it is clear that a need exists for efficient and cost-effective methods to produce canine antibodies for the treatment of diseases in dogs. More particularly, there is a need in the art for small, rapidly breeding, non-canine mammals capable of producing antigen-specific canine immunoglobulins. Such non-canine mammals are useful for generating hybridomas capable of large-scale production of canine monoclonal antibodies.

[00020] PCT Publication No. 2018/189520 describes rodents and cells with a genome that is engineered to express exogenous animal immunoglobulin variable region genes from companion animals such as dogs, cats, horses, birds, rabbits, goats, reptiles, fish and amphibians.

[00021] However, there still remains a need for improved methods for generating transgenic nonhuman animals which are capable of producing an antibody with canine V regions.

SUMMARY

[00022] This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify key or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter. Other features, details, utilities, and

advantages of the claimed subject matter will be apparent from the following written Detailed Description including those aspects illustrated in the accompanying drawings and defined in the appended claims.

[00023] Described herein is a non-canine mammalian cell and a non-canine mammal having a genome comprising an exogenously introduced partly canine immunoglobulin locus, where the introduced locus comprises coding sequences of the canine immunoglobulin variable region gene segments and non-coding sequences based on the endogenous immunoglobulin variable region locus of the non-canine mammalian host. Thus, the non-canine mammalian cell or mammal is capable of expressing a chimeric B cell receptor (BCR) or antibody comprising H and L chain variable regions that are fully canine in conjunction with the respective constant regions that are native to the non-canine mammalian host cell or mammal. Preferably, the transgenic cells and animals have genomes in which part or all of the endogenous immunoglobulin variable region gene locus is removed.

[00024] At a minimum, the production of chimeric canine monoclonal antibodies in a non-canine mammalian host requires the host to have at least one locus that expresses chimeric canine immunoglobulin H or L chain. In most aspects, there are one heavy chain locus and two light chain loci that, respectively, express chimeric canine immunoglobulin H and L chains.

[00025] In some aspects, the partly canine immunoglobulin locus comprises canine V_H coding sequences and non-coding regulatory or scaffold sequences present in the endogenous V_H gene locus of the non-canine mammalian host. In these aspects, the partly canine immunoglobulin locus further comprises canine D and J_H gene segment coding sequences in conjunction with the non-coding regulatory or scaffold sequences present in the vicinity of the endogenous D and J_H gene segments of the non-canine mammalian host cell genome. In one aspect, the partly canine immunoglobulin locus comprises canine V_H , D and J_H gene segment coding sequences embedded in non-coding regulatory or scaffold sequences present in an endogenous immunoglobulin heavy chain locus of the non-canine mammalian host. In one aspect, the partly canine immunoglobulin locus comprises canine V_H , D and J_H gene segment coding sequences embedded in non-coding regulatory or scaffold sequences present in an endogenous immunoglobulin heavy chain locus of a

rodent, such as a mouse. In other aspects, the partly canine immunoglobulin locus comprises canine V_L coding sequences and non-coding regulatory or scaffold sequences present in the endogenous V_L gene locus of the non-canine mammalian host. In one aspect, the exogenously introduced, partly canine immunoglobulin locus comprising canine V_L coding sequences further comprises canine L-chain J gene segment coding sequences and non-coding regulatory or scaffold sequences present in the vicinity of the endogenous L-chain J gene segments of the non-canine mammalian host cell genome. In one aspect, the partly canine immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences embedded in non-coding regulatory or scaffold sequences of an immunoglobulin light chain locus in the non-canine mammalian host cell. In one aspect, the partly canine immunoglobulin locus comprises canine V_κ and J_κ gene segment coding sequences embedded in non-coding regulatory or scaffold sequences of an immunoglobulin locus of the non-canine mammalian host. In one aspect, the endogenous κ locus of the non-canine mammalian host is inactivated or replaced by sequences encoding canine λ chain, to increase production of canine λ immunoglobulin light chain over canine κ chain. In one aspect, the endogenous κ locus of the non-canine mammalian host is inactivated but not replaced by sequences encoding canine λ chain.

[00026] In certain aspects, the non-canine mammal is a rodent, for example, a mouse or rat.

[00027] In one aspect, the engineered immunoglobulin locus includes a partly canine immunoglobulin light chain locus that includes one or more canine λ variable region gene segment coding sequences. In one aspect, the engineered immunoglobulin locus is a partly canine immunoglobulin light chain locus that includes one or more canine κ variable region gene segment coding sequences.

[00028] In one aspect, a transgenic rodent or rodent cell is provided that has a genome comprising an engineered partly canine immunoglobulin locus. In one aspect, a transgenic rodent or rodent cell is provided that has a genome comprising an engineered partly canine immunoglobulin light chain locus. In one aspect, the partly canine immunoglobulin light chain locus of the rodent or rodent cell includes one or more canine immunoglobulin λ variable region gene segment coding sequences. In one aspect, the partly canine immunoglobulin light chain locus of the rodent or rodent cell includes one or more canine immunoglobulin κ variable region gene segment coding sequences. In one aspect, the

engineered immunoglobulin locus is capable of expressing immunoglobulin comprising canine variable domains.

[00029] In one aspect, a transgenic rodent that produces more immunoglobulin comprising λ light chain than immunoglobulin comprising κ light chain is provided. In one aspect, the transgenic rodent produces at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% and up to about 100% λ light chain immunoglobulin. In one aspect, the transgenic rodent produces at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% and up to about 100% λ light chain immunoglobulin comprising a canine variable domain. In one aspect, more λ light chain-producing cells than κ light chain-producing cells are likely to be isolated from the transgenic rodent. In one aspect, more cells producing λ light chain with a canine variable domain are likely to be isolated from the transgenic rodent than cells producing κ light chain with a canine variable domain.

[00030] In one aspect, a transgenic rodent cell is provided that is more likely to produce immunoglobulin comprising λ light chain than immunoglobulin comprising κ light chain. In one aspect, the rodent cell is isolated from a transgenic rodent described herein. In one aspect, the rodent cell is recombinantly produced as described herein. In one aspect, the transgenic rodent cell or its progeny, has at least about a 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% and up to about 100%, probability of producing λ light chain immunoglobulin. In one aspect, the transgenic rodent cell or its progeny, has at least about about a 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, and up to about 100%, probability of producing λ light chain immunoglobulin with a canine variable domain

[00031] In one aspect, the engineered partly canine immunoglobulin locus comprises canine V_λ gene segment coding sequences and J_λ gene segment coding sequences and non-coding sequences such as regulatory or scaffold sequences of a rodent immunoglobulin light chain variable region gene locus.

[00032] In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment

coding sequences embedded in non-coding regulatory or scaffold sequences of the rodent immunoglobulin κ light chain variable region gene locus. In one aspect, the partly canine immunoglobulin locus comprises one or more canine V_λ gene segment coding sequences and J_λ gene segment coding sequences and one or more rodent immunoglobulin λ constant region coding sequences.

[00033] In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent region C_λ coding sequence. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent C_λ region coding and non-coding sequences. In one aspect, the rodent C_λ region coding sequence is selected from a rodent $C_{\lambda 1}$, $C_{\lambda 2}$ or $C_{\lambda 3}$ coding sequence. In one aspect, one or more canine V_λ gene segment coding sequences are located upstream of one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ gene segment coding sequence. In one aspect, one or more canine V_λ gene segment coding sequences are located upstream of one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ gene segment coding sequence and rodent C_λ non-coding sequences. In one aspect, the J-C units comprise canine J_λ gene segment coding sequences and rodent C_λ region coding sequences embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus.

[00034] In one aspect, a transgenic rodent or rodent cell is provided with an engineered immunoglobulin locus that includes a rodent immunoglobulin κ locus in which one or more rodent V_κ gene segment coding sequences and one or more rodent J_κ gene segment coding sequences have been deleted and replaced with one or more canine V_λ gene segment coding sequences and one or more J_λ gene segment coding sequences, respectively, and in which rodent C_κ coding sequence in the locus has been replaced by rodent $C_{\lambda 1}$, $C_{\lambda 2}$, or $C_{\lambda 3}$ coding sequence(s).

[00035] In one aspect, the engineered immunoglobulin locus includes one or more canine V_λ gene segment coding sequences upstream and in the same transcriptional orientation as

one or more canine J_λ gene segment coding sequences which are upstream of one or more rodent C_λ coding sequences.

[00036] In one aspect, the engineered immunoglobulin locus includes one or more canine V_λ gene segment coding sequences upstream and in the opposite transcriptional orientation as one or more canine J_λ gene segment coding sequences which are upstream of one or more rodent C_λ coding sequences.

[00037] In one aspect, a transgenic rodent or rodent cell is provided in which an endogenous rodent immunoglobulin κ light chain locus is deleted, inactivated, or made nonfunctional by one or more of:

- a. deleting or mutating all endogenous rodent V_κ gene segment coding sequences;
- b. deleting or mutating all endogenous rodent J_κ gene segment coding sequences;
- c. deleting or mutating endogenous rodent C_κ coding sequence;
- d. deleting or mutating a splice donor site, pyrimidine tract, or splice acceptor site within the intron between a J_κ gene segment and C_κ exon; and
- e. deleting, mutating, or disrupting an endogenous intronic κ enhancer (iE_κ), an 3' enhancer sequence ($3'E_\kappa$), or a combination thereof.

[00038] In one aspect, a transgenic rodent or rodent cell is provided in which expression of an endogenous rodent immunoglobulin λ light chain variable domain is suppressed or inactivated by one or more of:

- a. deleting or mutating all endogenous rodent V_λ gene segments;
- b. deleting or mutating all endogenous rodent J_λ gene segments;
- c. deleting or mutating all endogenous rodent C_λ coding sequences; and
- d. deleting or mutating a splice donor site, pyrimidine tract, splice acceptor site within the intron between a J_λ gene segment and C_λ expm, or a combination thereof.

[00039] In one aspect, a transgenic rodent or rodent cell is provided in which the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine variable domain and a rodent constant domain. In one aspect, a transgenic rodent or rodent cell is provided in which the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine λ variable domain and rodent λ constant domain. In one aspect, a transgenic rodent or rodent cell is provided in which the engineered

immunoglobulin locus expresses immunoglobulin light chains comprising a canine κ variable domain and rodent κ constant domain.

[00040] In one aspect, a transgenic rodent or rodent cell is provided in which the genome of the transgenic rodent or rodent cell comprises an engineered immunoglobulin locus comprising canine V_{κ} and J_{κ} gene segment coding sequences. In one aspect, the canine V_{κ} and J_{κ} gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus. In one aspect, the canine V_{κ} and J_{κ} gene segment coding sequences are embedded in rodent non-coding regulatory or scaffold sequences of the rodent immunoglobulin κ light chain variable region gene locus. In one aspect, the canine V_{κ} and J_{κ} coding sequences are inserted upstream of a rodent immunoglobulin κ light chain constant region coding sequence.

[00041] In one aspect, a transgenic rodent or rodent cell is provided in which the genome of the transgenic rodent or rodent cell comprises an engineered immunoglobulin locus comprising canine V_{κ} and J_{κ} gene segment coding sequences inserted into a rodent immunoglobulin λ light chain locus. In one aspect, the canine V_{κ} and J_{κ} gene segment coding sequences are embedded in rodent non-coding regulatory or scaffold sequences of the rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the genome of the transgenic rodent or rodent cell includes a rodent immunoglobulin κ light chain constant region coding sequence inserted downstream of the canine V_{κ} and J_{κ} gene segment coding sequences. In one aspect, the rodent immunoglobulin κ light chain constant region is inserted upstream of an endogenous rodent C_{λ} coding sequence. In one aspect, the rodent immunoglobulin κ light chain constant region is inserted upstream of an endogenous rodent $C_{\lambda 2}$ coding sequence. In one aspect, expression of an endogenous rodent immunoglobulin λ light chain variable domain is suppressed or inactivated by one or more of:

- a. deleting or mutating all endogenous rodent V_{λ} gene segment coding sequences.
- b. deleting or mutating all endogenous rodent J_{λ} gene segment coding sequences;
- c. deleting or mutating all endogenous C_{λ} coding sequences; and
- d. deleting or mutating a splice donor site, pyrimidine tract, or splice acceptor site within the intron between a J_{λ} gene segment and C_{λ} exon.

- [00042] In one aspect, the engineered partly canine immunoglobulin light chain locus comprises a rodent intronic κ enhancer (iE κ) and 3' κ enhancer (3'E κ) regulatory sequences.
- [00043] In one aspect, the transgenic rodent or rodent cell further comprises an engineered partly canine immunoglobulin heavy chain locus comprising canine immunoglobulin heavy chain variable region gene segment coding sequences and non-coding regulatory and scaffold sequences of the rodent immunoglobulin heavy chain locus. In one aspect, the engineered canine immunoglobulin heavy chain locus comprises canine V_H, D and J_H gene segment coding sequences. In one aspect, each canine/rodent chimeric V_H, D or J_H gene segment comprises V_H, D or J_H coding sequence embedded in non-coding regulatory and scaffold sequences of the rodent immunoglobulin heavy chain locus. In one aspect, the heavy chain scaffold sequences are interspersed by one or both functional ADAM6 genes.
- [00044] In one aspect, the rodent regulatory and scaffold sequences comprise one or more enhancers, promoters, splice sites, introns, recombination signal sequences, or a combination thereof.
- [00045] In one aspect, an endogenous rodent immunoglobulin locus of the transgenic rodent or rodent cell has been inactivated. In one aspect, an endogenous rodent immunoglobulin locus of the transgenic rodent or rodent cell has been deleted and replaced with the engineered partly canine immunoglobulin locus.
- [00046] In one aspect, the rodent is a mouse or a rat. In one aspect, the rodent cell is an embryonic stem (ES) cell or a cell of an early stage embryo. In one aspect, the rodent cell is a mouse or rat embryonic stem (ES) cell, or mouse or rat cell of an early stage embryo.
- [00047] In one aspect, a cell of B lymphocyte lineage is provided that is obtained from a transgenic rodent described herein, wherein the B cell expresses or is capable of expressing a chimeric immunoglobulin heavy chain or light chain comprising a canine variable region and a rodent immunoglobulin constant region. In one aspect, a hybridoma cell or immortalized cell line is provided that is derived from a cell of B lymphocyte lineage obtained from a transgenic rodent or rodent cell described herein.
- [00048] In one aspect, antibodies or antigen binding portions thereof are provided that are produced by a cell from a transgenic rodent or rodent cell described herein.

[00049] In one aspect, a nucleic acid sequence of a V_H , D, or J_H , or a V_L or J_L gene segment coding sequence is provided that is derived from an immunoglobulin produced by a transgenic rodent or rodent cell described herein. In one aspect, a method for generating a non-canine mammalian cell comprising a partly canine immunoglobulin locus is provided, said method comprising: a) introducing two or more recombinase targeting sites into the genome of a non-canine mammalian host cell and integrating at least one site upstream and at least one site downstream of a genomic region comprising endogenous immunoglobulin variable region genes wherein the endogenous immunoglobulin variable genes comprise V_H , D and J_H gene segments, or V_K and J_K gene segments, or V_L and J_L gene segments, or V_L , J_L and C_L gene segments; and b) introducing into the non-canine mammalian host cell via recombinase-mediated cassette exchange (RMCE) an engineered partly canine immunoglobulin variable gene locus comprising canine immunoglobulin variable region gene coding sequences and non-coding regulatory or scaffold sequences corresponding to the non-coding regulatory or scaffold sequences present in the endogenous immunoglobulin variable region gene locus of the non-canine mammalian host.

[00050] In another aspect, the method further comprises deleting the genomic region flanked by the two exogenously introduced recombinase targeting sites prior to step b.

[00051] In a specific aspect of this method, the exogenously introduced, engineered partly canine immunoglobulin heavy chain locus is provided that comprises canine V_H gene segment coding sequences, and further comprises i) canine D and J_H gene segment coding sequences and ii) non-coding regulatory or scaffold sequences upstream of the canine D gene segments (pre-D sequences, FIG. 1A) that correspond to the sequences present upstream of the endogenous D gene segments in the genome of the non-canine mammalian host. In one aspect, these upstream scaffold sequences are interspersed by non-immunoglobulin genes, such as ADAM6A or ADAM6B (FIG. 1A) needed for male fertility (Nishimura et al. Developmental Biol. 233(1): 204-213 (2011)). The partly canine immunoglobulin heavy chain locus is introduced into the host cell using recombinase targeting sites that have been previously introduced upstream of the endogenous immunoglobulin V_H gene locus and downstream of the endogenous J_H gene locus on the same chromosome. In other aspects, the non-coding regulatory or scaffold sequences

derive (at least partially) from other sources, e.g., they could be rationally designed artificial sequences or otherwise conserved sequences of unknown functions, sequences that are a combination of canine and artificial or other designed sequences, or sequences from other species. As used herein, “artificial sequence” refers to a sequence of a nucleic acid not derived from a sequence naturally occurring at a genetic locus. In one aspect, the non-coding regulatory or scaffold sequences are derived from non-coding regulatory or scaffold sequences of a rodent immunoglobulin heavy chain variable region locus. In one aspect, the non-coding regulatory or scaffold sequences have at least about 75%, 80%, 85%, 90%, 95% or 100% sequence identity to non-coding regulatory or scaffold sequences of a rodent immunoglobulin heavy chain variable region locus. In another aspect, the non-coding regulatory or scaffold sequences are rodent immunoglobulin heavy chain variable region non-coding or scaffold sequences.

[00052] In yet another specific aspect of the method, the introduced engineered partly canine immunoglobulin locus comprises canine immunoglobulin V_L gene segment coding sequences, and further comprises i) canine L-chain J gene segment coding sequences and ii) non-coding regulatory or scaffold sequences corresponding to the non-coding regulatory or scaffold sequences present in the endogenous L chain locus of the non-canine mammalian host cell genome. In one aspect, the engineered partly canine immunoglobulin locus is introduced into the host cell using recombinase targeting sites that have been previously introduced upstream of the endogenous immunoglobulin V_L gene locus and downstream of the endogenous J gene locus on the same chromosome.

[00053] In a more particular aspect of this method, an exogenously introduced, engineered partly canine immunoglobulin light chain locus is provided that comprises canine V_λ gene segment coding sequences and canine J_λ gene segment coding sequences. In one aspect, the partly canine immunoglobulin light chain locus is introduced into the host cell using recombinase targeting sites that have been previously introduced upstream of the endogenous immunoglobulin V_λ gene locus and downstream of the endogenous J_λ gene locus on the same chromosome.

[00054] In one aspect, the exogenously introduced, engineered partly canine immunoglobulin light chain locus comprises canine V_κ gene segment coding sequences and canine J_κ gene segment coding sequences. In one aspect, the partly canine

immunoglobulin light chain locus is introduced into the host cell using recombinase targeting sites that have been previously introduced upstream of the endogenous immunoglobulin V_κ gene locus and downstream of the endogenous J_κ gene locus on the same chromosome.

[00055] In one aspect, the non-coding regulatory or scaffold sequences are derived from non-coding regulatory or scaffold sequences of a rodent λ immunoglobulin light chain variable region locus. In one aspect, the non-coding regulatory or scaffold sequences have at least about 75%, 80%, 85%, 90%, 95% or 100% sequence identity to non-coding regulatory or scaffold sequences of a rodent immunoglobulin λ light chain variable region locus. In another aspect, the non-coding regulatory or scaffold sequences are rodent immunoglobulin λ light chain variable region non-coding or scaffold sequences.

[00056] In one aspect, the non-coding regulatory or scaffold sequences are derived from non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain variable region locus. In one aspect, the non-coding regulatory or scaffold sequences have at least about 75%, 80%, 85%, 90%, 95% or 100% sequence identity to non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain variable region locus. In another aspect, the non-coding regulatory or scaffold sequences are rodent immunoglobulin κ light chain variable region non-coding or scaffold sequences.

[00057] In one aspect, the engineered partly canine immunoglobulin locus is synthesized as a single nucleic acid, and introduced into the non-canine mammalian host cell as a single nucleic acid region. In one aspect, the engineered partly canine immunoglobulin locus is synthesized in two or more contiguous segments, and introduced to the mammalian host cell as discrete segments. In another aspect, the engineered partly canine immunoglobulin locus is produced using recombinant methods and isolated prior to being introduced into the non-canine mammalian host cell.

[00058] In another aspect, methods for generating a non-canine mammalian cell comprising an engineered partly canine immunoglobulin locus are provided, said method comprising: a) introducing into the genome of a non-canine mammalian host cell two or more sequence-specific recombination sites that are not capable of recombining with one another, wherein at least one recombination site is introduced upstream of an endogenous immunoglobulin variable region gene locus while at least one recombination site is introduced downstream

of the endogenous immunoglobulin variable region gene locus on the same chromosome; b) providing a vector comprising an engineered partly canine immunoglobulin locus having i) canine immunoglobulin variable region gene coding sequences and ii) non-coding regulatory or scaffold sequences based on an endogenous immunoglobulin variable region gene locus of the host cell genome, wherein the partly canine immunoglobulin locus is flanked by the same two sequence-specific recombination sites that flank the endogenous immunoglobulin variable region gene locus of the host cell of a); c) introducing into the host cell the vector of step b) and a site specific recombinase capable of recognizing the two recombinase sites; d) allowing a recombination event to occur between the genome of the cell of a) and the engineered partly canine immunoglobulin locus, resulting in a replacement of the endogenous immunoglobulin variable region gene locus with the engineered partly canine immunoglobulin variable region gene locus.

[00059] In one aspect, the partly canine immunoglobulin locus comprises V_H immunoglobulin gene segment coding sequences, and further comprises i) canine D and J_H gene segment coding sequences, ii) non-coding regulatory or scaffold sequences surrounding the codons of individual V_H , D, and J_H gene segments present endogenously in the genome of the non-canine mammalian host, and iii) pre-D sequences based on the endogenous genome of the non-canine mammalian host cell. The recombinase targeting sites are introduced upstream of the endogenous immunoglobulin V_H gene locus and downstream of the endogenous D and J_H gene locus.

[00060] In one aspect, there is provided a transgenic rodent with a genome deleted of a rodent endogenous immunoglobulin variable gene locus and in which the deleted rodent endogenous immunoglobulin variable gene locus has been replaced with an engineered partly canine immunoglobulin locus comprising canine immunoglobulin variable gene coding sequences and non-coding regulatory or scaffold sequences based on the rodent endogenous immunoglobulin variable gene locus, wherein the engineered partly canine immunoglobulin locus of the transgenic rodent is functional and expresses immunoglobulin chains with canine variable domains and rodent constant domains. In some aspects, the engineered partly canine immunoglobulin locus comprises canine V_H , D, and J_H coding sequences, and in some aspects, the engineered partly canine immunoglobulin locus comprises canine V_L and J_L coding sequences. In one aspect, the

partly canine immunoglobulin locus comprises canine V_{λ} and J_{λ} coding sequences. In another aspect, the partly canine immunoglobulin locus comprises canine V_{κ} and J_{κ} coding sequences.

[00061] Some aspects provide a cell of B lymphocyte lineage from the transgenic rodent, a part or whole immunoglobulin molecule comprising canine variable domains and rodent constant domains obtained from the cell of B lymphocyte lineage, a hybridoma cell derived from the cell of B lymphocyte lineage, a part or whole immunoglobulin molecule comprising canine variable domains and rodent constant domains obtained from the hybridoma cell, a part or whole immunoglobulin molecule comprising canine variable domains derived from an immunoglobulin molecule obtained from the hybridoma cell, an immortalized cell derived from the cell of B lymphocyte lineage, a part or whole immunoglobulin molecule comprising canine variable domains and rodent constant domains obtained from the immortalized cell, a part or whole immunoglobulin molecule comprising canine variable domains derived from an immunoglobulin molecule obtained from the immortalized cell.

[00062] In one aspect, a transgenic rodent is provided, wherein the engineered partly canine immunoglobulin locus comprises canine V_L and J_L coding sequences, and a transgenic rodent, wherein the engineered partly canine immunoglobulin loci comprise canine V_H , D , and J_H or V_L and J_L coding sequences. In some aspects, the rodent is a mouse. In some aspects, the non-coding regulatory sequences comprise the following sequences of endogenous host origin: promoters preceding each V gene segment coding sequence, introns, splice sites, and recombination signal sequences for V(D)J recombination; in other aspects, the engineered partly canine immunoglobulin locus further comprises one or more of the following sequences of endogenous host origin: ADAM6A or ADAM6B gene, a Pax-5-Activated Intergenic Repeat (PAIR) elements, or CTCF binding sites from a heavy chain intergenic control region 1.

[00063] In one aspect, the non-canine mammalian cell for use in each of the above methods is a mammalian cell, for example, a mammalian embryonic stem (ES) cell. In one aspect, the mammalian cell is a cell of an early stage embryo. In one aspect, the non-canine mammalian cell is a rodent cell. In one aspect, the non-canine mammalian cell is a mouse cell.

[00064] Once the cells have been subjected to the replacement of the endogenous immunoglobulin variable region gene locus by the introduced partly canine immunoglobulin variable region gene locus, the cells can be selected and isolated. In one aspect, the cells are non-canine mammalian ES cells, for example, rodent ES cells, and at least one isolated ES cell clone is then utilized to create a transgenic non-canine mammal expressing the engineered partly canine immunoglobulin variable region gene locus.

[00065] In one aspect, a method for generating the transgenic rodent is provided, said method comprising: a) integrating at least one target site for a site-specific recombinase in a rodent cell's genome upstream of an endogenous immunoglobulin variable gene locus and at least one target site for a site-specific recombinase downstream of the endogenous immunoglobulin variable gene locus, wherein the endogenous immunoglobulin variable locus comprises V_H , D and J_H gene segments, or V_K and J_K gene segments, or V_λ and J_λ gene segments, or V_λ , J_λ and C_λ gene segments; b) providing a vector comprising an engineered partly canine immunoglobulin locus, said engineered partly canine immunoglobulin locus comprising chimeric canine immunoglobulin gene segments, wherein each of the partly canine immunoglobulin gene segment comprises canine immunoglobulin variable gene coding sequences and rodent non-coding regulatory or scaffold sequences, with the partly canine immunoglobulin variable gene locus being flanked by target sites for a site-specific recombinase wherein the target sites are capable of recombining with the target sites introduced into the rodent cell; c) introducing into the cell the vector and a site-specific recombinase capable of recognizing the target sites; d) allowing a recombination event to occur between the genome of the cell and the engineered partly canine immunoglobulin locus resulting in a replacement of the endogenous immunoglobulin variable gene locus with the engineered partly canine immunoglobulin locus; e) selecting a cell that comprises the engineered partly canine immunoglobulin variable locus generated in step d); and utilizing the cell to create a transgenic rodent comprising partly canine the engineered partly canine immunoglobulin variable locus. In some aspects, the cell is a rodent embryonic stem (ES) cell, and in some aspects the cell is a mouse embryonic stem (ES) cell. Some aspects of this method further comprise after, after step a) and before step b), a step of deleting the endogenous immunoglobulin variable gene locus by introduction of a recombinase that recognizes a first set of target sites,

wherein the deleting step leaves in place at least one set of target sites that are not capable of recombining with one another in the rodent cell's genome. In some aspects, the vector comprises canine V_H, D, and J_H coding sequences, and in some aspects the vector comprises canine V_L and J_L coding sequences. In some aspects, the vector further comprises rodent promoters, introns, splice sites, and recombination signal sequences of variable region gene segments.

[00066] In another aspect, a method for generating a transgenic non-canine mammal comprising an exogenously introduced, engineered partly canine immunoglobulin variable region gene locus is provided, said method comprising: a) introducing into the genome of a non-canine mammalian host cell one or more sequence-specific recombination sites that flank an endogenous immunoglobulin variable region gene locus and are not capable of recombining with one another; b) providing a vector comprising a partly canine immunoglobulin locus having i) canine variable region gene coding sequences and ii) non-coding regulatory or scaffold sequences based on the endogenous host immunoglobulin variable region gene locus, wherein the coding and non-coding regulatory or scaffold sequences are flanked by the same sequence-specific recombination sites as those introduced to the genome of the host cell of a); c) introducing into the cell the vector of step b) and a site-specific recombinase capable of recognizing one set of recombinase sites; d) allowing a recombination event to occur between the genome of the cell of a) and the engineered partly canine immunoglobulin variable region gene locus, resulting in a replacement of the endogenous immunoglobulin variable region gene locus with the partly canine immunoglobulin locus; e) selecting a cell which comprises the partly canine immunoglobulin locus; and f) utilizing the cell to create a transgenic animal comprising the partly canine immunoglobulin locus.

[00067] In a specific aspect, the engineered partly canine immunoglobulin locus comprises canine V_H, D, and J_H gene segment coding sequences, and non-coding regulatory and scaffold pre-D sequences (including a fertility-enabling gene) present in the endogenous genome of the non-canine mammalian host. In one aspect, the sequence-specific recombination sites are then introduced upstream of the endogenous immunoglobulin V_H gene segments and downstream of the endogenous J_H gene segments.

[00068] In one aspect, a method for generating a transgenic non-canine animal comprising an engineered partly canine immunoglobulin locus is provided, said method comprising:

- a) providing a non-canine mammalian cell having a genome that comprises two sets of sequence-specific recombination sites that are not capable of recombining with one another, and which flank a portion of an endogenous immunoglobulin variable region gene locus of the host genome;
- b) deleting the portion of the endogenous immunoglobulin locus of the host genome by introduction of a recombinase that recognizes a first set of sequence-specific recombination sites, wherein such deletion in the genome retains a second set of sequence-specific recombination sites;
- c) providing a vector comprising an engineered partly canine immunoglobulin variable region gene locus having canine coding sequences and non-coding regulatory or scaffold sequences based on the endogenous immunoglobulin variable region gene locus, where the coding and non-coding regulatory or scaffold sequences are flanked by the second set of sequence-specific recombination sites;
- d) introducing the vector of step c) and a site-specific recombinase capable of recognizing the second set of sequence-specific recombination sites into the cell;
- e) allowing a recombination event to occur between the genome of the cell and the partly canine immunoglobulin locus, resulting in a replacement of the endogenous immunoglobulin locus with the engineered partly canine immunoglobulin variable locus;
- f) selecting a cell that comprises the partly canine immunoglobulin variable region gene locus; and
- g) utilizing the cell to create a transgenic animal comprising the engineered partly canine immunoglobulin variable region gene locus.

[00069] In one aspect, a method for generating a transgenic non-canine mammal comprising an engineered partly canine immunoglobulin locus is provided, said method comprising:

- a) providing a non-canine mammalian embryonic stem ES cell having a genome that contains two sequence-specific recombination sites that are not capable of recombining with each other, and which flank the endogenous immunoglobulin variable region gene locus;
- b) providing a vector comprising an engineered partly canine immunoglobulin locus comprising canine immunoglobulin variable gene coding sequences and non-coding regulatory or scaffold sequences based on the endogenous immunoglobulin variable region gene locus, where the partly canine immunoglobulin locus is flanked by the same two sequence-specific recombination sites that flank the endogenous immunoglobulin variable

region gene locus in the ES cell; c) bringing the ES cell and the vector into contact with a site-specific recombinase capable of recognizing the two recombinase sites under appropriate conditions to promote a recombination event resulting in the replacement of the endogenous immunoglobulin variable region gene locus with the engineered partly canine immunoglobulin variable region gene locus in the ES cell; d) selecting an ES cell that comprises the engineered partly canine immunoglobulin locus; and e) utilizing the cell to create a transgenic animal comprising the engineered partly canine immunoglobulin locus.

[00070] In one aspect, the transgenic non-canine mammal is a rodent, e.g., a mouse or a rat.

[00071] In one aspect, a non-canine mammalian cell and a non-canine transgenic mammal are provided that express an introduced immunoglobulin variable region gene locus having canine variable region gene coding sequences and non-coding regulatory or scaffold sequences based on the endogenous non-canine immunoglobulin locus of the host genome, where the non-canine mammalian cell and transgenic animal express chimeric antibodies with fully canine H or L chain variable domains in conjunction with their respective constant regions that are native to the non-canine mammalian cell or animal.

[00072] Further, B cells from transgenic animals are provided that are capable of expressing partly canine antibodies having fully canine variable sequences, wherein such B cells are immortalized to provide a source of a monoclonal antibody specific for a particular antigen. In one aspect, a cell of B lymphocyte lineage from a transgenic animal is provided that is capable of expressing partly canine heavy or light chain antibodies comprising a canine variable region and a rodent constant region.

[00073] In one aspect, canine immunoglobulin variable region gene sequences cloned from B cells are provided for use in the production or optimization of antibodies for diagnostic, preventative and therapeutic uses.

[00074] In one aspect, hybridoma cells that are provided that are capable of producing partly canine monoclonal antibodies having fully canine immunoglobulin variable region sequences. In one aspect, a hybridoma or immortalized cell line of B lymphocyte lineage is provided.

[00075] In another aspect, antibodies or antigen binding portions thereof produced by a transgenic animal or cell described herein are provided. In another aspect, antibodies or

antigen binding portions thereof comprising variable heavy chain or variable light chain sequences derived from antibodies produced by a transgenic animal or cell described herein are provided.

[00076] In one aspect, methods for determining the sequences of the H and L chain immunoglobulin variable domains from the monoclonal antibody-producing hybridomas or primary plasma cells or B cells and combining the V_H and V_L sequences with canine constant regions are provided for creating a fully canine antibody that is not immunogenic when injected into dogs.

[00077] These and other aspects, objects and features are described in more detail below.

BRIEF DESCRIPTION OF THE FIGURES

[00078] FIG. 1A is a schematic diagram of the endogenous mouse IGH locus located at the telomeric end of chromosome 12.

[00079] FIG. 1B is a schematic diagram of the endogenous mouse IGL locus located on chromosome 16.

[00080] FIG. 1C is a schematic diagram of the endogenous mouse IGK locus located on chromosome 6.

[00081] FIG. 2 is a schematic diagram illustrating the strategy of targeting by homologous recombination to introduce a first set of sequence-specific recombination sites into a region upstream of the H chain variable region gene locus in the genome of a non-canine mammalian host cell.

[00082] FIG. 3 is another schematic diagram illustrating the strategy of targeting by homologous recombination to introduce a first set of sequence-specific recombination sites into a region upstream of the H chain variable region gene locus in the genome of a non-canine mammalian host cell.

[00083] FIG. 4 is a schematic diagram illustrating the introduction of a second set of sequence-specific recombination sites into a region downstream of the H chain variable region gene locus in the genome of a non-canine mammalian cell via a homology targeting vector.

[00084] FIG. 5 is a schematic diagram illustrating deletion of the endogenous immunoglobulin H chain variable region gene locus from the genome of the non-canine mammalian host cell.

[00085] FIG. 6 is a schematic diagram illustrating the RMCE strategy to introduce an engineered partly canine immunoglobulin H chain locus into the non-canine mammalian host cell genome that has been previously modified to delete the endogenous immunoglobulin H chain variable region gene locus.

[00086] FIG. 7 is a schematic diagram illustrating the RMCE strategy to introduce an engineered partly canine immunoglobulin H chain locus comprising additional regulatory sequences into the non-canine mammalian host cell genome that has been previously modified to delete the endogenous immunoglobulin H chain variable region genes.

[00087] FIG. 8 is a schematic diagram illustrating the introduction of an engineered partly canine immunoglobulin H chain variable region gene locus into the endogenous immunoglobulin H chain locus of the mouse genome.

[00088] FIG. 9 is a schematic diagram illustrating the introduction of an engineered partly canine immunoglobulin κ L chain variable region gene locus into the endogenous immunoglobulin κ L chain locus of the mouse genome.

[00089] FIG. 10 is a schematic diagram illustrating the introduction of an engineered partly canine immunoglobulin λ L chain variable region gene locus into the endogenous immunoglobulin λ L chain locus of the mouse genome.

[00090] FIG. 11 is a schematic diagram illustrating the introduction of an engineered partly canine immunoglobulin locus comprising a canine V_H minilocus via RMCE.

[00091] FIG. 12A is a schematic diagram of the endogenous canine IGH locus located on chromosome 8 showing the entire Igh locus (1201) and an expanded view of the IGHC region (1202).

[00092] FIG. 12B is a schematic diagram of the endogenous canine IGL locus located on chromosome 26.

[00093] FIG. 12C is a schematic diagram of the endogenous canine IGK locus located on chromosome 17. Arrows indicate the transcriptional orientation of the V_k gene segments. In the native canine IGK locus (1220) some V_k gene segments are downstream of the C_k exon. In the partly canine Ig $_k$ locus described herein (1221), all of the V_k gene segment

coding sequences are upstream of the C_{κ} exon and in the same transcriptional orientation as the C_{κ} exon (See Example 4).

[00094] FIG. 13 is a schematic diagram illustrating an engineered partly canine immunoglobulin light chain variable region locus in which one or more canine V_{λ} gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus upstream of one or more canine J_{λ} gene segment coding sequences, which are upstream of one or more rodent C_{λ} region coding sequences.

[00095] FIG. 14 is a schematic diagram illustrating the introduction of an engineered partly canine light chain variable region locus in which one or more canine V_{λ} gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus upstream of an array of J_{λ} - C_{λ} tandem cassettes in which the J_{λ} is of canine origin and the C_{λ} is of mouse origin, $C_{\lambda 1}$, $C_{\lambda 2}$ or $C_{\lambda 3}$.

[00096] FIG. 15 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV3-5-mouse C_{μ} membrane form IgM^b allotype, and canine IGLV3-28/ $J_{\kappa 6}$ attached to various combinations of mouse C_{κ} and C_{λ} (1501), or canine IGKV2-5/ $J_{\kappa 1}$ attached to various combinations of mouse C_{κ} and C_{λ} (1502). The cells have been stained for cell surface hCD4 (1509) or for mouse IgM^b (1510).

[00097] FIG. 16 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV3-5-mouse C_{μ} membrane form IgM^b allotype, and canine IGLV3-28/ $J_{\kappa 6}$ attached to various combinations of mouse C_{κ} and C_{λ} (1601), or canine IGKV2-5/ $J_{\kappa 1}$ attached to various combinations of mouse C_{κ} and C_{λ} (1602). The cells have been stained for cell surface mouse λ LC (1601) or mouse κ LC (1602).

[00098] FIG. 17 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV4-1-mouse C_{μ} membrane form IgM^b allotype, and canine IGLV3-28/ $J_{\kappa 6}$ attached to various combinations of mouse C_{κ} and C_{λ} (1701), or canine IGKV2-5/ $J_{\kappa 1}$ attached to various combinations of mouse C_{κ} and C_{λ} (1702). The cells have been stained for cell surface hCD4 (1709) or for mouse IgM^b (1710).

[00099] FIG. 18 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV3-19-mouse C_{μ} membrane form IgM^b

allotype, and canine IGLV3-28/J_λ6 attached to various combinations of mouse C_κ and C_λ (1801), or canine IGKV2-5/J_κ1 attached to various combinations of mouse C_κ and C_λ (1802). The cells have been stained for cell surface hCD4 (1809) or for mouse IgM^b (1810).

[000100] FIG. 19A shows western blots of culture supernatants and FIG. 19B shows western blots of cell lysates of 393T/17 cells transfected with expression vectors encoding canine IGHV3-5 attached to mouse C_{γ2α} (1901), IGHV3-19 attached to mouse C_{γ2α} (1902) or IGHV4-1 attached to mouse C_{γ2α} (1903) and canine IGLV3-28/J_λ6 attached to various combinations of mouse C_κ (1907) and C_λ (1908-1910). The samples were electrophoresed under reducing conditions and the blot was probed with an anti-mouse IgG2a antibody.

[000101] FIG. 20A shows western blot loading control Myc for the cell lysates from FIG. 18 and FIG. 20B shows western blot loading control GAPDH for the cell lysates from FIG. 18.

[000102] FIG. 21A shows western blots of culture supernatants (non-reducing conditions) and FIG. 21B shows western blots of cell lysates (reducing conditions) of 393T/17 cells transfected with expression vectors encoding canine IGHV3-5-mouse C_{γ2α} and canine IGLV3-28/J_λ6 attached to various combinations of mouse C_κ (2102) and C_λ (2103, 2104) or transfected with expression vectors encoding canine IGHV3-5-mouse C_{γ2α} and canine IGKV2-5/J_κ1 attached to various combinations of mouse C_κ (2105) and C_λ (2106, 2107). The blots in FIG. 21A were probed with antibodies to mouse IgG2a and the blots in FIG. 21B were probed with antibodies to mouse κ LC.

[000103] FIG. 22 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV3-5 attached to mouse C_δ membrane form, and canine IGKV2-5/J_κ1 attached to mouse C_κ (2201) or canine IGLV3-28/J_λ6 attached to mouse C_{λ1}, C_{λ2} or C_{λ3} (2202-2204). The cells have been stained for cell surface hCD4 (2205), mouse CD79b (2206), mouse IgD (2207), mouse κ LC (2208), or mouse λ LC (2209).

[000104] FIG. 23 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV3-19 attached to mouse C_δ membrane form, and canine IGKV2-5/J_κ1 attached to mouse C_κ (2301) or canine IGLV3-28/J_λ6 attached to mouse C_{λ1}, C_{λ2} or C_{λ3} (2302-2304). The cells have been stained for cell surface

hCD4 (2205), mouse CD79b (2206), mouse IgD (2207), mouse κ LC (2208), or mouse λ LC (2209).

[000105] FIG. 24 shows flow cytometry profiles of 293T/17 cells transfected with expression vectors encoding human CD4 (hCD4), canine IGHV4-1 attached to mouse C δ membrane form, and canine IGKV2-5/J κ 1 attached to mouse C κ (2401) or canine IGLV3-28/J λ 6 attached to mouse C λ 1, C λ 2 or C λ 3 (2402-2404). The cells have been stained for cell surface hCD4 (2405), mouse CD79b (2406), mouse IgD (2407), mouse κ LC (2408), or mouse λ LC (2409).

DEFINITIONS

[000106] The terms used herein are intended to have the plain and ordinary meaning as understood by those of ordinary skill in the art. The following definitions are intended to aid the reader in understanding the present invention, but are not intended to vary or otherwise limit the meaning of such terms unless specifically indicated.

[000107] The term "locus" as used herein refers to a chromosomal segment or nucleic acid sequence that, respectively, is present endogenously in the genome or is (or about to be) exogenously introduced into the genome. For example, an immunoglobulin locus may include part or all of the genes (i.e., V, D, J gene segments as well as constant region genes) and intervening sequences (i.e., introns, enhancers, etc.) supporting the expression of immunoglobulin H or L chain polypeptides. Thus, a locus (e.g., immunoglobulin heavy chain variable region gene locus) may refer to a specific portion of a larger locus (e.g., a portion of the immunoglobulin H chain locus that includes the V_H, D_H and J_H gene segments). Similarly, an immunoglobulin light chain variable region gene locus may refer to a specific portion of a larger locus (e.g., a portion of the immunoglobulin L chain locus that includes the V_L and J_L gene segments). The term "immunoglobulin variable region gene" as used herein refers to a V, D, or J gene segment that encodes a portion of an immunoglobulin H or L chain variable domain. The term "immunoglobulin variable region gene locus" as used herein refers to part of, or the entire, chromosomal segment or nucleic acid strand containing clusters of the V, D, or J gene segments and may include the non-coding regulatory or scaffold sequences.

[000108] The term “gene segment” as used herein, refers to a nucleic acid sequence that encodes a part of the heavy chain or light chain variable domain of an immunoglobulin molecule. A gene segment can include coding and non-coding sequences. The coding sequence of a gene segment is a nucleic acid sequence that can be translated into a polypeptide, such the leader peptide and the N-terminal portion of a heavy chain or light chain variable domain. The non-coding sequences of a gene segment are sequences flanking the coding sequence, which may include the promoter, 5' untranslated sequence, intron intervening the coding sequences of the leader peptide, recombination signal sequence(s) (RSS), and splice sites. The gene segments in the immunoglobulin heavy chain (IGH) locus comprise the V_H, D and J_H gene segments (also referred to as IGHV, IGHD and IGHJ, respectively). The light chain variable region gene segments in the immunoglobulin κ and λ light loci can be referred to as V_L and J_L gene segments. In the κ light chain, the V_L and J_L gene segments can be referred to as V _{κ} and J _{κ} gene segments or IGKV and IGKJ. Similarly, in the λ light chain, the V_L and J_L gene segments can be referred to as V _{λ} and J _{λ} gene segments or IGLV and IGLJ.

[000109] The heavy chain constant region can be referred to as C_H or IGHC. The C_H region exons that encode IgM, IgD, IgG1-4, IgE, or IgA can be referred to as, respectively, C _{μ} , C _{δ} , C _{γ 1-4}, C _{ϵ} or C _{α} . Similarly, the immunoglobulin κ or λ constant region can be referred to as C _{κ} or C _{λ} , as well as IGKC or IGLC, respectively.

[000110] "Partly canine" as used herein refers to a strand of nucleic acids, or their expressed protein and RNA products, comprising sequences corresponding to the sequences found in a given locus of both a canine and a non-canine mammalian host. "Partly canine" as used herein also refers to an animal comprising nucleic acid sequences from both a canine and a non-canine mammal, for example, a rodent. In one aspect, the partly canine nucleic acids have coding sequences of canine immunoglobulin H or L chain variable region gene segments and sequences based on the non-coding regulatory or scaffold sequences of the endogenous immunoglobulin locus of the non-canine mammal.

[000111] The term "based on" when used with reference to endogenous non-coding regulatory or scaffold sequences from a non-canine mammalian host cell genome refers to the non-coding regulatory or scaffold sequences that are present in the corresponding endogenous locus of the mammalian host cell genome. In one aspect, the term “based on”

means that the non-coding regulatory or scaffold sequences that are present in the partly canine immunoglobulin locus share a relatively high degree of homology with the non-coding regulatory or scaffold sequences of the endogenous locus of the host mammal. In one aspect, the non-coding sequences in the partly canine immunoglobulin locus share at least about 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% homology with the corresponding non-coding sequences found in the endogenous locus of the host mammal. In one aspect, the non-coding sequences in the partly canine immunoglobulin locus are retained from an immunoglobulin locus of the host mammal. In one aspect, the canine coding sequences are embedded in the non-regulatory or scaffold sequences of the immunoglobulin locus of the host mammal. In one aspect, the host mammal is a rodent, such as a rat or mouse.

[000112] “Non-coding regulatory sequences” refer to sequences that are known to be essential for (i) V(D)J recombination, (ii) isotype switching, (iii) proper expression of the full-length immunoglobulin H or L chains following V(D)J recombination, and (iv) alternate splicing to generate, e.g., membrane and secreted forms of the immunoglobulin H chain. “Non-coding regulatory sequences” may further include the following sequences of endogenous origin: enhancer and locus control elements such as the CTCF and PAIR sequences (Proudhon, et al., *Adv. Immunol.* 128:123-182 (2015)); promoters preceding each endogenous V gene segment; splice sites; introns; recombination signal sequences flanking each V, D, or J gene segment. In one aspect, the “non-coding regulatory sequences” of the partly canine immunoglobulin locus share at least about 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% and up to 100% homology with the corresponding non-coding sequences found in the targeted endogenous immunoglobulin locus of the non-canine mammalian host cell.

[000113] “Scaffold sequences” refer to sequences intervening the gene segments present in the endogenous immunoglobulin locus of the host cell genome. In certain aspects, the scaffold sequences are interspersed by sequences essential for the expression of a functional non-immunoglobulin gene, for example, ADAM6A or ADAM6B. In certain aspects, the scaffold sequences are derived (at least partially) from other sources—e.g., they could be rationally designed or artificial sequences, sequences present in the immunoglobulin locus of the canine genome, sequences present in the immunoglobulin

locus of another species, or a combination thereof. It is to be understood that the phrase “non-coding regulatory or scaffold sequence” is inclusive in meaning (i.e., referring to both the non-coding regulatory sequence and the scaffold sequence existing in a given locus).

[000114] The term "homology targeting vector" refers to a nucleic acid sequence used to modify the endogenous genome of a mammalian host cell by homologous recombination; such nucleic acid sequence may comprise (i) targeting sequences with significant homologies to the corresponding endogenous sequences flanking a locus to be modified that is present in the genome of the non-canine mammalian host, (ii) at least one sequence-specific recombination site, (iii) non-coding regulatory or scaffold sequences, and (iv) optionally one or more selectable marker genes. As such, a homology targeting vector can be used to introduce a sequence-specific recombination site into particular region of a host cell genome.

[000115] "Site-specific recombination" or “sequence-specific recombination” refers to a process of DNA rearrangement between two compatible recombination sequences (also referred to as “sequence-specific recombination sites” or “site-specific recombination sequences”) including any of the following three events: a) deletion of a preselected nucleic acid flanked by the recombination sites; b) inversion of the nucleotide sequence of a preselected nucleic acid flanked by the recombination sites, and c) reciprocal exchange of nucleic acid sequences proximate to recombination sites located on different nucleic acid strands. It is to be understood that this reciprocal exchange of nucleic acid segments can be exploited as a targeting strategy to introduce an exogenous nucleic acid sequence into the genome of a host cell.

[000116] The term "targeting sequence" refers to a sequence homologous to DNA sequences in the genome of a cell that flank or are adjacent to the region of an immunoglobulin locus to be modified. The flanking or adjacent sequence may be within the locus itself or upstream or downstream of coding sequences in the genome of the host cell. Targeting sequences are inserted into recombinant DNA vectors which are used to transfect, e.g., ES cells, such that sequences to be inserted into the host cell genome, such as the sequence of a recombination site, are flanked by the targeting sequences of the vector.

[000117] The term "site-specific targeting vector" as used herein refers to a vector comprising a nucleic acid encoding a sequence-specific recombination site, an engineered partly canine

locus, and optionally a selectable marker gene, which is used to modify an endogenous immunoglobulin locus in a host using recombinase-mediated site-specific recombination. The recombination site of the targeting vector is suitable for site-specific recombination with another corresponding recombination site that has been inserted into a genomic sequence of the host cell (e.g., via a homology targeting vector), adjacent to an immunoglobulin locus that is to be modified. Integration of an engineered partly canine sequence into a recombination site in an immunoglobulin locus results in replacement of the endogenous locus by the exogenously introduced partly canine region.

[000118] The term "transgene" is used herein to describe genetic material that has been or is about to be artificially inserted into the genome of a cell, and particularly a cell of a mammalian host animal. The term "transgene" as used herein refers to a partly canine nucleic acid, e.g., a partly canine nucleic acid in the form of an engineered expression construct or a targeting vector.

[000119] "Transgenic animal" refers to a non-canine animal, usually a mammal, having an exogenous nucleic acid sequence present as an extrachromosomal element in a portion of its cells or stably integrated into its germ line DNA (i.e., in the genomic sequence of most or all of its cells). In one aspect, a partly canine nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal according to methods well known in the art.

[000120] A "vector" includes plasmids and viruses and any DNA or RNA molecule, whether self-replicating or not, which can be used to transform or transfect a cell.

[000121] Note that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a locus" refers to one or more loci, and reference to "the method" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

[000122] As used herein, the term "or" can mean "and/or", unless explicitly indicated to refer only to alternatives or the alternatives are mutually exclusive. The terms "including," "includes" and "included", are not limiting.

[000123] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this

invention belongs. All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing devices, formulations and methodologies that may be used in connection with the presently described invention.

[000124] Where a range of values is provided, it is understood that each intervening value, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[000125] The practice of the techniques described herein may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and sequencing technology, which are within the skill of those who practice in the art. Such conventional techniques include polymer array synthesis, hybridization and ligation of polynucleotides, polymerase chain reaction, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the examples herein. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as Green, et al., Eds. (1999), *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV); Weiner, Gabriel, Stephens, Eds. (2007), *Genetic Variation: A Laboratory Manual*; Dieffenbach and Veksler, Eds. (2007), *PCR Primer: A Laboratory Manual*; Bowtell and Sambrook (2003), *DNA Microarrays: A Molecular Cloning Manual*; Mount (2004), *Bioinformatics: Sequence and Genome Analysis*; Sambrook and Russell (2006), *Condensed Protocols from Molecular Cloning: A Laboratory Manual*; and Sambrook and Russell (2002), *Molecular Cloning: A Laboratory Manual* (all from Cold Spring Harbor Laboratory Press); Stryer, L. (1995) *Biochemistry* (4th Ed.) W.H. Freeman, New York N.Y.; Gait, "Oligonucleotide Synthesis: A Practical Approach" 1984, IRL Press, London; Nelson and Cox (2000), *Lehninger, Principles of Biochemistry* 3rd Ed., W. H. Freeman Pub., New York, N.Y.; and Berg et al. (2002) *Biochemistry*, 5th Ed., W.H.

Freeman Pub., New York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

DETAILED DESCRIPTION

[000126] In the following description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

[000127] Described herein is a transgenic rodent or rodent cell having a genome comprising an engineered partly canine immunoglobulin heavy chain or light chain locus. In one aspect, the partly canine immunoglobulin heavy chain locus comprises one or more canine immunoglobulin heavy chain variable region gene segments. In one aspect, the partly canine immunoglobulin light chain locus comprises one or more canine immunoglobulin λ light chain variable region gene segments. In one aspect, the partly canine immunoglobulin light chain locus comprises one or more canine immunoglobulin κ light chain variable region gene segments.

[000128] In one aspect, non-canine mammalian cells are provided that comprise an exogenously introduced, engineered partly canine nucleic acid sequence comprising coding sequences for canine variable regions and non-coding regulatory or scaffold sequences present in the immunoglobulin locus of the mammalian host genome, e.g., mouse genomic non-coding sequences when the host mammal is a mouse. In one aspect, one or more coding sequences for canine variable region gene segments are embedded in non-coding regulatory or scaffold sequences corresponding to those of an immunoglobulin locus in a mammalian host genome. In one aspect, the coding sequences for canine variable region gene segments are embedded in non-coding regulatory or scaffold sequences of a rodent or mouse immunoglobulin locus.

[000129] In one aspect, the partly canine immunoglobulin locus is synthetic and comprises canine V_H , D , or J_H or V_L or J_L gene segment coding sequences that are under the control of regulatory elements of the endogenous host. In one aspect, the partly canine immunoglobulin locus comprises canine V_H , D , or J_H or V_L or J_L gene segment coding

sequences embedded in non-coding regulatory or scaffold sequences corresponding to those of an immunoglobulin locus in a mammalian host genome.

[000130] Methods are also provided for generating a transgenic rodent or rodent ES cell comprising exogenously introduced, engineered partly canine immunoglobulin loci, wherein the resultant transgenic rodent is capable of producing more immunoglobulin comprising λ light chain than immunoglobulin comprising κ light chain.

[000131] There are many challenges presented when generating a non-canine mammal such as a transgenic mouse or rat, that is capable of producing antigen-specific canine antibodies that are addressed by the constructs and methods described herein, including, but not limited to:

1. How to obtain λ : κ light chain usage ratio of 90:10 in an organism such as a mouse or rat that preferentially uses 90% κ light chains;
2. Whether mouse B cells can express a large number of dog V_λ gene segments (the dog λ locus contains at least 70 functional, unique V_λ gene segments) when the mouse λ locus contains only 3 functional V_λ gene segments;
3. How to improve expression and usage of canine V_λ in a non-canine mammal, such as a mouse, in view of the differences in structure between the mouse and dog λ light chain loci locus.
 - a. The mouse λ light chain loci locus contains 2 clusters of V_λ gene segment(s), J_λ gene segment(s), and C_λ exon(s):
 - i. $V_{\lambda 2}$ - $V_{\lambda 3}$ - $J_{\lambda 2}$ - $C_{\lambda 2}$
 - ii. $V_{\lambda 1}$ - $J_{\lambda 3}$ - $C_{\lambda 3}$ - $J_{\lambda 1}$ - $C_{\lambda 1}$; and
 - b. the dog λ locus contains tandem V_λ gene segments upstream of J_λ - C_λ clusters.
4. Whether mouse B cells can develop normally if mouse IgD is expressed with dog V_H , in view of the fact that canine IgD is not functional and IgM and IgD are co-expressed as alternatively spliced forms in mouse and rat B cells.

Immunoglobulin Loci in mice and dog

[000132] In the humoral immune system, a diverse antibody repertoire is produced by combinatorial and junctional diversity of IGH and IGL chain gene loci by a process termed V(D)J recombination. In the developing B cell, the first recombination event to occur is between one D and one J_H gene segment of the heavy chain locus, and the DNA between these two gene segments is deleted. This D-J_H recombination is followed by the joining of one V_H gene segment from a region upstream of the newly formed DJ_H complex, forming a rearranged V_HDJ_H exon. All other sequences between the recombined V_H and D gene segments of the newly generated V_HDJ_H exon are deleted from the genome of the individual B cell. This rearranged exon is ultimately expressed on the B cell surface as the variable region of the H-chain polypeptide, which is associated with an L-chain polypeptide to form the B cell receptor (BCR).

[000133] The light chain repertoire in the mouse is believed to be shaped by the order of gene rearrangements. The IGK light chain locus on both chromosomes is believed to undergo V_κ-J_κ rearrangements first before the IGL light chain locus on either chromosome becomes receptive for V_λ-J_λ recombination. If an initial κ rearrangement is unproductive, additional rounds of secondary rearrangement can proceed, in a process known as receptor editing (Collins and Watson. (2018) Immunoglobulin light chain gene rearrangements, receptor editing and the development of a self-tolerant antibody repertoire. Front. Immunol. 9:2249.) A process of serial rearrangement of the κ chain locus may continue on one chromosome until all possibilities of recombination are exhausted. Recombination will then proceed on the second κ chromosome. A failure to produce a productive rearrangement on the second chromosome after multiple rounds of rearrangement will be followed by rearrangement on the λ loci (Collins and Watson (2018) Immunoglobulin light chain gene rearrangements, receptor editing and the development of a self-tolerant antibody repertoire. Front. Immunol. 9:2249.)

[000134] This preferential order of light chain rearrangements is believed to give rise to a light chain repertoire in mouse that is >90% κ and <10% λ. However, immunoglobulins in the dog immune system are dominated by λ light chain usage, which has been estimated to be at least 90% λ to <10% κ (Arun et al. (1996) Immunohistochemical examination of

light-chain expression (λ/κ ratio) in canine, feline, equine, bovine and porcine plasma cells. Zentralbl Veterinarmed A. 43(9):573-6).

[000135] The murine and canine Ig loci are highly complex in the numbers of features they contain and in how their coding regions are diversified by V(D)J rearrangement; however, this complexity does not extend to the basic details of the structure of each variable region gene segment. The V, D and J gene segments are highly uniform in their compositions and organizations. For example, V gene segments have the following features that are arranged in essentially invariant sequential fashion in immunoglobulin loci: a short transcriptional promoter region (<600bp in length), an exon encoding the 5' UTR and the majority of the signal peptide for the antibody chain; an intron; an exon encoding a small part of the signal peptide of the antibody chain and the majority of the antibody variable domain, and a 3' recombination signal sequence necessary for V(D)J rearrangement. Similarly, D gene segments have the following necessary and invariant features: a 5' recombination signal sequence, a coding region and a 3' recombination signal sequence. The J gene segments have the following necessary and invariant features: a 5' recombination signal sequence, a coding region and a 3' splice donor sequence.

[000136] The canine genome V_H region comprises approximately 39 functional V_H , 6 functional D and 5 functional J_H gene segments mapping to a 1.46 Mb region of canine chromosome 8. There are also numerous V_H pseudogenes and one J_H gene segment (IGHJ1) and one D gene segment (IGHD5) that are thought to be non-functional because of non-canonical heptamers in their RSS. (Such gene segments are referred to as Open Reading Frames (ORFs).) Figure 12A provides a schematic diagram of the endogenous canine IGH locus (1201) as well as an expanded view of the IGHC region (1202). The canine immunoglobulin heavy chain variable region locus, which includes V_H (1203), D (1204) and J_H (1205) gene segments, has all functional genes in the same transcriptional orientation as the constant region genes (1206), with two pseudogenes (IGHV3-4 and IGHV1-4-1) in the reverse transcriptional orientation (not shown). A transcriptional enhancer (1207) and the (1208) μ switch region are located within the J_H -C μ intron. See, Martin et al. (2018) Comprehensive annotation and evolutionary insights into the canine (*Canis lupus familiaris*) antigen receptor loci. Immunogenetics. 70:223-236. Among the IGHC genes, C δ (1210) is thought to be non-functional. Moreover, although cDNA clones

identified as encoding canine IgG1 (1212), IgG2 (1213), IgG3 (1211) and IgG4 (1214) have been isolated (Tang, et al. (2001) Cloning and characterization of cDNAs encoding four different canine immunoglobulin γ chains. Vet. Immunol. and Immunopath. 80:259 PMID 11457479), only the IgG2 constant region gene has been physically mapped to the canine IGHC locus on chromosome 8. Functional versions of C_{μ} (1209), C_{ϵ} (1215) and C_{α} (1216) have also been physically mapped there.

[000137] The sequences of the canine IGHC are in Table 4.

[000138] The canine IGL locus maps to canine chromosome 26, while the canine IGK coding region maps to canine chromosome 17. Figures 12B and 12C provide schematic diagrams of the endogenous canine IGL and IGK loci, respectively.

[000139] The sequences of the canine IGKC and IGLC are in Table 4.

[000140] The canine λ locus (1217) is large (2.6 Mbp) with 162 V_{λ} genes (1218), of which at least 76 are functional. The canine λ locus also includes 9 tandem cassettes or J-C units, each containing a J_{λ} gene segment and a C_{λ} exon (1219). See, Martin et al. (2018) Comprehensive annotation and evolutionary insights into the canine (*Canis lupus familiaris*) antigen receptor loci. Immunogenetics. 70:223-236.

[000141] The canine κ locus (1220) is small (400 Kbp) and has an unusual structure in that eight of the functional V_{κ} gene segments are located upstream (1222) and five are located downstream (1226) of the J_{κ} (1223) gene segments and C_{κ} (1224) exon. The canine upstream V_{κ} region has all functional gene segments in the same transcriptional orientation as the J_{κ} gene segment and C_{κ} exon, with two pseudogenes (IGKV3-3 and IGKV7-2) and one ORF (IGKV4-1) in the reverse transcriptional orientation (not shown). The canine downstream V_{κ} region has all functional gene segments in the opposite transcriptional orientation as the J_{κ} gene segment and C_{κ} exon and includes six pseudogenes. The Ribose 5-Phosphate Isomerase A (RPIA) gene (1225) is also found in the downstream V_{κ} region, between C_{κ} and IGKV2S19. See, Martin et al. (2018) Comprehensive annotation and evolutionary insights into the canine (*Canis lupus familiaris*) antigen receptor loci. Immunogenetics. 70:223-236.

[000142] The mouse immunoglobulin κ locus is located on chromosome 6. Figure 1B provides a schematic diagram of the endogenous mouse IGK locus. The IGK locus (112) spans 3300 Kbp and includes more than 100 variable V_{κ} gene segments (113) located

upstream of 5 joining (J_{κ}) gene segments (114) and one constant (C_{κ}) gene (115). The mouse κ locus includes an intronic enhancer (iE_{κ} , 116) located between J_{κ} and C_{κ} that activates κ rearrangement and helps maintain the earlier or more efficient rearrangement of κ versus λ (Inlay et al. (2004) Important Roles for E Protein Binding Sites within the Immunoglobulin κ chain intronic enhancer in activating $V_{\kappa}J_{\kappa}$ rearrangement. J. Exp. Med. 200(9):1205-1211). Another enhancer, the 3' enhancer ($3'E_{\kappa}$, 117) is located 9.1 Kb downstream of the C_{κ} exon and is also involved in κ rearrangement and transcription; mutant mice lacking both iE_{κ} and $3'E_{\kappa}$ have no $V_{\kappa}J_{\kappa}$ rearrangements in the κ locus (Inlay et al. (2002) Essential roles of the kappa light chain intronic enhancer and 3' enhancer in kappa rearrangement and demethylation. Nature Immunol. 3(5):463-468). However, disrupting the iE_{κ} , for example, by insertion of a neomycin-resistance gene is also sufficient to abolish most $V_{\kappa}J_{\kappa}$ rearrangements (Xu et al. (1996) Deletion of the Igk Light Chain Intronic Enhancer/Matrix Attachment Region Impairs but Does Not Abolish $V_{\kappa}J_{\kappa}$ Rearrangement).

[000143] The mouse immunoglobulin λ locus is located on chromosome 16. Figure 1C provides a schematic diagram of the endogenous mouse IGL locus (118). The organization of the mouse immunoglobulin λ locus is different from the mouse immunoglobulin κ locus. The locus spans 240 kb, with two clusters comprising 3 functional variable (V_{λ}) gene segments (IGLV2, 119; IGLV3, 120 and IGLV1, 123) and 3 tandem cassettes of λ joining (J_{λ}) gene segments and constant (C_{λ}) gene segments (IGLJ2, 121; IGLC2, 122; IGLJ3, 124; IGLC3, 125; IGLJ1, 126; IGLC1, 127) in which the V_{λ} gene segments are located upstream (5') from a variable number of J-C tandem cassettes. The locus also contains three transcriptional enhancers ($E_{\lambda 2-4}$, 128; E_{λ} , 129; $E_{\lambda 3-1}$, 130).

[000144] The partly canine nucleic acid sequence described herein allows the transgenic animal to produce a heavy chain or light chain repertoire comprising canine V_H or V_L regions, while retaining the regulatory sequences and other elements that can be found within the intervening sequences of the host genome (e.g., rodent) that help to promote efficient antibody production and antigen recognition in the host.

[000145] In one aspect, synthetic, or recombinantly produced, partly canine nucleic acids are engineered to comprise both canine coding sequences and non-canine non-coding

regulatory or scaffold sequences of an immunoglobulin V_H , V_λ or V_κ locus, or, in some aspects, a combination thereof.

[000146] In one aspect, a transgenic rodent or rodent cell that expresses immunoglobulin with a canine variable region can be generated by inserting one or more canine V_H gene segment coding sequences into a V_H locus of a rodent heavy chain immunoglobulin locus. In another aspect, a transgenic rodent or rodent cell that expresses immunoglobulin with canine a variable region can be generated by inserting one or more canine V_L gene segment coding sequences into a V_L locus of a rodent light chain immunoglobulin locus.

[000147] The existence of two light chain loci – κ and λ – means that a variety of light chain insertion combinations are possible for generating a transgenic rodent or rodent cell that expresses immunoglobulin with canine a variable region, including but not limited to: inserting one or more canine V_λ or J_λ gene segment coding sequences into a rodent V_λ locus, inserting one or more canine V_κ or J_κ gene segment coding sequences into a rodent V_κ locus, inserting one or more canine V_λ or J_λ gene segment coding sequences into a rodent V_κ locus and inserting one or more canine V_κ or J_κ gene segment coding sequences into a rodent V_λ locus.

[000148] The selection and development of a transgenic rodent or rodent cell that expresses partly canine immunoglobulin is complicated by the fact that more than 90% of light chains produced by mice are κ and less than 10% are λ , whereas more than 90% of light chains produced by dogs are λ and less than 10% κ and the fact that the canine immunoglobulin λ locus is large and includes over 100 V_λ gene segments, whereas the mouse immunoglobulin λ includes only 3 functional V_λ gene segments.

[000149] Since mice produce mainly κ LC-containing antibodies, one reasonable method to increase production of λ LC-containing partly canine immunoglobulin by the transgenic rodent would be to insert one or more canine V_λ or J_λ gene segment coding sequences into a rodent κ locus. However, as shown in the Example 9 below, coupling canine V_λ region exon with rodent C_κ region exon results in sub-optimal expression of the partly canine immunoglobulin in vitro.

[000150] Provided herein is a transgenic rodent or rodent cell that is capable of expressing immunoglobulin comprising canine variable domains, wherein the transgenic rodent produces more or is more likely to produce immunoglobulin comprising λ light chain than

immunoglobulin comprising κ light chain. While not wishing to be bound by theory, it is believed that a transgenic rodent or rodent cell that produces more, or is more likely to produce, immunoglobulin comprising λ light chain will result in a fuller antibody repertoire for the development of therapeutics.

[000151] A transgenic rodent or rodent cell having a genome comprising an engineered partly canine immunoglobulin light chain locus is provided herein. In one aspect, the partly canine immunoglobulin light chain locus comprises canine immunoglobulin λ light chain variable region gene segments. In one aspect, the engineered immunoglobulin locus is capable of expressing immunoglobulin comprising a canine variable domain. In one aspect, the engineered immunoglobulin locus is capable of expressing immunoglobulin comprising a canine λ variable domain. In one aspect, the engineered immunoglobulin locus is capable of expressing immunoglobulin comprising a canine κ variable domain. In one aspect, the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine variable domain and a rodent constant domain. In one aspect, the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine λ variable domain and a rodent λ constant domain. In one aspect, the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine κ variable domain and a rodent κ constant domain.

[000152] In one aspect, the transgenic rodent or rodent cell produces more, or is more likely to produce, immunoglobulin comprising λ light chain than immunoglobulin comprising κ light chain. In one aspect, a transgenic rodent is provided in which more λ light chain producing cells than κ light chain producing cells are likely to be isolated from the rodent. In one aspect, a transgenic rodent is provided that produces at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% and up to about 100% immunoglobulin comprising λ light chain. In one aspect, a transgenic rodent cell, or its progeny, is provided that is more likely to produce immunoglobulin with λ light chain than immunoglobulin with κ light chain. In one aspect, the transgenic rodent cell, or its progeny, has at least about a 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% and up to about 100%, probability of producing immunoglobulin comprising λ light chain. In one aspect, a transgenic rodent or rodent cell is provided in which an endogenous rodent light chain immunoglobulin locus has been

deleted and replaced with an engineered partly canine light chain immunoglobulin locus. In one aspect, the transgenic rodent is a mouse.

Immunoglobulin Light Chain Locus

[000153] In one aspect, a transgenic rodent or rodent cell is provided that has a genome comprising a recombinantly produced partly canine immunoglobulin variable region locus. In one aspect, the partly canine immunoglobulin variable region locus is a light chain variable region (V_L) locus. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences or one or more canine J_λ gene segment coding sequences. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more canine V_κ gene segment coding sequences or one or more canine J_κ gene segment coding sequences. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more rodent constant domain genes or coding sequences. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more rodent C_λ genes or coding sequences. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more rodent C_κ genes or coding sequences. In one aspect, an endogenous rodent light chain immunoglobulin locus has been inactivated. In one aspect, an endogenous rodent light chain immunoglobulin locus has been deleted and replaced with an engineered partly canine light chain immunoglobulin locus.

[000154] In one aspect, the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine λ variable domain and rodent λ constant domain. In one aspect, the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine κ variable domain and rodent κ constant domain.

[000155] In one aspect, the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising most or all of the V_λ gene segments coding sequences from a canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising at least 20, 30, 40, 50, 60, 70 and up to 76 canine V_λ gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%,

60%, 70%, 80%, 90% and up to 100% of the V_{λ} gene segment coding sequences from a canine genome.

[000156] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising most or all of the J_{λ} gene segment coding sequences found in the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 canine J_{λ} gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%, 75%, and up to 100% of the J_{λ} gene segment coding sequences found in the canine genome.

[000157] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising most or all of the V_{λ} and J_{λ} gene segment coding sequences from the canine genome. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_{λ} and J_{λ} gene segment coding sequences from the canine genome.

[000158] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising most or all of the V_{κ} gene segment coding sequences from the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and up to 14 canine V_{κ} gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_{κ} gene segment coding sequences from the canine genome.

[000159] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising most or all of the J_{κ} gene segment coding sequences found in the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising at least 1, 2, 3, 4 or 5 canine J_{κ} gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%, 75%, and up to 100% of the J_{κ} gene segment coding sequences found in the canine genome.

[000160] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_L locus comprising most or all of the V_κ and J_κ gene segment coding sequences from the canine genome. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_L locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_κ and J_κ gene segment coding sequences from the canine genome.

[000161] In one aspect, the engineered immunoglobulin locus comprises canine V_L gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ or J_λ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin light chain variable region gene locus. In one aspect, the rodent non-coding regulatory or scaffold sequences are from a rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the rodent non-coding regulatory or scaffold sequences are from a rodent immunoglobulin κ light chain variable region locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the partly canine immunoglobulin locus comprises one or more rodent immunoglobulin λ constant region (C_λ) coding sequences. In one aspect, the partly canine immunoglobulin locus comprises one or more canine V_λ and J_λ gene segment coding sequences and one or more rodent immunoglobulin C_λ coding sequences. In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences and one or more rodent C_λ coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin λ light chain variable region gene locus.

[000162] In one aspect, the engineered immunoglobulin locus comprises canine V_λ or J_λ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin κ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ or J_λ gene segment coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent

immunoglobulin κ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences and one or more rodent immunoglobulin C_λ coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin κ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences and one or more rodent immunoglobulin C_λ coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain variable region gene locus.

[000163] In one aspect, one or more canine V_λ gene segment coding sequences are located upstream of one or more J_λ gene segment coding sequences, which are located upstream of one or more rodent C_λ genes. In one aspect, one or more canine V_λ gene segment coding sequences are located upstream and in the same transcriptional orientation as one or more J_λ gene segment coding sequences, which are located upstream of one or more rodent C_λ genes.

[000164] In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences, one or more canine J_λ gene segment coding sequences and one or more rodent C_λ genes. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences, one or more canine J_λ gene segment coding sequence and one or more rodent C_λ region genes, wherein the V_λ and J_λ gene segment coding sequences and the rodent C_λ region genes are inserted into a rodent immunoglobulin κ light chain locus. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences, one or more canine J_λ gene segment coding sequence and one or more rodent C_λ genes, wherein the V_λ and J_λ gene segment coding sequences and the rodent (C_λ) region genes are embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus.

[000165] In one aspect, one or more canine V_λ gene segment coding sequences are located upstream of one or more J_λ gene segment coding sequences, which are located upstream of one or more rodent C_λ genes, wherein the V_λ and J_λ gene segment coding sequences and rodent C_λ genes are inserted into a rodent immunoglobulin κ light chain locus. In one

aspect, one or more canine V_λ gene segment coding sequences are located upstream of one or more J_λ gene segment coding sequences, which are located upstream of one or more rodent C_λ genes, wherein the V_λ and J_λ gene segment coding sequences and rodent C_λ genes are embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus.

[000166] In one aspect, the rodent C_λ coding sequence is selected from a rodent $C_{\lambda 1}$, $C_{\lambda 2}$, or $C_{\lambda 3}$ coding sequence.

[000167] In one aspect, a transgenic rodent or rodent cell is provided, wherein the engineered immunoglobulin locus comprises a rodent immunoglobulin κ locus in which one or more rodent V_κ gene segment coding sequences and one or more rodent J_κ gene segment coding sequences have been deleted and replaced by one or more canine V_λ gene segment coding sequences and one or more J_λ gene segment coding sequences, respectively, and in which rodent C_κ coding sequences in the locus have been replaced by rodent $C_{\lambda 1}$, $C_{\lambda 2}$, or $C_{\lambda 3}$ coding sequence.

[000168] In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ gene. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent C_λ region coding sequence, wherein the V_λ gene segment coding sequences and the J-C units are inserted into a rodent immunoglobulin κ light chain locus. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent C_λ coding sequence, wherein the V_λ gene segment coding sequences and the J-C units are embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus.

[000169] In one aspect, one or more canine V_λ gene segment coding sequences are located upstream and in the same transcriptional orientation as one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ gene. In one

aspect, one or more canine V_λ gene segment coding sequences are located upstream and in the same transcriptional orientation as one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ coding sequence. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences located upstream of one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent C_λ coding sequence, wherein the V_λ gene segment coding sequences and the J-C units are inserted into a rodent immunoglobulin κ light chain locus. In one aspect, the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences upstream and in the same transcriptional orientation as one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and rodent C_λ coding sequence, wherein the V_λ gene segment coding sequences and the J-C units are embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus. In one aspect, the rodent C_λ coding sequence is selected from a rodent $C_{\lambda 1}$, $C_{\lambda 2}$, or $C_{\lambda 3}$ coding sequence.

[000170] In one aspect, the engineered immunoglobulin locus comprises canine V_κ coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_κ or J_κ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin light chain variable region gene locus. In one aspect, the rodent non-coding regulatory or scaffold sequences are from a rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the rodent non-coding regulatory or scaffold sequences are from a rodent immunoglobulin κ light chain variable region locus. In one aspect, the engineered immunoglobulin locus comprises canine V_κ and J_κ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin κ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_κ and J_κ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin λ light chain variable region gene locus. In one aspect, the partly canine immunoglobulin locus comprises one

rodent immunoglobulin C_κ coding sequences. In one aspect, the partly canine immunoglobulin locus comprises one or more rodent immunoglobulin C_λ coding sequences. In one aspect, the partly canine immunoglobulin locus comprises one or more canine V_κ and J_κ gene segment coding sequences and one rodent immunoglobulin C_κ coding sequences. In one aspect, the engineered immunoglobulin locus comprises canine V_κ and J_κ gene segment coding sequences and one rodent immunoglobulin C_κ coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent κ light chain variable region gene locus. In one aspect, the engineered immunoglobulin locus comprises canine V_κ and J_κ gene segment coding sequences and one rodent immunoglobulin C_κ coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin λ light chain variable region gene locus.

[000171] While not wishing to be bound by theory, it is believed that inactivating or rendering nonfunctional an endogenous rodent κ light chain locus may increase expression of λ light chain immunoglobulin from the partly canine immunoglobulin locus. This has been shown to be the case in otherwise conventional mice in which the κ light chain locus has been inactivated in the germline (Zon, et al. (1995) Subtle differences in antibody responses and hypermutation of λ light chains in mice with a disrupted κ constant region. *Eur. J. Immunol.* 25:2154-2162). In one aspect, inactivating or rendering nonfunctional an endogenous rodent κ light chain locus may increase the relative amount of immunoglobulin comprising λ light chain relative to the amount of immunoglobulin comprising κ light chain produced by the transgenic rodent or rodent cell.

[000172] In one aspect, a transgenic rodent or rodent cell is provided in which an endogenous rodent immunoglobulin κ light chain locus is deleted, inactivated, or made nonfunctional. In one aspect, the endogenous rodent immunoglobulin κ light chain locus is inactivated or made nonfunctional by one or more of the following deleting or mutating all endogenous rodent V_κ gene segment coding sequences; deleting or mutating all endogenous rodent J_κ gene segment coding sequences; deleting or mutating the endogenous rodent C_κ coding sequence; deleting, mutating, or disrupting the endogenous intronic κ enhancer (iE_κ) and 3' enhancer sequence (3'E_κ); or a combination thereof.

[000173] In one aspect, a transgenic rodent or rodent cell is provided in which an endogenous rodent immunoglobulin λ light chain variable domain is deleted, inactivated, or made nonfunctional. In one aspect, the endogenous rodent immunoglobulin λ light chain variable domain is inactivated or made nonfunctional by one or more of the following: deleting or mutating all endogenous rodent V_{κ} gene segments; deleting or mutating all endogenous rodent J_{λ} gene segments; deleting or mutating all endogenous rodent C_{λ} coding sequences; or a combination thereof.

[000174] In one aspect, the partly canine immunoglobulin locus comprises rodent regulatory or scaffold sequences, including, but not limited to enhancers, promoters, splice sites, introns, recombination signal sequences, and combinations thereof. In one aspect, the partly canine immunoglobulin locus comprises rodent λ regulatory or scaffold sequences. In one aspect, the partly canine immunoglobulin locus comprises rodent κ regulatory or scaffold sequences.

[000175] In one aspect, the partly canine immunoglobulin locus includes a promoter to drive gene expression. In one aspect, the partly canine immunoglobulin locus includes a κ V-region promoter. In one aspect, the partly canine immunoglobulin locus includes a λ V-region promoter. In one aspect, the partly canine immunoglobulin locus includes a λ V-region promoter to drive expression of one or more λ LC gene coding sequences created after V_{λ} to J_{λ} gene segment rearrangement. In one aspect, the partly canine immunoglobulin locus includes a λ V-region promoter to drive expression of one or more κ LC gene coding sequences created after V_{κ} to J_{κ} gene segment rearrangement. In one aspect, the partly canine immunoglobulin locus includes a κ V-region promoter to drive expression of one or more λ LC gene coding sequences created after V_{λ} to J_{λ} gene segment rearrangement. In one aspect, the partly canine immunoglobulin locus includes a κ V-region promoter to drive expression of one or more κ LC gene coding sequences created after V_{κ} to J_{κ} gene segment rearrangement.

[000176] In one aspect, the partly canine immunoglobulin locus includes one or more enhancers. In one aspect, the partly canine immunoglobulin locus includes a mouse κ iE $_{\kappa}$ or 3'E $_{\kappa}$ enhancer. In one aspect, the partly canine immunoglobulin locus includes one or more V_{λ} or J_{λ} gene segment coding sequences and a mouse κ iE $_{\kappa}$ or 3'E $_{\kappa}$ enhancer. In one

aspect, the partly canine immunoglobulin locus includes one or more V_{κ} or J_{κ} gene segment coding sequences and a κ iE κ or 3'E κ enhancer.

Immunoglobulin Heavy Chain Locus

[000177] In one aspect, a transgenic rodent or rodent cell has a genome comprising a recombinantly produced partly canine immunoglobulin heavy chain variable region (V_H) locus. In one aspect, the partly canine immunoglobulin variable region locus comprises one or more canine V_H , D or J_H gene segment coding sequences. In one aspect, the partly canine immunoglobulin heavy chain variable region locus comprises one or more rodent constant domain (C_H) genes or coding sequences. In one aspect, an endogenous rodent heavy chain immunoglobulin locus has been inactivated. In one aspect, an endogenous rodent heavy chain immunoglobulin locus has been deleted and replaced with an engineered partly canine heavy chain immunoglobulin locus.

[000178] In one aspect, the synthetic H chain DNA segment contains the ADAM6A or ADAM6B gene needed for male fertility, Pax-5-Activated Intergenic Repeats (PAIR) elements involved in Igh locus contraction and CTCF binding sites from the heavy chain intergenic control region 1, involved in regulating normal VDJ rearrangement ((Proudhon, et al., Adv. Immunol., 128:123-182 (2015)), or various combinations thereof. The locations of these endogenous non-coding regulatory and scaffold sequences in the mouse IGH locus are depicted in FIG 1, which illustrates from left to right: the ~100 functional heavy chain variable region gene segments (101); PAIR, Pax-5 Activated Intergenic Repeats involved in IGH locus contraction for VDJ recombination (102); ADAM6A or ADAM6B, a disintegrin and metallopeptidase domain 6A gene required for male fertility (103); Pre-D region, a 21609 bp fragment upstream of the most distal D_H gene segment, IGHD-5 D (104); Intergenic Control Region 1 (IGCR1) that contains CTCF insulator sites to regulate V_H gene segment usage (106); D, diversity gene segments (10-15 depending on the mouse strain) (105); four joining J_H gene segments (107); E_{μ} , the intronic enhancer involved in VDJ recombination (108); S_{μ} , the μ switch region for isotype switching (109); eight heavy chain constant region genes: C_{μ} , C_{δ} , $C_{\gamma 3}$, $C_{\gamma 1}$, $C_{\gamma 2b}$, $C_{2\gamma a/c}$, C_{ϵ} , and C_{α} (110); 3' Regulatory Region (3'RR) that controls isotype switching and somatic hypermutation (111). FIG. 1A is modified from a figure taken from Proudhon, et al., Adv. Immunol., 128:123-182 (2015).

[000179] In one aspect, the engineered partly canine region to be integrated into a mammalian host cell comprises all or a substantial number of the known canine V_H gene segments. In some instances, however, it may be desirable to use a subset of such V_H gene segments, and in specific instances even as few as one canine V_H coding sequence may be introduced into the cell or the animal.

[000180] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising most or all of the V_H gene segment coding sequences from the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising at least 20, 30 and up to 39 functional canine V_H gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_H locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_H gene segment coding sequences from the canine genome.

[000181] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising most or all of the V_H gene segment coding sequences from the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising at least 20, 30, 40, 50, 60, 70 and up to 80 canine V_H gene segment coding sequences. In this aspect the V_H gene segment pseudogenes are reverted to restore their functionality, e.g., by mutating an in-frame stop codon into a functional codon, using methods well known in the art. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_H locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_H gene segment coding sequences from the canine genome.

[000182] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising most or all of the D gene segment coding sequences found in the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising at least 1, 2, 3, 4, 5 and up to 6 canine D gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_H locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the D gene segment coding sequences found in the canine genome.

[000183] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising most or all of the J_H gene segment coding sequences found in the canine genome. In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising at least 1, 2, 3, 4, 5 and up to 6 canine J_H gene segment coding sequences. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_H locus comprising at least about 50%, 75%, and up to 100% of J_H gene segment coding sequences found in the canine genome.

[000184] In one aspect, the engineered partly canine immunoglobulin locus variable region comprises a V_H locus comprising most or all of the V_H , D and J_H gene segment coding sequences from the canine genome. In one aspect the engineered partly canine immunoglobulin variable region locus comprises a V_H locus comprising at least about 50%, 60%, 70%, 80%, 90% and up to 100% of the V_H , D and J_H gene segment coding sequences from the canine genome.

[000185] In one aspect, a transgenic rodent or rodent cell is provided that includes an engineered partly canine immunoglobulin heavy chain locus comprising canine immunoglobulin heavy chain variable region gene coding sequences and non-coding regulatory or scaffold sequences of the rodent immunoglobulin heavy chain locus. In one aspect, the engineered canine immunoglobulin heavy chain locus comprises canine V_H , D or J_H gene segment coding sequences. In one aspect, the engineered canine immunoglobulin heavy chain locus comprises canine V_H , D or J_H gene segment coding sequences embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin heavy chain locus.

[000186] In one aspect, non-canine mammals and mammalian cells comprising an engineered partly canine immunoglobulin locus that comprises coding sequences of canine V_H , canine D, and canine J_H genes are provided that further comprises non-coding regulatory and scaffold sequences, including pre-D sequences, based on the endogenous IGH locus of the non-canine mammalian host. In certain aspects, the exogenously introduced, engineered partly canine region can comprise a fully recombined V(D)J exon.

[000187] In one aspect, the transgenic non-canine mammal is a rodent, for example, a mouse, comprising an exogenously introduced, engineered partly canine immunoglobulin locus comprising codons for multiple canine V_H , canine D, and canine J_H genes with intervening

sequences, including a pre-D region, based on the intervening (non-coding regulatory or scaffold) sequences in the rodent. In one aspect, the transgenic rodent further comprises partly canine IGL loci comprising coding sequences of canine V_{κ} or V_{λ} genes and J_{κ} or J_{λ} genes, respectively, in conjunction with their intervening (non-coding regulatory or scaffold) sequences corresponding to the immunoglobulin intervening sequences present in the IGL loci of the rodent.

[000188] In an exemplary embodiment, as set forth in more detail in the Examples section, the entire endogenous V_H immunoglobulin locus of the mouse genome is deleted and subsequently replaced with a partly canine immunoglobulin locus comprising 39 canine V_H gene segments containing interspersed non-coding sequences corresponding to the non-coding sequences of the J558 V_H locus of the mouse genome. The complete, exogenously introduced, engineered immunoglobulin locus further comprises canine D and J_H gene segments, as well as the mouse pre-D region. Thus, the canine V_H , D and J_H codon sequences are embedded in the rodent intergenic and intronic sequences.

Preparation of a Partly Canine Immunoglobulin Locus

[000189] In one aspect, an endogenous immunoglobulin locus variable region of a non-canine mammal, such as a rodent, for example a rat or mouse, which contains V_H , D and J_H or V_L and J_L gene segments, is deleted using site-specific recombinases and replaced with an engineered partly canine immunoglobulin locus. In one aspect, the partly canine immunoglobulin locus is inserted into the genome of the host animal as a single nucleic acid or cassette. Because a cassette that includes the partly canine immunoglobulin locus is used to replace the endogenous immunoglobulin locus variable region, the canine coding sequences can be inserted into the host genome in a single insertion step, thus providing a rapid and straightforward process for obtaining a transgenic animal.

[000190] In one aspect, the engineered partly canine immunoglobulin locus variable region is prepared by deleting murine V_H , D and J_H or V_L and J_L coding sequences from a mouse immunoglobulin locus variable region and replacing the murine coding sequences with canine coding sequences. In one aspect, the non-coding flanking sequences of the murine immunoglobulin locus, which include regulatory sequences and other elements, are left intact.

[000191] In one aspect, the nucleotide sequence for the engineered partly canine immunoglobulin locus is prepared *in silico* and the locus is synthesized using known techniques for gene synthesis. In one aspect, coding sequences from a canine immunoglobulin variable region locus and sequences of the host animal immunoglobulin locus are identified using a search tool such as BLAST (Basic Local Alignment Search Tool). After obtaining the genomic sequences of the host immunoglobulin locus and the coding sequences of the canine immunoglobulin variable region locus, the host coding sequences can be replaced *in silico* with the canine coding sequences using known computational approaches to locate and delete the endogenous host animal immunoglobulin coding segments and replace the coding sequences with canine coding sequences, leaving the endogenous regulatory and flanking sequences intact.

Homologous Recombination

[000192] In one aspect, a combination of homologous recombination and site-specific recombination is used to create the cells and animals described herein. In some embodiments, a homology targeting vector is first used to introduce the sequence-specific recombination sites into the mammalian host cell genome at a desired location in the endogenous immunoglobulin loci. In one aspect, in the absence of a recombinase protein, the sequence-specific recombination site inserted into the genome of a mammalian host cell by homologous recombination does not affect expression and amino acid codons of any genes in the mammalian host cell. This approach maintains the proper transcription and translation of the immunoglobulin genes which produce the desired antibody after insertion of recombination sites and, optionally, any additional sequence such as a selectable marker gene. However, in some cases it is possible to insert a recombinase site and other sequences into an immunoglobulin locus sequence such that an amino acid sequence of the antibody molecule is altered by the insertion, but the antibody still retains sufficient functionality for the desired purpose. Examples of such codon-altering homologous recombination may include the introduction of polymorphisms into the endogenous locus and changing the constant region exons so that a different isotype is expressed from the endogenous locus. In one aspect, the immunoglobulin locus includes one or more of such insertions.

[000193] In one aspect, the homology targeting vector can be utilized to replace certain sequences within the endogenous genome as well as to insert certain sequence-specific recombination sites and one or more selectable marker genes into the host cell genome. It is understood by those of ordinary skill in the art that a selectable marker gene as used herein can be exploited to weed out individual cells that have not undergone homologous recombination and cells that harbor random integration of the targeting vector.

[000194] Exemplary methodologies for homologous recombination are described in U.S. Pat. Nos. 6,689,610; 6,204,061; 5,631,153; 5,627,059; 5,487,992; and 5,464,764, each of which is incorporated by reference in its entirety.

Site/Sequence-Specific Recombination

[000195] Site/sequence-specific recombination differs from general homologous recombination in that short specific DNA sequences, which are required for recognition by a recombinase, are the only sites at which recombination occurs. Depending on the orientations of these sites on a particular DNA strand or chromosome, the specialized recombinases that recognize these specific sequences can catalyze i) DNA excision or ii) DNA inversion or rotation. Site-specific recombination can also occur between two DNA strands if these sites are not present on the same chromosome. A number of bacteriophage- and yeast-derived site-specific recombination systems, each comprising a recombinase and specific cognate sites, have been shown to work in eukaryotic cells and are therefore applicable for use in connection with the methods described herein, and these include the bacteriophage P1 Cre/lox, yeast FLP-FRT system, and the Dre system of the tyrosine family of site-specific recombinases. Such systems and methods of use are described, e.g., in U.S. Pat. Nos. 7,422,889; 7,112,715; 6,956,146; 6,774,279; 5,677,177; 5,885,836; 5,654,182; and 4,959,317, each of which is incorporated herein by reference to teach methods of using such recombinases.

[000196] Other systems of the tyrosine family of site-specific recombinases such as bacteriophage lambda integrase, HK2022 integrase, and in addition systems belonging to the separate serine family of recombinases such as bacteriophage phiC31, R4Tp901 integrases are known to work in mammalian cells using their respective recombination sites, and are also applicable for use in the methods described herein.

[000197] Since site-specific recombination can occur between two different DNA strands, site-specific recombination occurrence can be utilized as a mechanism to introduce an exogenous locus into a host cell genome by a process called recombinase-mediated cassette exchange (RMCE). The RMCE process can be exploited by the combined usage of wild-type and mutant sequence-specific recombination sites for the same recombinase protein together with negative selection. For example, a chromosomal locus to be targeted may be flanked by a wild-type LoxP site on one end and by a mutant LoxP site on the other. Likewise, an exogenous vector containing a sequence to be inserted into the host cell genome may be similarly flanked by a wild-type LoxP site on one end and by a mutant LoxP site on the other. When this exogenous vector is transfected into the host cell in the presence of Cre recombinase, Cre recombinase will catalyze RMCE between the two DNA strands, rather than the excision reaction on the same DNA strands, because the wild-type LoxP and mutant LoxP sites on each DNA strand are incompatible for recombination with each other. Thus, the LoxP site on one DNA strand will recombine with a LoxP site on the other DNA strand; similarly, the mutated LoxP site on one DNA strand will only recombine with a likewise mutated LoxP site on the other DNA strand.

[000198] In one aspect, combined variants of the sequence-specific recombination sites are used that are recognized by the same recombinase for RMCE. Examples of such sequence-specific recombination site variants include those that contain a combination of inverted repeats or those which comprise recombination sites having mutant spacer sequences. For example, two classes of variant recombinase sites are available to engineer stable Cre-loxP integrative recombination. Both exploit sequence mutations in the Cre recognition sequence, either within the 8 bp spacer region or the 13-bp inverted repeats. Spacer mutants such as lox511 (Hoess, et al., *Nucleic Acids Res*, 14:2287-2300 (1986)), lox5171 and lox2272 (Lee and Saito, *Gene*, 216:55-65 (1998)), m2, m3, m7, and m11 (Langer, et al., *Nucleic Acids Res*, 30:3067-3077 (2002)) recombine readily with themselves but have a markedly reduced rate of recombination with the wild-type site. This class of mutants has been exploited for DNA insertion by RMCE using non-interacting Cre-Lox recombination sites and non-interacting FLP recombination sites (Baer and Bode, *Curr Opin Biotechnol*, 12:473-480 (2001); Albert, et al., *Plant J*, 7:649-659 (1995); Seibler and Bode,

Biochemistry, 36:1740-1747 (1997); Schlake and Bode, Biochemistry, 33:12746-12751 (1994)).

[000199] Inverted repeat mutants represent the second class of variant recombinase sites. For example, LoxP sites can contain altered bases in the left inverted repeat (LE mutant) or the right inverted repeat (RE mutant). An LE mutant, lox71, has 5 bp on the 5' end of the left inverted repeat that is changed from the wild type sequence to TACCG (Araki, et al, Nucleic Acids Res, 25:868-872 (1997)). Similarly, the RE mutant, lox66, has the five 3'-most bases changed to CGGTA. Inverted repeat mutants are used for integrating plasmid inserts into chromosomal DNA with the LE mutant designated as the "target" chromosomal loxP site into which the "donor" RE mutant recombines. Post-recombination, loxP sites are located in *cis*, flanking the inserted segment. The mechanism of recombination is such that post-recombination one loxP site is a double mutant (containing both the LE and RE inverted repeat mutations) and the other is wild type (Lee and Sadowski, Prog Nucleic Acid Res Mol Biol, 80:1-42 (2005); Lee and Sadowski, J Mol Biol, 326:397-412 (2003)). The double mutant is sufficiently different from the wild-type site that it is unrecognized by Cre recombinase and the inserted segment is not excised.

[000200] In certain aspects, sequence-specific recombination sites can be introduced into introns, as opposed to coding nucleic acid regions or regulatory sequences. This avoids inadvertently disrupting any regulatory sequences or coding regions necessary for proper antibody expression upon insertion of sequence-specific recombination sites into the genome of the animal cell.

[000201] Introduction of the sequence-specific recombination sites may be achieved by conventional homologous recombination techniques. Such techniques are described in references such as e.g., Sambrook and Russell (2001) (Molecular cloning: a laboratory manual 3rd ed. (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press) and Nagy, A. (2003). (Manipulating the mouse embryo: a laboratory manual, 3rd ed. (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press). Renault and Duchateau, Eds. (2013) (Site-directed insertion of transgenes. Topics in Current Genetics 23. Springer). Tsubouchi, H. Ed. (2011) (DNA recombination, Methods and Protocols. Humana Press).

[000202] Specific recombination into the genome can be facilitated using vectors designed for positive or negative selection as known in the art. In order to facilitate identification of

cells that have undergone the replacement reaction, an appropriate genetic marker system may be employed and cells selected by, for example, use of a selection tissue culture medium. However, in order to ensure that the genome sequence is substantially free of extraneous nucleic acid sequences at or adjacent to the two end points of the replacement interval, desirably the marker system/gene can be removed following selection of the cells containing the replaced nucleic acid.

[000203] In one aspect, cells in which the replacement of all or part of the endogenous immunoglobulin locus has taken place are negatively selected against upon exposure to a toxin or drug. For example, cells that retain expression of HSV-TK can be selected against by using nucleoside analogues such as ganciclovir. In another aspect, cells comprising the deletion of the endogenous immunoglobulin locus may be positively selected for by use of a marker gene, which can optionally be removed from the cells following or as a result of the recombination event. A positive selection system that may be used is based on the use of two non-functional portions of a marker gene, such as HPRT, that are brought together through the recombination event. These two portions are brought into functional association upon a successful replacement reaction being carried out and wherein the functionally reconstituted marker gene is flanked on either side by further sequence-specific recombination sites (which are different from the sequence-specific recombination sites used for the replacement reaction), such that the marker gene can be excised from the genome, using an appropriate site-specific recombinase.

[000204] The recombinase may be provided as a purified protein, or as a protein expressed from a vector construct transiently transfected into the host cell or stably integrated into the host cell genome. Alternatively, the cell may be used first to generate a transgenic animal, which then may be crossed with an animal that expresses said recombinase.

[000205] Because the methods described herein can take advantage of two or more sets of sequence-specific recombination sites within the engineered genome, multiple rounds of RMCE can be exploited to insert the partly canine immunoglobulin variable region genes into a non-canine mammalian host cell genome.

[000206] Although not yet routine for the insertion of large DNA segments, CRISPR-Cas technology is another method to introduce the chimeric canine Ig locus.

Generation of Transgenic Animals

[000207] In one aspect, methods for the creation of transgenic animals, for example rodents, such as mice, are provided that comprise the introduced partly canine immunoglobulin locus.

[000208] In one aspect, the host cell utilized for replacement of the endogenous immunoglobulin genes is an embryonic stem (ES) cell, which can then be utilized to create a transgenic mammal. In one aspect, the host cell is a cell of an early stage embryo. In one aspect, the host cell is a pronuclear stage embryo or zygote. Thus, in accordance with one aspect, the methods described herein further comprise: isolating an embryonic stem cell or a cell of an early stage embryo such as a pronuclear stage embryo or zygote, which comprises the introduced partly canine immunoglobulin locus and using said ES cell to generate a transgenic animal that contains the replaced partly canine immunoglobulin locus.

Methods of Use

[000209] In one aspect, a method of producing antibodies comprising canine variable regions is provided. In one aspect, the method includes providing a transgenic rodent or rodent cell described herein and isolating antibodies comprising canine variable regions expressed by the transgenic rodent. In one aspect, a method of producing monoclonal antibodies comprising canine variable regions is provided. In one aspect, the method includes providing B-cells from a transgenic rodent or cell described herein, immortalizing the B-cells; and isolating antibodies comprising canine variable domains expressed by the immortalized B-cells.

[000210] In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine HC variable domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise mouse HC constant domains. These can be of any isotype, IgM, IgD, IgG1, IgG2a/c, IgG2b, IgG3, IgE or IgA.

[000211] In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine HC variable domains and mouse HC constant domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine LC variable domains and mouse LC constant domains. In one aspect, the antibodies

expressed by the transgenic rodent or rodent cell comprise canine HC variable domains and canine LC variable domains and mouse HC constant domains and mouse LC constant domains.

[000212] In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine λ LC variable domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise mouse λ constant domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine λ LC variable domains and mouse λ constant domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine κ LC variable domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise mouse κ constant domains. In one aspect, the antibodies expressed by the transgenic rodent or rodent cell comprise canine κ LC variable domains and mouse κ constant domains.

[000213] In one aspect, a method of producing antibodies or antigen binding fragments comprising canine variable regions is provided. In one aspect, the method includes providing a transgenic rodent or cell described herein and isolating antibodies comprising canine variable regions expressed by the transgenic rodent or rodent cell. In one aspect, the variable regions of the antibody expressed by the transgenic rodent or rodent cell are sequenced. Antibodies comprising canine variable regions obtained from the antibodies expressed by the transgenic rodent or rodent cell can be recombinantly produced using known methods.

[000214] In one aspect, a method of producing an immunoglobulin specific to an antigen of interest is provided. In one aspect, the method includes immunizing a transgenic rodent as described herein with the antigen and isolating immunoglobulin specific to the antigen expressed by the transgenic rodent or rodent cell. In one aspect, the variable domains of the antibody expressed by the rodent or rodent cell are sequenced and antibodies comprising canine variable regions that specifically bind the antigen of interest are recombinantly produced using known methods. In one aspect, the recombinantly produced antibody or antigen binding fragment comprises canine HC and LC, κ or λ , constant domains.

Incorporation by Reference

[000215] All references cited herein, including patents, patent applications, papers, text books and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety for all purposes.

EXAMPLES

[000216] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention, nor are they intended to represent or imply that the experiments below are all of or the only experiments performed. It will be appreciated by persons skilled in the art that numerous variations or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[000217] Efforts have been made to ensure accuracy with respect to terms and numbers used (e.g., vectors, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees centigrade, and pressure is at or near atmospheric.

[000218] The examples illustrate targeting by both a 5' vector and a 3' vector that flank a site of recombination and introduction of synthetic DNA. It will be apparent to one skilled in the art upon reading the specification that the 5' vector targeting can take place first followed by the 3', or the 3' vector targeting can take place first followed by the 5' vector. In some circumstances, targeting can be carried out simultaneously with dual detection mechanisms.

Example 1: Introduction of an Engineered Partly Canine Immunoglobulin Variable Region Gene Locus into the Immunoglobulin H Chain Variable Region Gene Locus of a Non-Canine Mammalian Host Cell Genome

[000219] An exemplary method illustrating the introduction of an engineered partly canine immunoglobulin locus into the genomic locus of a non-mammalian ES cell is illustrated in more detail in FIGS. 2-6. In FIG. 2, a homology targeting vector (201) is provided comprising a puromycin phosphotransferase-thymidine kinase fusion protein (puro-TK) (203) flanked by two different recombinase recognition sites (e.g., FRT (207) and loxP (205) for Flp and Cre, respectively) and two different mutant sites (e.g., modified mutant FRT (209) and mutant loxP (211)) that lack the ability to recombine with their respective wild-type counterparts/sites (i.e., wild-type FRT (207) and wild-type loxP (205)). The targeting vector comprises a diphtheria toxin receptor (DTR) cDNA (217) for use in negative selection of cells containing the introduced construct in future steps. The targeting vector also optionally comprises a visual marker such as a green fluorescent protein (GFP) (not shown). The regions 213 and 215 are homologous to the 5' and 3' portions, respectively, of a contiguous region (229) in the endogenous non-canine locus that is 5' of the genomic region comprising the endogenous non-canine V_H gene segments (219). The homology targeting vector (201) is introduced (202) into the ES cell, which has an immunoglobulin locus (231) comprising endogenous V_H gene segments (219), the pre-D region (221), the D gene segments (223), J_H gene segments (225), and the immunoglobulin constant gene region genes (227). The site-specific recombination sequences and the DTR cDNA from the homology targeting vector (201) are integrated (204) into the non-canine genome at a site 5' of the endogenous mouse V_H gene locus, resulting in the genomic structure illustrated at 233. The ES cells that do not have the exogenous vector (201) integrated into their genome can be selected against (killed) by including puromycin in the culture medium; only the ES cells that have stably integrated the exogenous vector (201) into their genome and constitutively express the puro-TK gene are resistant to puromycin.

[000220] FIG. 3 illustrates effectively the same approach as FIG. 2, except that an additional set of sequence-specific recombination sites is added, e.g., a Rox site (331) and a modified Rox site (335) for use with the Dre recombinase. In FIG. 3, a homology targeting vector (301) is provided comprising a puro-TK fusion protein (303) flanked by wild type

recombinase recognition sites for FRT (307), loxP (305), and Rox (331) and mutant sites for FRT (309) loxP (311) and Rox (335) recombinases that lack the ability to recombine with the wild-type sites 307, 305 and 331, respectively. The targeting vector also comprises a diphtheria toxin receptor (DTR) cDNA (317). The regions 313 and 315 are homologous to the 5' and 3' portions, respectively, of a contiguous region (329) in the endogenous non-canine locus that is 5' of the genomic region comprising the endogenous mouse V_H gene segments (319). The homology targeting is introduced (302) into the mouse immunoglobulin locus (339), which comprises the endogenous V_H gene segments (319), the pre-D region (321), the D gene segments (323), J_H (325) gene segments, and the constant region genes (327) of the Igh locus. The site-specific recombination sequences and the DTR cDNA (317) in the homology targeting vector (301) are integrated (304) into the mouse genome at a site 5' of the endogenous mouse V_H gene locus, resulting in the genomic structure illustrated at 333.

[000221] As illustrated in FIG. 4, a second homology targeting vector (401) is provided comprising an optional hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene (435) that can be used for positive selection in HPRT-deficient ES cells; a neomycin resistance gene (437); recombinase recognition sites FRT (407) and loxP (405), for Flp and Cre, respectively, which have the ability to recombine with FRT (407) and loxP (405) sites previously integrated into the mouse genome from the first homology targeting vector. The previous homology targeting vector also includes mutant FRT site (409), mutant loxP site (411), a puro-TK fusion protein (403), and a DTR cDNA at a site 5' of the endogenous mouse V_H gene locus (419). The regions 429 and 439 are homologous to the 5' and 3' portions, respectively, of a contiguous region (441) in the endogenous mouse non-canine locus that is downstream of the endogenous J_H gene segments (425) and upstream of the constant region genes (427). The homology targeting vector is introduced (402) into the modified mouse immunoglobulin locus (431), which comprises the endogenous V_H gene segments (419), the pre-D region (421), the D gene segments (423) the J_H gene segments (425), and the constant region genes (427). The site-specific recombination sequences (407, 405), the HPRT gene (435) and a neomycin resistance gene (437) of the homology targeting vector are integrated (404) into the mouse genome upstream of the endogenous mouse constant region genes (427), resulting in the genomic structure illustrated at 433.

[000222] Once the recombination sites are integrated into the mammalian host cell genome, the endogenous region of the immunoglobulin domain is then subjected to recombination by introducing one of the recombinases corresponding to the sequence-specific recombination sites integrated into the genome, e.g., either Flp or Cre. Illustrated in FIG. 5 is a modified Igh locus of the mammalian host cell genome comprising two integrated DNA fragments. One fragment comprising mutant FRT site (509), mutant LoxP site (511), puro-TK gene (503), wild-type FRT site (507), and wild-type LoxP site (505), and DTR cDNA (517) is integrated upstream of the V_H gene locus (519). The other DNA fragment comprising HPRT gene (535), neomycin resistance gene (537), wild-type FRT site (507), and wild-type LoxP site (505) is integrated downstream of the pre-D (521), D (523) and J_H (525) gene loci, but upstream of the constant region genes (527). In the presence of Flp or Cre (502), all the intervening sequences between the wild-type FRT or wild-type LoxP sites including the DTR gene (517), the endogenous IGH variable region gene loci (519, 521, 525), and the HPRT (535) and neomycin resistance (537) genes are deleted, resulting in a genomic structure illustrated at 539. The procedure depends on the second targeting having occurred on the same chromosome rather than on its homolog (i.e., in *cis* rather than in *trans*). If the targeting occurs in *cis* as intended, the cells are not sensitive to negative selection after Cre- or Flp-mediated recombination by diphtheria toxin introduced into the media, because the DTR gene which causes sensitivity to diphtheria toxin in rodents should be absent (deleted) from the host cell genome. Likewise, ES cells that harbor random integration of the first or second targeting vector(s) are rendered sensitive to diphtheria toxin by presence of the undeleted DTR gene.

[000223] ES cells that are insensitive to diphtheria toxin are then screened for the deletion of the endogenous variable region gene loci. The primary screening method for the deleted endogenous immunoglobulin locus can be carried out by Southern blotting, or by polymerase chain reaction (PCR) followed by confirmation with a secondary screening technique such as Southern blotting.

[000224] FIG. 6 illustrates introduction of the engineered partly canine sequence into a non-canine genome previously modified to delete part of the endogenous Igh locus (V_H, D and J_H) that encodes the heavy chain variable region domains as well as all the intervening sequences between the V_H and J_H gene locus. A site-specific targeting vector (629)

comprising partly canine V_H gene locus (619), endogenous non-canine pre-D gene region (621), partly canine D gene locus (623), partly canine J_H gene locus (625), as well as flanking mutant FRT (609), mutant LoxP (611), wild-type FRT (607), and wild-type LoxP (605) sites is introduced (602) into the host cell. Specifically, the partly canine V_H locus (619) comprises 39 functional canine V_H coding sequences in conjunction with the intervening sequences based on the endogenous non-canine genome sequences; the pre-D region (621) comprises a 21.6 kb mouse sequence with significant homology to the corresponding region of the endogenous canine IGH locus; the D gene locus (623) comprises codons of 6 D gene segments embedded in the intervening sequences surrounding the endogenous non-canine D gene segments; and the J_H gene locus (625) comprises codons of 6 canine J_H gene segments embedded in the intervening sequences based on the endogenous non-canine genome. The IGH locus (601) of the host cell genome has been previously modified to delete all the V_H, D, and J_H gene segments including the intervening sequences as described in FIG. 5. As a consequence of this modification, the endogenous non-canine host cell Igh locus (601) is left with a puro-TK fusion gene (603), which is flanked by a mutant FRT site (609) and a mutant LoxP site (611) upstream as well as a wild-type FRT (607) and a wild-type LoxP (605) downstream. Upon introduction of the appropriate recombinase (604), the partly canine immunoglobulin locus is integrated into the genome upstream of the endogenous non-canine constant region genes (627), resulting in the genomic structure illustrated at 631.

[000225] The sequences of the canine V_H, D and J_H gene segment coding regions are in Table 1.

[000226] Primary screening procedure for the introduction of the partly canine immunoglobulin locus can be carried out by Southern blotting, or by PCR followed by confirmation with a secondary screening method such as Southern blotting. The screening methods are designed to detect the presence of the inserted V_H, D and J_H gene loci, as well as all the intervening sequences.

Example 2: Introduction of an Engineered Partly Canine Immunoglobulin Variable Region Gene Locus Comprising Additional Non-Coding Regulatory or Scaffold Sequences into the Immunoglobulin H Chain Variable Region Gene Locus of a Non-Canine Mammalian Host Cell Genome

[000227] In certain aspects, the partly canine immunoglobulin locus comprises the elements as described in Example 1, but with additional non-coding regulatory or scaffold sequences e.g., sequences strategically added to introduce additional regulatory sequences, to ensure the desired spacing within the introduced immunoglobulin locus, to ensure that certain coding sequences are in adequate juxtaposition with other sequences adjacent to the replaced immunoglobulin locus, and the like. FIG. 7 illustrates the introduction of a second exemplary engineered partly canine sequence into the modified non-canine genome as produced in FIGS. 2-5 and described in Example 1 above.

[000228] FIG. 7 illustrates introduction of the engineered partly canine sequence into the mouse genome previously modified to delete part of the endogenous non-canine IGH locus (V_H , D and J_H) that encodes the heavy chain variable region domains as well as all the intervening sequences between the endogenous V_H and J_H gene loci. A site-specific targeting vector (731) comprising an engineered partly canine immunoglobulin locus to be inserted into the non-canine host genome is introduced (702) into the genomic region (701). The site-specific targeting vector (731) comprising a partly canine V_H gene locus (719), mouse pre-D region (721), partly canine D gene locus (723), partly canine J_H gene locus (725), PAIR elements (741), as well as flanking mutant FRT (709), mutant LoxP (711) wild-type FRT (707) and wild-type LoxP (705) sites is introduced (702) into the host cell. Specifically, the engineered partly canine V_H gene locus (719) comprises 80 canine V_H gene segment coding regions in conjunction with intervening sequences based on the endogenous non- canine genome sequences; the pre-D region (721) comprises a 21.6 kb non- canine sequence present upstream of the endogenous non-canine genome; the D region (723) comprises codons of 6 canine D gene segments embedded in the intervening sequences surrounding the endogenous non-canine D gene segments; and the J_H gene locus (725) comprises codons of 6 canine J_H gene segments embedded in the intervening sequences based on the endogenous non- canine genome sequences. The IGH locus (701) of the host cell genome has been previously modified to delete all the V_H , D and J_H gene

segments including the intervening sequences as described in relation to FIG. 5. As a consequence of this modification, the endogenous non- canine Igh locus (701) is left with a puro-TK fusion gene (703), which is flanked by a mutant FRT site (709) and a mutant LoxP site (711) upstream as well as a wild-type FRT (707) and a wild-type LoxP (705) downstream. Upon introduction of the appropriate recombinase (704), the engineered partly canine immunoglobulin locus is integrated into the genome upstream of the endogenous mouse constant region genes (727), resulting in the genomic structure illustrated at 729.

[000229] The primary screening procedure for the introduction of the engineered partly canine immunoglobulin region can be carried out by Southern blotting, or by PCR with confirmation by a secondary screening method such as Southern blotting. The screening methods are designed to detect the presence of the inserted PAIR elements, the V_H, D and J_H gene loci, as well as all the intervening sequences.

Example 3: Introduction of an Engineered Partly Canine Immunoglobulin Locus into the Immunoglobulin Heavy Chain Gene Locus of a Mouse Genome

[000230] A method for replacing a portion of a mouse genome with an engineered partly canine immunoglobulin locus is illustrated in FIG. 8. This method uses introduction of a first site-specific recombinase recognition sequence into the mouse genome followed by the introduction of a second site-specific recombinase recognition sequence into the mouse genome. The two sites flank the entire clusters of endogenous mouse V_H, D and J_H region gene segments. The flanked region is deleted using the relevant site-specific recombinase, as described herein.

[000231] The targeting vectors (803, 805) employed for introducing the site-specific recombinase sequences on either side of the V_H (815), D (817) and J_H (819) gene segment clusters and upstream of the constant region genes (821) in the wild-type mouse immunoglobulin locus (801) include an additional site-specific recombination sequence that has been modified so that it is still recognized efficiently by the recombinase, but does not recombine with unmodified sites. This mutant modified site (e.g., lox5171) is positioned in the targeting vector such that after deletion of the endogenous V_H, D_H and J_H gene segments (802) it can be used for a second site-specific recombination event in which

a non-native piece of DNA is moved into the modified IGH locus by RMCE. In this example, the non-native DNA is a synthetic nucleic acid comprising both canine and non-canine sequences (809).

[000232] Two gene targeting vectors are constructed to accomplish the process just outlined. One of the vectors (803) comprises mouse genomic DNA taken from the 5' end of the Igh locus, upstream of the most distal V_H gene segment. The other vector (805) comprises mouse genomic DNA taken from within the locus downstream of the J_H gene segments.

[000233] The key features of the 5' vector (803) in order from 5' to 3' are as follows: a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (823); 4.5 Kb of mouse genomic DNA mapping upstream of the most distal V_H gene segment in the Igh locus (825); a FRT recognition sequence for the Flp recombinase (827); a piece of genomic DNA containing the mouse Polr2a gene promoter (829); a translation initiation sequence (methionine codon embedded in a "Kozak" consensus sequence, 835)); a mutated loxP recognition sequence (lox5171) for the Cre recombinase (831); a transcription termination/polyadenylation sequence (pA. 833); a loxP recognition sequence for the Cre recombinase (837); a gene encoding a fusion protein with a protein conferring resistance to puromycin fused to a truncated form of the thymidine kinase (pu-TK) under transcriptional control of the promoter from the mouse phosphoglycerate kinase 1 gene (839); and 3 Kb of mouse genomic DNA (841) mapping close to the 4.5 Kb mouse genomic DNA sequence present near the 5' end of the vector and arranged in the native relative orientation.

[000234] The key features of the 3' vector (805) in order from 5' to 3' are as follows; 3.7 Kb of mouse genomic DNA mapping within the intron between the J_H and C_H gene loci (843); an HPRT gene under transcriptional control of the mouse Polr2a gene promoter (845); a neomycin resistance gene under the control of the mouse phosphoglycerate kinase 1 gene promoter (847); a loxP recognition sequence for the Cre recombinase (837); 2.1 Kb of mouse genomic DNA (849) that maps immediately downstream of the 3.7 Kb mouse genomic DNA fragment present near the 5' end of the vector and arranged in the native relative orientation; and a gene encoding the DTA subunit under transcriptional control of

a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (823).

[000235] Mouse embryonic stem (ES) cells (derived from C57B1/6NTac mice) are transfected by electroporation with the 3' vector (805) according to widely used procedures. Prior to electroporation, the vector DNA is linearized with a rare-cutting restriction enzyme that cuts only in the prokaryotic plasmid sequence or the polylinker associated with it. The transfected cells are plated and after ~24 hours they are placed under positive selection for cells that have integrated the 3' vector into their DNA by using the neomycin analogue drug G418. There is also negative selection for cells that have integrated the vector into their DNA but not by homologous recombination. Non-homologous recombination results in retention of the DTA gene (823), which kills the cells when the gene is expressed, whereas the DTA gene is deleted by homologous recombination since it lies outside of the region of vector homology with the mouse IGH locus. Colonies of drug-resistant ES cells are physically extracted from their plates after they became visible to the naked eye about a week later. These picked colonies are disaggregated, re-plated in micro-well plates, and cultured for several days. Thereafter, each of the clones of cells is divided such that some of the cells can be frozen as an archive, and the rest used for isolation of DNA for analytical purposes.

[000236] DNA from the ES cell clones is screened by PCR using a widely practiced gene-targeting assay design. For this assay, one of the PCR oligonucleotide primer sequences maps outside the region of identity shared between the 3' vector (805) and the genomic DNA, while the other maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (845) or neomycin resistance (847) genes. According to the standard design, these assays detect pieces of DNA that would only be present in clones of ES cells derived from transfected cells that undergo fully legitimate homologous recombination between the 3' targeting vector and the endogenous mouse IGH locus. Two separate transfections are performed with the 3' vector (805). PCR-positive clones from the two transfections are selected for expansion followed by further analysis using Southern blot assays.

[000237] The Southern blot assays are performed according to widely used procedures using three probes and genomic DNA digested with multiple restriction enzymes chosen so that

the combination of probes and digests allow the structure of the targeted locus in the clones to be identified as properly modified by homologous recombination. One of the probes maps to DNA sequence flanking the 5' side of the region of identity shared between the 3' targeting vector and the genomic DNA; a second probe maps outside the region of identity but on the 3' side; and the third probe maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (845) or neomycin resistance (847) genes. The Southern blot identifies the presence of the expected restriction enzyme-generated fragment of DNA corresponding to the correctly mutated, i.e., by homologous recombination with the 3' Igh targeting vector, part of the IGH locus as detected by one of the external probes and by the neomycin or HPRT probe. The external probe detects the mutant fragment and also a wild-type fragment from the non-mutant copy of the immunoglobulin Igh locus on the homologous chromosome.

[000238] Karyotypes of PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most commonly arising chromosomal aberrations that arise in mouse ES cells. Clones with such aberrations are excluded from further use. ES cell clones that are judged to have the expected correct genomic structure based on the Southern blot data—and that also do not have detectable chromosomal aberrations based on the karyotype analysis—are selected for further use.

[000239] Acceptable clones are then modified with the 5' vector (803) using procedures and screening assays that are similar in design to those used with the 3' vector (805) except that puromycin selection is used instead of G418/neomycin for selection. The PCR assays, probes and digests are also tailored to match the genomic region being modified by the 5' vector (805).

[000240] Clones of ES cells that have been mutated in the expected fashion by both the 3' and the 5' vectors, i.e., doubly targeted cells carrying both engineered mutations, are isolated following vector targeting and analysis. The clones must have undergone gene targeting on the same chromosome, as opposed to homologous chromosomes (i.e., the engineered mutations created by the targeting vectors must be in *cis* on the same DNA strand rather than in *trans* on separate homologous DNA strands). Clones with the *cis* arrangement are distinguished from those with the *trans* arrangement by analytical

procedures such as fluorescence *in situ* hybridization of metaphase spreads using probes that hybridize to the novel DNA present in the two gene targeting vectors (803 and 805) between their arms of genomic identity. The two types of clones can also be distinguished from one another by transfecting them with a vector expressing the Cre recombinase, which deletes the pu-TK (839), HPRT (845) and neomycin resistance (847) genes if the targeting vectors have been integrated in *cis*, and then comparing the number of colonies that survive ganciclovir selection against the thymidine kinase gene introduced by the 5' vector (803) and by analyzing the drug resistance phenotype of the surviving clones by a "sibling selection" screening procedure in which some of the cells from the clone are tested for resistance to puromycin or G418/neomycin. Cells with the *cis* arrangement of mutations are expected to yield approximately 10^3 more ganciclovir-resistant clones than cells with the *trans* arrangement. The majority of the resulting *cis*-derived ganciclovir-resistant clones are also sensitive to both puromycin and G418/neomycin, in contrast to the *trans*-derived ganciclovir-resistant clones, which should retain resistance to both drugs. Doubly targeted clones of cells with the *cis*-arrangement of engineered mutations in the heavy chain locus are selected for further use.

[000241] The doubly targeted clones of cells are transiently transfected with a vector expressing the Cre recombinase and the transfected cells subsequently are placed under ganciclovir selection, as in the analytical experiment summarized above. Ganciclovir-resistant clones of cells are isolated and analyzed by PCR and Southern blot for the presence of the expected deletion between the two engineered mutations created by the 5' (803) and the 3' (805) targeting vectors. In these clones, the Cre recombinase causes a recombination (802) to occur between the loxP sites (837) introduced into the heavy chain locus by the two vectors to create the genomic DNA configuration shown at 807. Because the loxP sites are arranged in the same relative orientations in the two vectors, recombination results in excision of a circle of DNA comprising the entire genomic interval between the two loxP sites. The circle does not contain an origin of replication and thus is not replicated during mitosis and therefore is lost from the cells as they undergo proliferation. The resulting clones carry a deletion of the DNA that was originally between the two loxP sites. Clones that have the expected deletion are selected for further use.

[000242] ES cell clones carrying the deletion of sequence in one of the two homologous copies of their immunoglobulin heavy chain locus are retransfected (804) with a Cre recombinase expression vector together with a piece of DNA (809) comprising a partly canine immunoglobulin heavy chain locus containing canine V_H, D and J_H region gene coding region sequences flanked by mouse regulatory and flanking sequences. The key features of this piece of synthetic DNA (809) are the following: a lox5171 site (831); a neomycin resistance gene open reading frame (847) lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site a FRT site (827); an array of 39 functional canine V_H heavy chain variable region genes (851), each with canine coding sequences embedded in mouse noncoding sequences; optionally a 21.6 kb pre-D region from the mouse heavy chain locus (not shown); a 58 Kb piece of DNA containing the 6 canine D_H gene segments (853) and 6 canine J_H gene segments (855) where the canine V_H, D and J_H coding sequences are embedded in mouse noncoding sequences; a loxP site (837) in opposite relative orientation to the lox5171 site (831).

[000243] The transfected clones are placed under G418 selection, which enriches for clones of cells that have undergone RMCE in which the engineered partly canine donor immunoglobulin locus (809) is integrated in its entirety into the deleted endogenous immunoglobulin heavy chain locus between the lox5171 (831) and loxP (837) sites to create the DNA region illustrated at 811. Only cells that have properly undergone RMCE have the capability to express the neomycin resistance gene (847) because the promoter (829) as well as the initiator methionine codon (835) required for its expression are not present in the vector (809) but are already pre-existing in the host cell IGH locus (807). The remaining elements from the 5' vector (803) are removed via Flp-mediated recombination (806) *in vitro* or *in vivo*, resulting in the final canine-based locus as shown at 813.

[000244] G418-resistant ES cell clones are analyzed by PCR and Southern blot to determine if they have undergone the expected RMCE process without unwanted rearrangements or deletions. Clones that have the expected genomic structure are selected for further use.

[000245] ES cell clones carrying the partly canine immunoglobulin heavy chain DNA (813) in the mouse heavy chain locus are microinjected into mouse blastocysts from strain

DBA/2 to create partially ES cell-derived chimeric mice according to standard procedures. Male chimeric mice with the highest levels of ES cell-derived contribution to their coats are selected for mating to female mice. The female mice of choice here are of C57B1/6NTac strain, and also carry a transgene encoding the Flp recombinase that is expressed in their germline. Offspring from these matings are analyzed for the presence of the partly canine immunoglobulin heavy chain locus, and for loss of the FRT-flanked neomycin resistance gene that was created in the RMCE step. Mice that carry the partly canine locus are used to establish a colony of mice.

Example 4: Introduction of an Engineered Partly Canine Immunoglobulin Locus into the Immunoglobulin κ Chain Gene Locus of a Mouse Genome

[000246] Another method for replacing a portion of a mouse genome with partly canine immunoglobulin locus is illustrated in FIG. 9. This method includes introducing a first site-specific recombinase recognition sequence into the mouse genome, which may be introduced either 5' or 3' of the cluster of endogenous V_{κ} (915) and J_{κ} (919) region gene segments of the mouse genome, followed by the introduction of a second site-specific recombinase recognition sequence into the mouse genome, which in combination with the first sequence-specific recombination site flanks the entire locus comprising clusters of V_{κ} and J_{κ} gene segments upstream of the constant region gene (921). The flanked region is deleted and then replaced with a partly canine immunoglobulin locus using the relevant site-specific recombinase, as described herein.

[000247] The targeting vectors employed for introducing the site-specific recombination sequences on either side of the V_{κ} (915) and J_{κ} (919) gene segments also include an additional site-specific recombination sequence that has been modified so that it is still recognized efficiently by the recombinase, but does not recombine with unmodified sites. This site is positioned in the targeting vector such that after deletion of the V_{κ} and J_{κ} gene segment clusters it can be used for a second site specific recombination event in which a non-native piece of DNA is moved into the modified V_{κ} locus via RMCE. In this example, the non-native DNA is a synthetic nucleic acid comprising canine V_{κ} and J_{κ} gene segment coding sequences embedded in mouse regulatory and flanking sequences.

[000248] Two gene targeting vectors are constructed to accomplish the process just outlined. One of the vectors (903) comprises mouse genomic DNA taken from the 5' end of the locus, upstream of the most distal V_κ gene segment. The other vector (905) comprises mouse genomic DNA taken from within the locus downstream (3') of the J_κ gene segments (919) and upstream of the constant region genes (921).

[000249] The key features of the 5' vector (903) are as follows: a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (923); 6 Kb of mouse genomic DNA (925) mapping upstream of the most distal variable region gene in the κ chain locus; a FRT recognition sequence for the Flp recombinase (927); a piece of genomic DNA containing the mouse Polr2a gene promoter (929); a translation initiation sequence (935, methionine codon embedded in a "Kozak" consensus sequence); a mutated loxP recognition sequence (lox5171) for the Cre recombinase (931); a transcription termination/polyadenylation sequence (933); a loxP recognition sequence for the Cre recombinase (937); a gene encoding a fusion protein with a protein conferring resistance to puromycin fused to a truncated form of the thymidine kinase (pu-TK) under transcriptional control of the promoter from the mouse phosphoglycerate kinase 1 gene (939); 2.5 Kb of mouse genomic DNA (941) mapping close to the 6 Kb sequence at the 5' end in the vector and arranged in the native relative orientation.

[000250] The key features of the 3' vector (905) are as follows: 6 Kb of mouse genomic DNA (943) mapping within the intron between the J_κ (919) and C_κ (921) gene loci; a gene encoding the human hypoxanthine-guanine phosphoribosyl transferase (HPRT) under transcriptional control of the mouse Polr2a gene promoter (945); a neomycin resistance gene under the control of the mouse phosphoglycerate kinase 1 gene promoter (947); a loxP recognition sequence for the Cre recombinase (937); 3.6 Kb of mouse genomic DNA (949) that maps immediately downstream in the genome of the 6 Kb DNA fragment included at the 5' end in the vector, with the two fragments oriented in the same relative way as in the mouse genome; a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (923).

[000251] Mouse embryonic stem (ES) cells derived from C57B1/6NTac mice are transfected by electroporation with the 3' vector (905) according to widely used procedures. Prior to electroporation, the vector DNA is linearized with a rare-cutting restriction enzyme that cuts only in the prokaryotic plasmid sequence or the polylinker associated with it. The transfected cells are plated and after ~24 hours they are placed under positive selection for cells that have integrated the 3' vector into their DNA by using the neomycin analogue drug G418. There is also negative selection for cells that have integrated the vector into their DNA but not by homologous recombination. Non-homologous recombination results in retention of the DTA gene, which kills the cells when the gene is expressed, whereas the DTA gene is deleted by homologous recombination since it lies outside of the region of vector homology with the mouse Igk locus. Colonies of drug-resistant ES cells are physically extracted from their plates after they became visible to the naked eye about a week later. These picked colonies are disaggregated, re-plated in micro-well plates, and cultured for several days. Thereafter, each of the clones of cells is divided such that some of the cells could be frozen as an archive, and the rest used for isolation of DNA for analytical purposes.

[000252] DNA from the ES cell clones is screened by PCR using a widely used gene-targeting assay design. For this assay, one of the PCR oligonucleotide primer sequences maps outside the region of identity shared between the 3' vector (905) and the genomic DNA (901), while the other maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (945) or neomycin resistance (947) genes. According to the standard design, these assays detect pieces of DNA that are only present in clones of ES cells derived from transfected cells that had undergone fully legitimate homologous recombination between the 3' vector (905) and the endogenous mouse Igk locus. Two separate transfections are performed with the 3' vector (905). PCR-positive clones from the two transfections are selected for expansion followed by further analysis using Southern blot assays.

[000253] The Southern blot assays are performed according to widely used procedures; they involve three probes and genomic DNA digested with multiple restriction enzymes chosen so that the combination of probes and digests allowed for conclusions to be drawn about the structure of the targeted locus in the clones and whether it is properly modified by

homologous recombination. One of the probes maps to DNA sequence flanking the 5' side of the region of identity shared between the 3' κ targeting vector (905) and the genomic DNA; a second probe also maps outside the region of identity but on the 3' side; the third probe maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (945) or neomycin resistance (947) genes. The Southern blot identifies the presence of the expected restriction enzyme-generated fragment of DNA corresponding to the correctly mutated, i.e., by homologous recombination with the 3' κ targeting vector (905) part of the κ locus, as detected by one of the external probes and by the neomycin resistance or HPRT gene probe. The external probe detects the mutant fragment and also a wild-type fragment from the non-mutant copy of the immunoglobulin κ locus on the homologous chromosome.

[000254] Karyotypes of PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most commonly arising chromosomal aberrations that arise in mouse ES cells. Clones with such aberrations are excluded from further use. Karyotypically normal clones that are judged to have the expected correct genomic structure based on the Southern blot data are selected for further use.

[000255] Acceptable clones are then modified with the 5' vector (903) using procedures and screening assays that are similar in design to those used with the 3' vector (905), except that puromycin selection is used instead of G418/neomycin selection, and the protocols are tailored to match the genomic region modified by the 5' vector (903). The goal of the 5' vector (903) transfection experiments is to isolate clones of ES cells that have been mutated in the expected fashion by both the 3' vector (905) and the 5' vector (903), i.e., doubly targeted cells carrying both engineered mutations. In these clones, the Cre recombinase causes a recombination (902) to occur between the loxP sites introduced into the κ locus by the two vectors, resulting in the genomic DNA configuration shown at 907.

[000256] Further, the clones must have undergone gene targeting on the same chromosome, as opposed to homologous chromosomes; i.e., the engineered mutations created by the targeting vectors must be in *cis* on the same DNA strand rather than in *trans* on separate homologous DNA strands. Clones with the *cis* arrangement are distinguished from those with the *trans* arrangement by analytical procedures such as fluorescence *in situ*

hybridization of metaphase spreads using probes that hybridize to the novel DNA present in the two gene targeting vectors (903 and 905) between their arms of genomic identity. The two types of clones can also be distinguished from one another by transfecting them with a vector expressing the Cre recombinase, which deletes the pu-Tk (939), HPRT (945) and neomycin resistance (947) genes if the targeting vectors have been integrated in *cis*, and comparing the number of colonies that survive ganciclovir selection against the thymidine kinase gene introduced by the 5' vector (903) and by analyzing the drug resistance phenotype of the surviving clones by a "sibling selection" screening procedure in which some of the cells from the clone are tested for resistance to puromycin or G418/neomycin. Cells with the *cis* arrangement of mutations are expected to yield approximately 10^3 more ganciclovir-resistant clones than cells with the *trans* arrangement. The majority of the resulting *cis*-derived ganciclovir-resistant clones should also be sensitive to both puromycin and G418/neomycin, in contrast to the *trans*-derived ganciclovir-resistant clones, which should retain resistance to both drugs. Clones of cells with the *cis*-arrangement of engineered mutations in the κ chain locus are selected for further use.

[000257] The doubly targeted clones of cells are transiently transfected with a vector expressing the Cre recombinase (902) and the transfected cells are subsequently placed under ganciclovir selection, as in the analytical experiment summarized above. Ganciclovir-resistant clones of cells are isolated and analyzed by PCR and Southern blot for the presence of the expected deletion (907) between the two engineered mutations created by the 5' vector (903) and the 3' vector (905). In these clones, the Cre recombinase has caused a recombination to occur between the loxP sites (937) introduced into the κ chain locus by the two vectors. Because the loxP sites are arranged in the same relative orientations in the two vectors, recombination results in excision of a circle of DNA comprising the entire genomic interval between the two loxP sites. The circle does not contain an origin of replication and thus is not replicated during mitosis and is therefore lost from the clones of cells as they undergo clonal expansion. The resulting clones carry a deletion of the DNA that was originally between the two loxP sites. Clones that have the expected deletion are selected for further use.

[000258] The ES cell clones carrying the deletion of sequence in one of the two homologous copies of their immunoglobulin κ chain locus are retransfected (904) with a Cre recombinase expression vector together with a piece of DNA (909) comprising a partly canine immunoglobulin κ chain locus containing V_{κ} (951) and J_{κ} (955) gene segment coding sequences. The key features of this piece of DNA (referred to as "K-K") are the following: a lox5171 site (931); a neomycin resistance gene open reading frame (947, lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site (931)); a FRT site (927); an array of 14 canine V_{κ} gene segments (951), each with canine coding sequences embedded in mouse noncoding sequences; optionally a 13.5 Kb piece of genomic DNA from immediately upstream of the cluster of J_{κ} region gene segments in the mouse κ chain locus (not shown); a 2 Kb piece of DNA containing the 5 canine J_{κ} region gene segments (955) embedded in mouse noncoding DNA; a loxP site (937) in opposite relative orientation to the lox5171 site (931).

[000259] The sequences of the canine V_{κ} and J_{κ} gene coding regions are in Table 2.

[000260] In a second independent experiment, an alternative piece of partly canine DNA (909) is used in place of the K-K DNA. The key features of this DNA (referred to as "L-K") are the following: a lox5171 site (931); a neomycin resistance gene open reading frame (947) lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site (931); a FRT site (927); an array of 76 functional canine V_{λ} variable region gene segments (951), each with canine coding sequences embedded in mouse noncoding regulatory or scaffold sequences; optionally, a 13.5 Kb piece of genomic DNA from immediately upstream of the cluster of the J_{κ} region gene segments in the mouse κ chain locus (not shown); a 2 Kb piece of DNA containing 7 canine J_{λ} region gene segments embedded in mouse noncoding DNA (955); a loxP site (937) in opposite relative orientation to the lox5171 site (931). (The dog has 9 functional J_{λ} region gene segments, however, the encoded protein sequence of $J_{\lambda 4}$ and $J_{\lambda 9}$ and of $J_{\lambda 7}$ and $J_{\lambda 8}$ are identical, and so only 7 J_{λ} gene segments are included.)

[000261] The transfected clones from the K-K and L-K transfection experiments are placed under G418 selection, which enriches for clones of cells that have undergone RMCE, in which the partly canine donor DNA (909) is integrated in its entirety into the deleted immunoglobulin κ chain locus between the lox5171 (931) and loxP (937) sites that were

placed there by 5' (903) and 3' (905) vectors, respectively. Only cells that have properly undergone RMCE have the capability to express the neomycin resistance gene (947) because the promoter (929) as well as the initiator methionine codon (935) required for its expression are not present in the vector (909) and are already pre-existing in the host cell Igh locus (907). The DNA region created using the K-K sequence is illustrated at 911. The remaining elements from the 5' vector (903) are removed via Flp-mediated recombination (906) *in vitro* or *in vivo*, resulting in the final canine-based light chain locus as shown at 913.

[000262] G418-resistant ES cell clones are analyzed by PCR and Southern blotting to determine if they have undergone the expected RMCE process without unwanted rearrangements or deletions. Both K-K and L-K clones that have the expected genomic structure are selected for further use.

[000263] The K-K ES cell clones and the L-K ES cell clones carrying the partly canine immunoglobulin DNA in the mouse κ chain locus (913) are microinjected into mouse blastocysts from strain DBA/2 to create partly ES cell-derived chimeric mice according to standard procedures. Male chimeric mice with the highest levels of ES cell-derived contribution to their coats are selected for mating to female mice. The female mice of choice for use in the mating are of the C57B1/6NTac strain, and also carry a transgene encoding the Flp recombinase that is expressed in their germline. Offspring from these matings are analyzed for the presence of the partly canine immunoglobulin κ or λ light chain locus, and for loss of the FRT-flanked neomycin resistance gene that was created in the RMCE step. Mice that carry the partly canine locus are used to establish colonies of K-K and L-K mice.

[000264] Mice carrying the partly canine heavy chain locus, produced as described in Example 3, can be bred with mice carrying a canine-based κ chain locus. Their offspring are in turn bred together in a scheme that ultimately produces mice that are homozygous for both canine-based loci, i.e., canine-based for heavy chain and κ . Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine κ proteins with canine κ variable domains and the mouse κ constant domain from their κ loci. Monoclonal antibodies recovered from these mice have canine heavy chain variable domains paired with canine κ variable domains.

[000265] A variation on the breeding scheme involves generating mice that are homozygous for the canine-based heavy chain locus, but heterozygous at the κ locus such that on one chromosome they have the K-K canine-based locus and on the other chromosome they have the L-K canine-based locus. Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine κ proteins with canine κ variable domains and the mouse κ constant domain from one of their κ loci. From the other κ locus, they produce partly canine λ proteins with canine λ variable domains the mouse κ constant domain. Monoclonal antibodies recovered from these mice have canine variable domains paired in some cases with canine κ variable domains and in other cases with canine λ variable domains.

Example 5: Introduction of an Engineered Partly Canine Immunoglobulin Locus into the Immunoglobulin λ Chain Gene Locus of a Mouse Genome

[000266] Another method for replacing a portion of a mouse genome with an engineered partly canine immunoglobulin locus is illustrated in FIG. 10. This method comprises deleting approximately 194 Kb of DNA from the wild-type mouse immunoglobulin λ locus (1001)—comprising $V_{\lambda x}/V_{\lambda 2}$ gene segments (1013), $J_{\lambda 2}/C_{\lambda 2}$ gene cluster (1015), and $V_{\lambda 1}$ gene segment (1017)—by a homologous recombination process involving a targeting vector (1003) that shares identity with the locus both upstream of the $V_{\lambda x}/V_{\lambda 2}$ gene segments (1013) and downstream of the $V_{\lambda 1}$ gene segment (1017) in the immediate vicinity of the $J_{\lambda 3}$, $C_{\lambda 3}$, $J_{\lambda 1}$ and $C_{\lambda 1}$ λ gene cluster (1023). The vector replaces the 194 Kb of DNA with elements designed to permit a subsequent site-specific recombination in which a non-native piece of DNA is moved into the modified V_{λ} locus via RMCE (1004). In this example, the non-native DNA is a synthetic nucleic acid comprising both canine and mouse sequences.

[000267] The key features of the gene targeting vector (1003) for accomplishing the 194 Kb deletion are as follows: a negative selection gene such as a gene encoding the A subunit of the diphtheria toxin (DTA, 1059) or a herpes simplex virus thymidine kinase gene (not shown); 4 Kb of genomic DNA from 5' of the mouse $V_{\lambda x}/V_{\lambda 2}$ variable region gene segments in the λ locus (1025); a FRT site (1027); a piece of genomic DNA containing the mouse

Polr2a gene promoter (1029); a translation initiation sequence (methionine codon embedded in a "Kozak" consensus sequence) (1035); a mutated loxP recognition sequence (lox5171) for the Cre recombinase (1031); a transcription termination/polyadenylation sequence (1033); an open reading frame encoding a protein that confers resistance to puromycin (1037), whereas this open reading frame is on the antisense strand relative to the Polr2a promoter and the translation initiation sequence next to it and is followed by its own transcription termination/polyadenylation sequence (1033); a loxP recognition sequence for the Cre recombinase (1039); a translation initiation sequence (a methionine codon embedded in a "Kozak" consensus sequence) (1035) on the same, antisense strand as the puromycin resistance gene open reading frame; a chicken beta actin promoter and cytomegalovirus early enhancer element (1041) oriented such that it directs transcription of the puromycin resistance open reading frame, with translation initiating at the initiation codon downstream of the loxP site and continuing back through the loxP site into the puromycin open reading frame all on the antisense strand relative to the Polr2a promoter and the translation initiation sequence next to it; a mutated recognition site for the Flp recombinase known as an "F3" site (1043); a piece of genomic DNA upstream of the $J_{\lambda 3}$, $C_{\lambda 3}$, $J_{\lambda 1}$ and $C_{\lambda 1}$ gene segments (1045).

[000268] Mouse embryonic stem (ES) cells derived from C57B1/6NTac mice are transfected (1002) by electroporation with the targeting vector (1003) according to widely used procedures. Homologous recombination replaces the native DNA with the sequences from the targeting vector (1003) in the 196 Kb region resulting in the genomic DNA configuration depicted at 1005.

[000269] Prior to electroporation, the vector DNA is linearized with a rare-cutting restriction enzyme that cuts only in the prokaryotic plasmid sequence or the polylinker associated with it. The transfected cells are plated and after ~24 hours placed under positive drug selection using puromycin. There is also negative selection for cells that have integrated the vector into their DNA but not by homologous recombination. Non-homologous recombination results in retention of the DTA gene, which kills the cells when the gene is expressed, whereas the DTA gene is deleted by homologous recombination since it lies outside of the region of vector homology with the mouse IGL locus. Colonies of drug-resistant ES cells are physically extracted from their plates after they became visible to the

naked eye approximately a week later. These picked colonies are disaggregated, re-plated in micro-well plates, and cultured for several days. Thereafter, each of the clones of cells are divided such that some of the cells are frozen as an archive, and the rest used for isolation of DNA for analytical purposes.

[000270] DNA from the ES cell clones is screened by PCR using a widely used gene-targeting assay design. For these assays, one of the PCR oligonucleotide primer sequences maps outside the regions of identity shared between the targeting vector and the genomic DNA, while the other maps within the novel DNA between the two arms of genomic identity in the vector, e.g., in the puro gene (1037). According to the standard design, these assays detect pieces of DNA that would only be present in clones of cells derived from transfected cells that had undergone fully legitimate homologous recombination between the targeting vector (1003) and the native DNA (1001).

[000271] Six PCR-positive clones from the transfection (1002) are selected for expansion followed by further analysis using Southern blot assays. The Southern blots involve three probes and genomic DNA from the clones that has been digested with multiple restriction enzymes chosen so that the combination of probes and digests allow identification of whether the ES cell DNA has been properly modified by homologous recombination.

[000272] Karyotypes of the six PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most common chromosomal aberrations that arise in mouse ES cells. Clones that show evidence of aberrations are excluded from further use. Karyotypically normal clones that are judged to have the expected correct genomic structure based on the Southern blot data are selected for further use.

[000273] The ES cell clones carrying the deletion in one of the two homologous copies of their immunoglobulin λ chain locus are retransfected (1004) with a Cre recombinase expression vector together with a piece of DNA (1007) comprising a partly canine immunoglobulin λ chain locus containing V_λ , J_λ and C_λ region gene segments. The key features of this piece of DNA (1007) are as follows: a lox5171 site (1031); a neomycin resistance gene open reading frame lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site (1047); a FRT site (1027); an array of 76 functional canine λ region gene segments, each with canine λ

coding sequences embedded in mouse λ noncoding sequences (1051); an array of J-C units where each unit has a canine J_λ gene segment and a mouse λ constant domain gene segment embedded within noncoding sequences from the mouse λ locus (1055) (the canine J_λ gene segments are those encoding $J_{\lambda 1}$, $J_{\lambda 2}$, $J_{\lambda 3}$, $J_{\lambda 4}$, $J_{\lambda 5}$, $J_{\lambda 6}$, and $J_{\lambda 7}$, while the mouse λ constant domain gene segments are $C_{\lambda 1}$ or $C_{\lambda 2}$ or $C_{\lambda 3}$); a mutated recognition site for the Flp recombinase known as an "F3" site (1043); an open reading frame conferring hygromycin resistance (1057), which is located on the antisense strand relative to the immunoglobulin gene segment coding information in the construct; a loxP site (1039) in opposite relative orientation to the lox5171 site.

[000274] The sequences of the canine V_λ and J_λ gene coding regions are in Table 3.

[000275] The transfected clones are placed under G418 or hygromycin selection, which enriches for clones of cells that have undergone a RMCE process, in which the partly canine donor DNA is integrated in its entirety into the deleted immunoglobulin λ chain locus between the lox5171 and loxP sites that were placed there by the gene targeting vector. The remaining elements from the targeting vector (1003) are removed via FLP-mediated recombination (1006) *in vitro* or *in vivo* resulting in the final caninized locus as shown at 1011.

[000276] G418/hygromycin-resistant ES cell clones are analyzed by PCR and Southern blotting to determine if they have undergone the expected recombinase-mediated cassette exchange process without unwanted rearrangements or deletions. Clones that have the expected genomic structure are selected for further use.

[000277] The ES cell clones carrying the partly canine immunoglobulin DNA (1011) in the mouse λ chain locus are microinjected into mouse blastocysts from strain DBA/2 to create partially ES cell-derived chimeric mice according to standard procedures. Male chimeric mice with the highest levels of ES cell-derived contribution to their coats are selected for mating to female mice. The female mice of choice here are of the C57B1/6NTac strain, which carry a transgene encoding the Flp recombinase expressed in their germline. Offspring from these matings are analyzed for the presence of the partly canine immunoglobulin λ chain locus, and for loss of the FRT-flanked neomycin resistance gene and the F3-flanked hygromycin resistance gene that were created in the RMCE step. Mice that carry the partly canine locus are used to establish a colony of mice.

[000278] In some aspects, the mice comprising the canine-based heavy chain and κ locus (as described in Examples 3 and 4) are bred to mice that carry the canine-based λ locus. Mice generated from this type of breeding scheme are homozygous for the canine-based heavy chain locus, and can be homozygous for the K-K canine-based locus or the L-K canine-based locus. Alternatively, they can be heterozygous at the κ locus carrying the K-K locus on one chromosome and the L-K locus on the other chromosome. Each of these mouse strains is homozygous for the canine-based λ locus. Monoclonal antibodies recovered from these mice has canine heavy chain variable domains paired in some cases with canine κ variable domains and in other cases with canine λ variable domains. The λ variable domains are derived from either the canine-based L-K locus or the canine-based λ locus.

Example 6: Introduction of an Engineered Partly Canine Immunoglobulin Minilocus into a Mouse Genome

[000279] In certain other aspects, the partly canine immunoglobulin locus comprises a canine variable domain minilocus such as the one illustrated in FIG. 11. Here instead of a partly canine immunoglobulin locus comprising all or substantially all of the canine V_H gene segment coding sequences, the mouse immunoglobulin locus is replaced with a minilocus (1119) comprising fewer chimeric canine V_H gene segments, e.g. 1-39 canine V_H gene segments determined to be functional; that is, not pseudogenes.

[000280] A site-specific targeting vector (1131) comprising the partly canine immunoglobulin locus to be integrated into the mammalian host genome is introduced (1102) into the genomic region (1101) with the deleted endogenous immunoglobulin locus comprising the puro-TK gene (1105) and the following flanking sequence-specific recombination sites: mutant FRT site (1109), mutant LoxP site (1111), wild-type FRT site (1107), and wild-type LoxP site (1105). The site-specific targeting vector comprises i) an array of optional PAIR elements (1141); ii) a V_H locus (1119) comprising, e.g., 1-39 functional canine V_H coding regions and intervening sequences based on the mouse genome endogenous sequences; iii) a 21.6 kb pre-D region (1121) comprising mouse sequence; iv) a D locus (1123) and a J_H locus (1125) comprising 6 D and 6 J_H canine coding sequences and intervening sequences based on the mouse genome endogenous sequences. The partly canine immunoglobulin locus is flanked by recombination sites—mutant FRT

(1109), mutant LoxP (1111), wild-type FRT (1107), and wild-type LoxP (1105)—that allow recombination with the modified endogenous locus. Upon introduction of the appropriate recombinase, e.g., Cre (1104), the partly canine immunoglobulin locus is integrated into the genome upstream of the constant gene region (1127) as shown at 1129.

[000281] As described in Example 1, the primary screening for introduction of the partly canine immunoglobulin variable region locus is carried out by primary PCR screens supported by secondary Southern blotting assays. The deletion of the puro-TK gene (1105) as part of the recombination event allows identification of the cells that did not undergo the recombination event using ganciclovir negative selection.

Example 7: Introduction of an Engineered Partly Canine Immunoglobulin Locus with Canine λ Variable Region Coding Sequences with Mouse λ Constant Region Sequences embedded in κ Immunoglobulin Non-coding Sequences

[000282] Dog antibodies mostly contain λ light chains, whereas mouse antibodies mostly contain κ light chains. To increase production of antibodies containing a λ LC, the endogenous mouse V_{κ} and J_{κ} are replaced with a partly canine locus containing V_{λ} and J_{λ} gene segment coding sequences embedded in mouse V_{κ} region flanking and regulatory sequences, the L-K mouse of Example 4. In such a mouse, the endogenous regulatory sequences promoting high level κ locus rearrangement and expression are predicted to have an equivalent effect on the ectopic λ locus. However, *in vitro* studies demonstrated that canine V_{λ} domains do not function well with mouse C_{κ} (see Example 9). Thus, the expected increase in λ LC-containing antibodies in the L-K mouse might not occur. As an alternate strategy, the endogenous mouse V_{κ} and J_{κ} are replaced with a partly canine locus containing V_{λ} and J_{λ} gene segment coding sequences embedded in mouse V_{κ} region flanking and regulatory sequences and mouse C_{κ} is replaced with mouse C_{λ} .

[000283] FIG. 13 is a schematic diagram illustrating the introduction of an engineered partly canine light chain variable region locus in which one or more canine V_{λ} gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus upstream of one or more canine J_{λ} gene segment coding sequences, which are upstream of one or more rodent C_{λ} region coding sequences.

[000284] The method for replacing a portion of a mouse genome with a partly canine immunoglobulin locus is illustrated in FIG. 13. This method includes introducing a first site-specific recombinase recognition sequence into the mouse genome, which may be introduced either 5' or 3' of the cluster of endogenous V_{κ} (1315) and J_{κ} (1319) region gene segments and the C_{κ} (1321) exon of the mouse genome, followed by the introduction of a second site-specific recombinase recognition sequence into the mouse genome, which in combination with the first sequence-specific recombination site flanks the entire locus comprising clusters of V_{κ} and J_{κ} gene segments and the C_{κ} exon. The flanked region is deleted and then replaced with a partly canine immunoglobulin locus using the relevant site-specific recombinase, as described herein.

[000285] The targeting vectors employed for introducing the site-specific recombination sequences on either side of the V_{κ} (1315) gene segments and the C_{κ} exon (1321) also include an additional site-specific recombination sequence that has been modified so that it is still recognized efficiently by the recombinase, but does not recombine with unmodified sites. This site is positioned in the targeting vector such that after deletion of the V_{κ} and J_{κ} gene segment clusters and the C_{κ} exon it can be used for a second site specific recombination event in which a non-native piece of DNA is moved into the modified V_{κ} locus via RMCE. In this example, the non-native DNA is a synthetic nucleic acid comprises canine V_{λ} and J_{λ} gene segment coding sequences and mouse C_{λ} exon(s) embedded in mouse IGK regulatory and flanking sequences.

[000286] Two gene targeting vectors are constructed to accomplish the process just outlined. One of the vectors (1303) comprises mouse genomic DNA taken from the 5' end of the locus, upstream of the most distal V_{κ} gene segment. The other vector (1305) comprises mouse genomic DNA taken from within the locus in a region spanning upstream (5') and downstream (3') of the C_{κ} exon (1321).

[000287] The key features of the 5' vector (1303) are as follows: a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (1323); 6 Kb of mouse genomic DNA (1325) mapping upstream of the most distal variable region gene in the κ chain locus; a FRT recognition sequence for the Flp recombinase (1327); a piece of genomic DNA containing the mouse

Polr2a gene promoter (1329); a translation initiation sequence (1335, methionine codon embedded in a "Kozak" consensus sequence); a mutated loxP recognition sequence (lox5171) for the Cre recombinase (1331); a transcription termination/polyadenylation sequence (1333); a loxP recognition sequence for the Cre recombinase (1337); a gene encoding a fusion protein with a protein conferring resistance to puromycin fused to a truncated form of the thymidine kinase (pu-TK) under transcriptional control of the promoter from the mouse phosphoglycerate kinase 1 gene (1339); 2.5 Kb of mouse genomic DNA (1341) mapping close to the 6 Kb sequence at the 5' end in the vector and arranged in the native relative orientation.

[000288] The key features of the 3' vector (1305) are as follows: 6 Kb of mouse genomic DNA (1343) mapping within the locus in a region spanning upstream (5') and downstream (3') of the C_κ exon (1321); a gene encoding the human hypoxanthine-guanine phosphoribosyl transferase (HPRT) under transcriptional control of the mouse Polr2a gene promoter (1345); a neomycin resistance gene under the control of the mouse phosphoglycerate kinase 1 gene promoter (1347); a loxP recognition sequence for the Cre recombinase (1337); 3.6 Kb of mouse genomic DNA (1349) that maps immediately downstream in the genome of the 6 Kb DNA fragment included at the 5' end in the vector, with the two fragments oriented in the same relative way as in the mouse genome; a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (1323).

[000289] One strategy to delete the endogenous mouse IGK locus is to insert the 3' vector (1305) in the flanking region downstream of the mouse C_κ exon (1321). However, the 3'κ enhancer, which needs to be retained in the modified locus, is located 9.1 Kb downstream of the C_κ exon, which is too short to accommodate the upstream and downstream homology arms of the 3' vector, which total 9.6 Kb. Therefore, the upstream region of homology was extended.

[000290] Mouse embryonic stem (ES) cells derived from C57B1/6NTac mice are transfected by electroporation with the 3' vector (1305) according to widely used procedures. Prior to electroporation, the vector DNA is linearized with a rare-cutting restriction enzyme that cuts only in the prokaryotic plasmid sequence or the polylinker associated with it. The

transfected cells are plated and after ~24 hours they are placed under positive selection for cells that have integrated the 3' vector into their DNA using the neomycin analogue drug G418. There is also negative selection for cells that have integrated the vector into their DNA but not by homologous recombination. Non-homologous recombination retains the DTA gene, which kills the cells when the gene is expressed, but the DTA gene is deleted by homologous recombination since it lies outside of the region of vector homology with the mouse Igk locus. Colonies of drug-resistant ES cells are physically extracted from their plates after they are visible to the naked eye about a week later. These colonies are disaggregated, re-plated in micro-well plates, and cultured for several days. Thereafter, each of the clones of cells is divided - some of the cells are frozen as an archive, and the rest are used to isolate DNA for analytical purposes.

[000291] DNA from the ES cell clones is screened by PCR using a widely used gene-targeting assay design. For this assay, one of the PCR oligonucleotide primer sequences maps outside the region of identity shared between the 3' vector (1305) and the genomic DNA (1301), while the other maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (1345) or neomycin resistance (1347) genes. According to the standard design, these assays detect pieces of DNA that are only present in clones of ES cells derived from transfected cells that had undergone fully legitimate homologous recombination between the 3' vector (1305) and the endogenous mouse Igk locus. Two separate transfections are performed with the 3' vector (1305). PCR-positive clones from the two transfections are selected for expansion followed by further analysis using Southern blot assays.

[000292] Southern blot assays are performed according to widely used procedures using three probes and genomic DNA digested with multiple restriction enzymes chosen so that the combination of probes and digests allowed for conclusions to be drawn about the structure of the targeted locus in the clones and whether it is properly modified by homologous recombination. A first probe maps to DNA sequence flanking the 5' side of the region of identity shared between the 3' κ targeting vector (1305) and the genomic DNA; a second probe also maps outside the region of identity but on the 3' side; a third probe maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the HPRT (1345) or neomycin resistance (1347) genes. The Southern blot identifies the presence of

the expected restriction enzyme-generated fragment of DNA corresponding to the correctly mutated, i.e., by homologous recombination with the 3' κ targeting vector (1305) part of the κ locus, as detected by one of the external probes and by the neomycin resistance or HPRT gene probe. The external probe detects the mutant fragment and also a wild-type fragment from the non-mutant copy of the immunoglobulin κ locus on the homologous chromosome.

[000293] Karyotypes of PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most commonly arising chromosomal aberrations that arise in mouse ES cells. Clones with such aberrations are excluded from further use. Karyotypically normal clones that are judged to have the expected correct genomic structure based on the Southern blot data are selected for further use.

[000294] Acceptable clones are then modified with the 5' vector (1303) using procedures and screening assays that are similar in design to those used with the 3' vector (1305), except that puromycin selection is used instead of G418/neomycin selection, and the protocols are tailored to match the genomic region modified by the 5' vector (1303). The goal of the 5' vector (1303) transfection experiments is to isolate clones of ES cells that have been mutated in the expected fashion by both the 3' vector (1305) and the 5' vector (1303), i.e., doubly targeted cells carrying both engineered mutations. In these clones, the Cre recombinase causes a recombination (1302) to occur between the loxP sites introduced into the κ locus by the two vectors, resulting in the genomic DNA configuration shown at 1307.

[000295] Further, the clones must have undergone gene targeting on the same chromosome, as opposed to homologous chromosomes; i.e., the engineered mutations created by the targeting vectors must be in *cis* on the same DNA strand rather than in *trans* on separate homologous DNA strands. Clones with the *cis* arrangement are distinguished from those with the *trans* arrangement by analytical procedures such as fluorescence *in situ* hybridization of metaphase spreads using probes that hybridize to the novel DNA present in the two gene targeting vectors (1303 and 1305) between their arms of genomic identity. The two types of clones can also be distinguished from one another by transfecting them with a vector expressing the Cre recombinase, which deletes the pu-Tk (1339), HPRT (1345) and neomycin resistance (1347) genes if the targeting vectors have been integrated

in *cis*, and comparing the number of colonies that survive ganciclovir selection against the thymidine kinase gene introduced by the 5' vector (1303) and by analyzing the drug resistance phenotype of the surviving clones by a "sibling selection" screening procedure in which some of the cells from the clone are tested for resistance to puromycin or G418/neomycin. Cells with the *cis* arrangement of mutations are expected to yield approximately 10^3 more ganciclovir-resistant clones than cells with the *trans* arrangement. The majority of the resulting *cis*-derived ganciclovir-resistant clones should also be sensitive to both puromycin and G418/neomycin, in contrast to the *trans*-derived ganciclovir-resistant clones, which should retain resistance to both drugs. Clones of cells with the *cis*-arrangement of engineered mutations in the κ chain locus are selected for further use.

[000296] The doubly targeted clones of cells are transiently transfected with a vector expressing the Cre recombinase (1302) and the transfected cells are subsequently placed under ganciclovir selection, as in the analytical experiment summarized above. Ganciclovir-resistant clones of cells are isolated and analyzed by PCR and Southern blot for the presence of the expected deletion (1307) between the two engineered mutations created by the 5' vector (1303) and the 3' vector (1305). In these clones, the Cre recombinase causes a recombination to occur between the loxP sites (1337) introduced into the κ chain locus by the two vectors. Because the loxP sites are arranged in the same relative orientations in the two vectors, recombination results in excision of a circle of DNA comprising the entire genomic interval between the two loxP sites. The circle does not contain an origin of replication and thus is not replicated during mitosis and is therefore lost from the clones of cells as they undergo clonal expansion. The resulting clones carry a deletion of the DNA that was originally between the two loxP sites and have the genomic structure show at 1307. Clones that have the expected deletion are selected for further use.

[000297] The ES cell clones carrying the sequence deletion in one of the two homologous copies of their immunoglobulin κ chain locus are retransfected (1304) with a Cre recombinase expression vector together with a piece of DNA (1309) comprising a partly canine immunoglobulin λ chain locus containing V_λ (1351) and J_λ (1355) gene segment coding sequences and mouse C_λ exon(s) (1357). The key features of this piece of DNA are the following: a lox5171 site (1331); a neomycin resistance gene open reading frame (1347,

lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site (1331); a FRT site (1327); an array of 1-76 functional canine V_{λ} variable region gene segments (1351), each with canine coding sequences embedded in mouse noncoding regulatory or scaffold sequences; optionally, a 13.5 Kb piece of genomic DNA from immediately upstream of the cluster of the J_{κ} region gene segments in the mouse κ chain locus (not shown); a 2 Kb piece of DNA containing 1-7 canine J_{λ} region gene segments embedded in mouse noncoding DNA (1355) and mouse C_{λ} exon(s) (1357); a loxP site (1337) in opposite relative orientation to the lox5171 site (1331). The piece of DNA also contains the deleted iE κ (not shown).

[000298] The sequences of the canine V_{λ} and J_{λ} gene coding regions are in Table 3.

[000299] The transfected cells are placed under G418 selection, which enriches for clones of cells that have undergone RMCE, in which the partly canine donor DNA (1309) is integrated in its entirety into the deleted immunoglobulin κ chain locus between the lox5171 (1331) and loxP (1337) sites that were placed there by 5' (1303) and 3' (1305) vectors, respectively. Only cells that have properly undergone RMCE have the capability to express the neomycin resistance gene (1347) because the promoter (1329) as well as the initiator methionine codon (1335) required for its expression are not present in the vector (1309) and are already pre-existing in the host cell IGK locus (1307). The DNA region created by RMCE is illustrated at 1311. The remaining elements from the 5' vector (1303) are removed via Flp-mediated recombination (1306) *in vitro* or *in vivo*, resulting in the final canine-based light chain locus as shown at 1313.

[000300] G418-resistant ES cell clones are analyzed by PCR and Southern blotting to determine if they have undergone the expected RMCE process without unwanted rearrangements or deletions. Clones that have the expected genomic structure are selected for further use.

[000301] Clones carrying the partly canine immunoglobulin DNA in the mouse κ chain locus (1313) are microinjected into mouse blastocysts from strain DBA/2 to create partly ES cell-derived chimeric mice according to standard procedures. Male chimeric mice with the highest levels of ES cell-derived contribution to their coats are selected for mating to female mice. The female mice of choice for use in the mating are of the C57B1/6NTac strain, and also carry a transgene encoding the Flp recombinase that is expressed in their

germline. Offspring from these matings are analyzed for the presence of the partly canine immunoglobulin λ light chain locus, and for loss of the FRT-flanked neomycin resistance gene that was created in the RMCE step. Mice that carry the partly canine locus are used to establish colonies of mice.

[000302] Mice carrying the partly canine heavy chain locus, produced as described in Example 3, can be bred with mice carrying a canine λ -based κ chain locus. Their offspring are in turn bred together in a scheme that ultimately produces mice that are homozygous for both canine-based loci, i.e., canine-based for heavy chain and λ -based λ . Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine λ proteins with canine λ variable domains and the mouse λ constant domain from their κ loci. Monoclonal antibodies recovered from these mice have canine heavy chain variable domains paired with canine λ variable domains.

[000303] A variation on the breeding scheme involves generating mice that are homozygous for the canine-based heavy chain locus, but heterozygous at the κ locus such that on one chromosome they have the K-K canine-based locus described in Example 4 and on the other chromosome they have the partly canine λ -based κ locus described in this example. Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine κ proteins with canine κ variable domains and the mouse κ constant domain from one of their κ loci. From the other κ locus, partly canine λ proteins comprising canine λ variable domains and the mouse λ constant domain are produced. Monoclonal antibodies recovered from these mice include canine variable domains paired in some cases with canine κ variable domains and in other cases with canine λ variable domains.

Example 8. Introduction of an Engineered Partly Canine Immunoglobulin Locus with Canine λ Variable Region Coding Sequences with Mouse λ Constant Region Sequences embedded in Mouse κ Immunoglobulin Non-coding Sequences

[000304] This example describes an alternate strategy to Example 7 in which the endogenous mouse V_{κ} and J_{κ} are replaced with a partly canine locus containing canine V_{λ} and J_{λ} gene

segment coding sequences embedded in mouse V_{κ} region flanking and regulatory sequences and mouse C_{κ} is replaced with mouse C_{λ} . However, in this example the structure of the targeting vector containing the partly canine locus is different. The canine V gene locus coding sequences include an array of anywhere from 1 to 76 functional V_{λ} gene segment coding sequences, followed by an array of J_{λ} - C_{λ} tandem cassettes in which the J_{λ} is of canine origin and the C_{λ} is of mouse origin, for example, $C_{\lambda 1}$, $C_{\lambda 2}$ or $C_{\lambda 3}$. The number of cassettes ranges from one to seven, the number of unique functional canine J_{λ} gene segments. The overall structure of the partly canine λ locus in this example is similar to the endogenous mouse λ locus, whereas the structure of the locus in Example 7 is similar to the endogenous mouse κ locus, which is being replaced by the partly canine λ locus in that example.

[000305] FIG. 14 is a schematic diagram illustrating the introduction of an engineered partly canine light chain variable region locus in which one or more canine V_{λ} gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus upstream of an array of J_{λ} - C_{λ} tandem cassettes in which the J_{λ} is of canine origin and the C_{λ} is of mouse origin, for example, $C_{\lambda 1}$, $C_{\lambda 2}$ or $C_{\lambda 3}$.

[000306] The method for replacing a portion of a mouse genome with a partly canine immunoglobulin locus is illustrated in FIG. 14. This method provides introducing a first site-specific recombinase recognition sequence into the mouse genome, which may be introduced either 5' or 3' of the cluster of endogenous V_{κ} (1415) and J_{κ} (1419) region gene segments and the C_{κ} (1421) exon of the mouse genome, followed by the introduction of a second site-specific recombinase recognition sequence into the mouse genome, which in combination with the first sequence-specific recombination site flanks the entire locus comprising clusters of V_{κ} and J_{κ} gene segments and the C_{κ} exon. The flanked region is deleted and then replaced with a partly canine immunoglobulin locus using the relevant site-specific recombinase, as described herein.

[000307] The targeting vectors employed for introducing the site-specific recombination sequences on either side of the V_{κ} (1415) gene segments and the C_{κ} exon (1421) also include an additional site-specific recombination sequence that has been modified so that it is still recognized efficiently by the recombinase, but does not recombine with

unmodified sites. This site is positioned in the targeting vector such that after deletion of the V_{κ} and J_{κ} gene segment clusters and the C_{κ} exon it can be used for a second site specific recombination event in which a non-native piece of DNA is moved into the modified V_{κ} locus via RMCE. In this example, the non-native DNA is a synthetic nucleic acid comprising an array of canine V_{λ} gene segment coding sequences and an array of J_{λ} - C_{λ} tandem cassettes in which the J_{λ} is of canine origin and the C_{λ} is of mouse origin, for example, $C_{\lambda 1}$, $C_{\lambda 2}$ or $C_{\lambda 3}$ embedded in mouse IGK regulatory and flanking sequences.

[000308] Two gene targeting vectors are constructed to accomplish the process just outlined. One of the vectors (1403) comprises mouse genomic DNA taken from the 5' end of the locus, upstream of the most distal V_{κ} gene segment. The other vector (1405) comprises mouse genomic DNA taken from within the locus in a region spanning upstream (5') and downstream (3') of the C_{κ} exon (1321).

[000309] The key features of the 5' vector (1403) and the 3' vector (1405) are described in Example 7.

[000310] Mouse embryonic stem (ES) cells derived from C57B1/6NTac mice are transfected by electroporation with the 3' vector (1405) according to widely used procedures as described in Example 7. DNA from the ES cell clones is screened by PCR using a widely used gene-targeting assay as described in Example 7. The Southern blot assays are performed according to widely used procedures as described in Example 7.

[000311] Karyotypes of PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most commonly arising chromosomal aberrations that arise in mouse ES cells. Clones with such aberrations are excluded from further use. Karyotypically normal clones that are judged to have the expected correct genomic structure based on the Southern blot data are selected for further use.

[000312] Acceptable clones are modified with the 5' vector (1403) using procedures and screening assays as described in Example 7. The resulting correctly targeted ES clones have the genomic DNA configuration of the endogenous κ locus in which the 5' vector (1403) is inserted upstream of endogenous V_{κ} gene segments and the 3' vector (1405) is inserted downstream of the endogenous C_{κ} . In these clones, the Cre recombinase causes

recombination (1402) to occur between the loxP sites introduced into the κ locus by the two vectors, resulting in the genomic DNA configuration shown at 1407.

[000313] Acceptable clones undergo gene targeting on the same chromosome, as opposed to homologous chromosomes; such that the engineered mutations created by the targeting vectors are in *cis* on the same DNA strand rather than in *trans* on separate homologous DNA strands. Clones with the *cis* arrangement are distinguished from those with the *trans* arrangement by analytical procedures as described in Example 7.

[000314] The doubly targeted clones of cells are transiently transfected with a vector expressing the Cre recombinase (1402) and the transfected cells are subsequently placed under ganciclovir selection and analyses using procedures described in Example 7. In selected clones, the Cre recombinase has caused a recombination to occur between the loxP sites (1437) introduced into the κ chain locus by the two vectors. Because the loxP sites are arranged in the same relative orientations in the two vectors, recombination results in excision of a circle of DNA comprising the entire genomic interval between the two loxP sites. The circle does not contain an origin of replication and thus is not replicated during mitosis and is therefore lost from the clones of cells as they undergo clonal expansion. The resulting clones carry a deletion of the DNA that was originally between the two loxP sites and have the genomic structure show at 1407. Clones that have the expected deletion are selected for further use.

[000315] The ES cell clones carrying the deletion of sequence in one of the two homologous copies of their immunoglobulin κ chain locus are retransfected (1404) with a Cre recombinase expression vector together with a piece of DNA (1409) comprising a partly canine immunoglobulin λ chain locus containing V_λ (1451) segment coding sequences and a tandem array of cassettes containing canine J_λ gene segment coding sequences and mouse C_λ exon(s) embedded in mouse IGK flanking and regulatory DNA sequences (1457). The key features of this piece of DNA are the following: a lox5171 site (1431); a neomycin resistance gene open reading frame (1447, lacking the initiator methionine codon, but in-frame and contiguous with an uninterrupted open reading frame in the lox5171 site (1431); a FRT site (1427); an array of 1-76 functional canine V_λ variable region gene segments (1451), each containing canine coding sequences embedded in mouse noncoding regulatory or scaffold sequences; optionally, a 13.5 Kb piece of genomic DNA from

immediately upstream of the cluster of the J_κ region gene segments in the mouse κ chain locus (not shown); DNA containing a tandem array of cassettes containing canine J_λ gene segment coding sequences and mouse C_λ exon(s) embedded in mouse IGK flanking and regulatory DNA sequences (1457); a loxP site (1437) in opposite relative orientation to the lox5171 site (1431).

[000316] The sequences of the canine V_λ and J_λ gene coding regions are in Table 3.

[000317] The transfected cells are placed under G418 selection, which enriches for clones of cells that have undergone RMCE, in which the partly canine donor DNA (1409) is integrated in its entirety into the deleted immunoglobulin κ chain locus between the lox5171 (1431) and loxP (1437) sites placed there by the 5' (1403) and 3' (1405) vectors, respectively. Only cells that properly undergo RMCE have the capability to express the neomycin resistance gene (1447) because the promoter (1429) as well as the initiator methionine codon (1435) required for its expression are not present in the vector (1409) and are already pre-existing in the host cell IGK locus (1407). The DNA region created by RMCE is illustrated at 1411. The remaining elements from the 5' vector (1403) are removed via Flp-mediated recombination (1406) *in vitro* or *in vivo*, resulting in the final canine-based light chain locus as shown at 1413.

[000318] G418-resistant ES cell clones are analyzed by PCR and Southern blotting to determine if they have undergone the expected RMCE process without unwanted rearrangements or deletions. Clones that have the expected genomic structure are selected for further use.

[000319] Clones carrying the partly canine immunoglobulin DNA in the mouse κ chain locus (1413) are microinjected into mouse blastocysts from strain DBA/2 to create partly ES cell-derived chimeric mice according to standard procedures. Male chimeric mice with the highest levels of ES cell-derived contribution to their coats are selected for mating to female mice. The female mice of choice for use in the mating are of the C57B1/6NTac strain, and also carry a transgene encoding the Flp recombinase that is expressed in their germline. Offspring from these matings are analyzed for the presence of the partly canine immunoglobulin λ light chain locus, and for loss of the FRT-flanked neomycin resistance gene that was created in the RMCE step. Mice that carry the partly canine locus are used to establish colonies of mice.

[000320] Mice carrying the partly canine heavy chain locus, produced as described in Example 3, can be bred with mice carrying a canine λ -based κ chain locus. Their offspring are in turn bred together in a scheme that ultimately produces mice that are homozygous for both canine-based loci, i.e., canine-based for heavy chain and λ -based κ . Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine λ proteins with canine λ variable domains and the mouse λ constant domain from their κ loci. Monoclonal antibodies recovered from these mice have canine heavy chain variable domains paired with canine λ variable domains.

[000321] A variation on the breeding scheme involves generating mice that are homozygous for the canine-based heavy chain locus, but heterozygous at the κ locus such that on one chromosome they have the K-K canine-based locus described in Example 4 and on the other chromosome they have the partly canine λ -based κ locus described in this example. Such mice produce partly canine heavy chains with canine variable domains and mouse constant domains. They also produce partly canine κ proteins with canine κ variable domains and the mouse κ constant domain from one of their κ loci. From the other κ locus, they produce partly canine λ proteins with canine λ variable domains and the mouse λ constant domain. Monoclonal antibodies recovered from these mice have canine variable domains paired in some cases with canine κ variable domains and in other cases with canine λ variable domains.

[000322] The method described above for introducing an engineered partly canine immunoglobulin locus with canine λ variable region coding sequences and mouse λ constant region sequences embedded in mouse κ immunoglobulin non-coding sequences involve deletion of the mouse C_κ exon. An alternate method involves inactivating the C_κ exon by mutating its splice acceptor site. Introns must be removed from primary mRNA transcripts by a process known as RNA splicing in which the spliceosome, a large molecular machine located in the nucleus, recognizes sequences at the 5' (splice donor) and 3' (splice acceptor) ends of the intron, as well as other features of the intron including a polypyrimidine tract located just upstream of the splice acceptor. The splice donor sequence in the DNA is NGT, where "N" is any deoxynucleotide and the splice acceptor

is AGN (Cech TR, Steitz JA and Atkins JF Eds. (2019) (RNA Worlds: New Tools for Deep Exploration, CSHL Press) ISBN 978-1-621822-24-0).

[000323] The mouse C_{κ} exon is inactivated by mutating its splice acceptor sequence and the polypyrimidine tract. The wild type sequence upstream of the C_{κ} exon is CTCCTTCCTCAG (SEQ ID NO: 470) (the splice acceptor site is underlined). It is mutated to AAATTAATTAACC (SEQ ID NO: 471), resulting in a non-functional splice acceptor site and thus a non-functional C_{κ} exon. The mutant sequence also introduces a PacI restriction enzyme site (underlined). As an eight base pair recognition sequence, this restriction site is expected to be present only rarely in the mouse genome (~ every 65,000 bp), making it simple to detect whether the mutant sequence has been inserted into the IGK locus by Southern blot analysis of the ES cell DNA that has been digested with PacI and another, more frequently cutting restriction enzyme. The wild type sequence is replaced with the mutant sequence by homologous recombination, a technique widely known in the art, as to insert the 3' RMCE vector. The key features of the homologous recombination vector (MSA, 1457) to mutate the C_{κ} exon splice acceptor sequence and the polypyrimidine tract are as follows: 6 Kb of mouse genomic DNA (1443) mapping within the κ locus in a region spanning upstream (5') and downstream (3') of the C_{κ} exon (1421) and containing the mutant AAATTAATTAACC (SEQ ID NO: 471) (1459) sequence instead of the wild type CTCCTTCCTCAG (SEQ ID NO: 470) sequence in its natural position just upstream of the C_{κ} exon; a neomycin resistance gene under the control of the mouse phosphoglycerate kinase 1 gene promoter (1447) and flanked by mutant FRT sites (1461); 3.6 Kb of mouse genomic DNA (1449) that maps immediately downstream in the genome of the 6 Kb DNA fragment included at the 5' end in the vector, with the two fragments oriented in the same relative way as in the mouse genome; a gene encoding the diphtheria toxin A (DTA) subunit under transcriptional control of a modified herpes simplex virus type I thymidine kinase gene promoter coupled to two mutant transcriptional enhancers from the polyoma virus (1423). Mutant FRT sites (1461), e.g., FRT F3 or FRT F5 (Schlake and Bode (1994) Use of mutated FLP recognition target (FRT) sites for the exchange of expression cassettes at defined chromosomal loci. Biochemistry 33:12746-12751 PMID: 7947678 DOI: 10.1021/bi00209a003), are being used here because, once the splicing mutation is introduced and the Neo gene is deleted by transient transfection of a FLP

recombinase expression vector (1406), the ES cells are subjected to further genetic manipulation. This process requires wild type FRT sites to delete another Neo selection gene (1447 at 1403). If the FRT site (1461) remaining in the IGK locus (1469) after introduction of the splicing mutation is wild type, attempted FRT-mediated deletion of this second Neo gene (1406 at 1413) may inadvertently result in deletion of the entire newly-introduced partly canine locus and the inactivated mouse C_κ exon.

[000324] Mouse embryonic stem (ES) cells derived from C57B1/6NTac mice are transfected by electroporation with the MSA vector (1457) according to widely used procedures. Prior to electroporation, the vector DNA is linearized with a rare-cutting restriction enzyme that cuts only in the prokaryotic plasmid sequence or the polylinker associated with it. The transfected cells are plated and after ~24 hours they are placed under positive selection for cells that have integrated the MSA vector into their DNA by using the neomycin analogue drug G418. There is also negative selection for cells that have integrated the vector into their DNA but not by homologous recombination. Non-homologous recombination results in retention of the DTA gene, which kills the cells when the gene is expressed, whereas the DTA gene is deleted by homologous recombination since it lies outside of the region of vector homology with the mouse IGK locus. Colonies of drug-resistant ES cells are physically extracted from their plates after they became visible to the naked eye about a week later. These picked colonies are disaggregated, re-plated in micro-well plates, and cultured for several days. Thereafter, each of the clones of cells is divided such that some of the cells are frozen as an archive, and the rest used to isolate DNA for analytical purposes.

[000325] The IGK locus in ES cells that are correctly targeted by homologous recombination has the configuration depicted at 1463.

[000326] DNA from the ES cell clones is screened by PCR using a widely used gene-targeting assay design. For this assay, one of the PCR oligonucleotide primer sequences maps outside the region of identity shared between the MSA vector (1457) and the genomic DNA (1401), while the other maps within the novel DNA between the two arms of genomic identity in the vector, i.e., the neomycin resistance (1447) gene. According to the standard design, these assays detect pieces of DNA that are only present in clones of ES cells derived from transfected cells that had undergone fully legitimate homologous recombination

between the MSA vector (1457) and the endogenous mouse IGK locus. Two separate transfections are performed with the MSA vector (1457). PCR-positive clones from the two transfections are selected for expansion followed by further analysis using Southern blot assays.

[000327] The Southern blot assays are performed according to widely used procedure using three probes and genomic DNA digested with multiple restriction enzymes chosen so that the combination of probes and digests allowed for conclusions to be drawn about the structure of the targeted locus in the clones and whether it is properly modified by homologous recombination. In in this particular example, the DNA is double digested with PacI and another restriction enzyme such as EcoRI or HindIII, as only cells with the integrated MSA vector contains the PacI site. A first probe maps to DNA sequence flanking the 5' side of the region of identity shared between the MSA vector (1457) and the genomic DNA; a second probe also maps outside the region of identity but on the 3' side; a third probe maps within the novel DNA between the two arms of genomic identity in the vector, i.e., in the neomycin resistance (1447) gene. The Southern blot identifies the presence of the expected restriction enzyme-generated fragment of DNA corresponding to the correctly mutated, i.e., by homologous recombination with the MSA κ targeting vector (1457) part of the κ locus, as detected by one of the external probes and by the neomycin resistance gene probe. The external probe detects the mutant fragment and also a wild-type fragment from the non-mutant copy of the immunoglobulin κ locus on the homologous chromosome. The Southern blot assays are performed according to widely used procedures described in Example 7.

[000328] Karyotypes of PCR- and Southern blot-positive clones of ES cells are analyzed using an *in situ* fluorescence hybridization procedure designed to distinguish the most commonly arising chromosomal aberrations that arise in mouse ES cells. Clones with such aberrations are excluded from further use. Karyotypically normal clones that are judged to have the expected correct genomic structure based on the Southern blot data are selected for further use.

[000329] Although the ability of the ES cell DNA to be digested by PacI in the mutated IGK allele confirms the presence of the TTAATTAA sequence, DNA sequencing focusing on the region upstream of the C κ exon is performed to confirm the presence of the complete

expected splicing mutation. The region is amplified by genomic PCR using primers that flank the mutation [1465 and 1467 (Table 6: SEQ ID NO: 417 and SEQ ID NO:418)]. An alternate primer pair is shown in SEQ ID NO: 419 and SEQ ID NO: 420. These primers are designed using NCBI Primer-Blast and verified *in silico* to lack any predicted off-target binding sites in the mouse genome.

[000330] Sequence-verified ES cell clones are transiently transfected (1406) with a FLP recombinase expression vector to delete the neomycin resistance gene (1427). The cells are then subcloned and the deletion is confirmed by PCR. The IGK locus in the ES cells have the genomic configuration depicted at 1469.

[000331] The ES cells are electroporated with the 5' and 3' RMCE vectors, as described above. The only differences are that the 3' vector (1405) is inserted upstream of the mutant C_κ exon at the position shown in FIG. 9 at 901 and upstream and downstream homology arms of the 3' vector (1405) is replaced by the sequences 943 and 949, respectively of the 3' vector (905) shown in FIG. 9. As a result, PCR primers and Southern blot probes used to test for correct integration of the 3' vector (1405) are derived from sequences 943 and 949 instead of 1443 and 1449. The iE_κ enhancer is not included in the targeting vector (1409), since this sequence was not deleted.

Example 9: Canine V_λ domains do not function well with mouse C_κ domains and canine V_κ domains do not function well with mouse C_λ domains.

[000332] For the proposed L-K mouse (Example 4), canine V_λ and J_λ gene segment coding sequences flanked by mouse non-coding and regulatory sequences are embedded in the mouse IGK locus from which endogenous V_κ and J_κ gene segments have been deleted. After productive V_λ→J_λ gene rearrangement, the resulting Ig gene encodes a LC with a canine λ variable domain and a mouse κ constant domain. To test whether such a hybrid LC was properly expressed and forms an intact Ig molecule, a series of transient transfection assays were performed with different combinations of V_s, both V_κ and V_λ, and C light chain exons, both C_κ and C_λ, together with an Ig HC and tested for cell surface and intracellular expression and secretion of the encoded Ig.

[000333] For these experiments canine IGHV3-5 (Accession No. MF785020.1), IGHV3-19 (Accession No. FJ197781.1) or IGHV4-1 (Accession No. DN362337.1) linked to a mouse IgM^b allotype HC was individually cloned into a pCMV vector. Each V_H-encoding DNA contained the endogenous canine L1-intron-L2 and germline, i.e., unmutated VDJ sequence. Unmutated canine IGLV3-28 (Accession No. EU305423) or IGKV2-5 (Accession No. EU295719.1) were cloned into a pFUSE vector. Each canine V_L exon was linked to the constant region of mouse C_κ, C_{λ1} or C_{λ2} (C_{λ3} was presumed to have the same properties as C_{λ2} since they have nearly identical protein sequence.) L1-intron-L2 sequences in each VL were of canine origin. 293T/17 cells were co-transfected with a human CD4 expression vector as a transfection control plus one of the HC and LC constructs and a CD79a/b expression vector. The CD79a/b heterodimer was required for cell surface expression of the IgM. Approximately 24h later, the transfected cells were subjected to cell surface or intracellular staining by flow cytometry. For analysis of Ig secretion the same V_H genes as above were cloned into a pFUSE vector containing mouse IgG2a Fc. 293T/17 cells were co-transfected with a human CD4 (hCD4) expression vector as a transfection control plus one of the HC and LC constructs described above. (In these experiments C_{λ3} was also tested.) Approximately 48hr later, the transfected cells and their corresponding supernatants were harvested and analyzed for HC/LC expression/secretion by western blotting.

[000334] To summarize the data obtained from these experiments, when canine IGLV3-28 was linked to mouse C_κ, IgM expression on the cell surface was at least two times less than when the same dog V_λ was linked to C_{λ1} or C_{λ2}. Likewise, when IGKV2-5 was linked to mouse C_λ, the level of surface IgM was drastically decreased. The extent of the expression defect was dependent of the particular V_H gene being used; some V_H genes allowed for some cell surface expression of the hybrid light chains, but others were more stringent. The same trends were seen with Ig secretion.

[000335] FIG. 15 shows the results of flow cytometry analysis of cells expressing IGHV3-5, which was one of the less stringent V_H genes, with canine IGLV3-28/IGLJ6 (1501) or with canine IGKV2-5/IGJK1 (1502). The top row panels are transfection controls stained with hCD4 mAb antibody (1509) and the bottom panels were stained with mouse IgM^b allotype mAb (1510). The non-transfected, hCD4⁻ cells (1513) and transfected, hCD4⁺ cells (1514)

are indicated in all panels by the different shaded histograms. The frequency of non-transfected, hCD4⁻ cells is indicated by the number in the upper left of each panel in the top row and the frequency of transfected, hCD4⁺ cells is indicated by the number in the upper right of each panel in the top row. Transfection efficiency was similar in all cases. However, when canine V_λ was linked to mouse C_κ (1503, bottom row) IgM expression on the cell surface was less than when the same canine V_λ was linked to mouse C_{λ1} or C_{λ2} (1504, 1505, bottom row). Similarly, the canine IgM with V_κ was expressed better when linked to C_κ (1506, bottom row) than to C_{λ1} or C_{λ2} (1507, 1508, bottom row). The numbers in the upper right of each panel in the bottom row indicate the mean fluorescence intensity (MFI) of the cell surface IgM^b staining, which is a quantitative indication of the level of expression.

[000336] FIG. 16 shows the results of flow cytometry analysis of cells expressing IGHV3-5, which was one of the less stringent V_H genes, with canine IGVL3-28/IGLJ6 (1601) or with canine IGVK2-5/IGJK1 (1602). These were the same cells as in FIG. 15, but were stained for cell surface mouse κ LC (1609) or mouse λ LC (1610), confirming the results shown in FIG. 15.

[000337] FIG. 17 shows the results of flow cytometry analysis of cells expressing IGHV4-1, which was more stringent than IGHV3-5, with canine IGVL3-28/IGLJ6 (1701) or with canine IGVK2-5/IGJK1 (1702). The top row panels are transfection controls stained with hCD4 mAb antibody (1709) and the bottom panels are stained with mouse IgM^b allotype mAb (1710). The non-transfected, hCD4⁻ cells (1713) and transfected, hCD4⁺ cells (1714) are indicated in all lower panels by the different shaded histograms. The frequency of non-transfected, hCD4⁻ cells is indicated by the number in the upper left of each panel in the top row and the frequency of transfected, hCD4⁺ cells is indicated by the number in the upper right of each panel in the top row. Transfection efficiency was similar in all cases. However, when canine V_λ was linked to mouse C_κ (1703, bottom row) IgM expression on the cell surface was much less than when the same canine V_λ was linked to mouse C_{λ1} or C_{λ2} (1704, 1705, bottom row), although the best expression in this case was with C_{λ2} (1705, bottom row). Similarly, the canine IgM with V_κ was expressed much better when linked to C_κ (1706, bottom row) than to C_{λ1} or C_{λ2} (1707, 1708, bottom row). In fact, in this case, expression of IgM with C_{λ1} or C_{λ2} was essentially undetectable. The numbers in the upper

right of each panel in the bottom row indicate the mean fluorescence intensity (MFI) of the cell surface IgM^b staining, which is a quantitative indication of the level of expression. Staining with antibodies specific for mouse λ LC or κ LC was performed in all experiments and confirmed the results of staining with the IgM^b allotype mAb (not shown).

[000338] FIG. 18 shows the results of flow cytometry analysis of cells expressing IGHV3-19, which was the most stringent of the IGHV genes tested in terms of the ability of canine V λ to function with mouse C κ , with canine IGVL3-28/IGLJ6 (1801) or with canine IGVK2-5/IGJK1 (1802). The top row panels are transfection controls stained with hCD4 mAb antibody (1809) and the bottom panels are stained with mouse IgM^b allotype mAb (1810). The non-transfected, hCD4⁻ cells (1813) and transfected, hCD4⁺ cells (1814) are indicated in all lower panels by the different shaded histograms. The frequency of non-transfected, hCD4⁻ cells is indicated by the number in the upper left of each panel in the top row and the frequency of transfected, hCD4⁺ cells is indicated by the number in the upper right of each panel in the top row. Transfection efficiency was similar in all cases. There was essentially no surface IgM expression when the canine V λ was linked to mouse C κ (1803, bottom row) and only low-level expression when the canine V κ was linked to mouse C λ 1 or C λ 2 (1807, 1808, bottom row). The numbers in the upper right of each panel in the bottom row indicate the mean fluorescence intensity (MFI) of the cell surface IgM^b staining, which is a quantitative indication of the level of expression. Staining with antibodies specific for mouse λ LC or κ LC was performed in all experiments and confirmed the results of staining with the IgM^b allotype mAb (not shown).

[000339] The results of this analysis indicate that hybrid light chains that include canine V λ and mouse C κ or canine V κ and mouse C λ 1 or C λ 2 were often poorly expressed on the cell surface with μ HC. The level of cell surface IgM was dependent on the particular V_H used by the μ HC, but there was no discernable pattern that would allow prediction of whether a particular V_H would allow modest or no cell surface IgM expression. Since B cell survival depends on IgM BCR expression, pairing of canine V λ and mouse C κ would result in a major reduction in the development of λ LC-expressing B cells. Similarly, pairing of canine V κ with mouse C λ 1 or C λ 2 would reduce the development of κ -LC expressing B cells.

[000340] Expression and secretion of the Ig with hybrid or homologous LC was also tested. Supernatants and cell lysates of the transiently transfected cells were analyzed by western

blotting. FIG. 19A shows the results of supernatants of cells using canine IGVL3-28 paired with mouse C_κ, C_{λ1}, C_{λ2} or C_{λ3} and a mouse IgG2a HC containing canine IGHVH3-5 (1901), IGHVH3-19 (1902) or IGHVH4-1 (1903). FIG. 19B shows the results of lysates of cells using canine IGVL3-28 paired with mouse C_κ, C_{λ1}, C_{λ2} or C_{λ3} and a mouse IgG2a HC containing canine IGHVH3-5 (1904), IGHVH3-19 (1905) or IGHVH4-1 (1906). The samples were electrophoresed under non-reducing (not shown) or reducing conditions and the blot was probed with an IgG2a antibody. The amount of IgG2a secreted when canine IGVL3-28 was paired with mouse C_κ (1907) was consistently much less than when it was paired with C_{λ1} (1908) C_{λ2} (1909) or C_{λ3} (1910) (FIG. 18A). This difference was not due to lower expression or enhanced degradation of the γ2a HC in the canine IGVL3-28-mouse C_κ cells, since the levels were similar in each group of the transfectants (FIG. 19B), or to less protein being analyzed. Loading controls, Myc (FIG. 20A) and GAPDH (FIG. 20B) showed that protein amounts in each group were nearly identical. (The blot used in FIG. 19B was stripped and sequentially reprobed with antibodies to Myc and GAPDH and so the lanes in FIG. 20A and 20B are identical to FIG. 19B).

[000341] In another set of experiments, the stability of the canine IGVL3-28-mouse C_κ LC in transfected cells (FIG. 21B, reducing conditions) was examined in parallel with the secretion analysis (FIG. 21A, non-reducing conditions). Again, much less IgG2a was secreted when the LC was canine IGVL3-28-mouse C_κ (FIG. 2A, 2102) than when it was canine IGVL3-28-mouse C_{λ1} (FIG. 2A, 2103) or IGVL3-28-mouse C_{λ2} (FIG. 2A, 2104). However there was a significant amount of intracellular κLC in IGVL3-28-mouse C_κ cell lysates detectable with an anti-κ antibody (FIG. 2B, 2102), similar to the levels seen when the LC was canine IGVK2-5-mouse C_κ (FIG. 20B, 2105). Thus the hybrid IGVL3-28-mouse C_κ was expressed well and not rapidly degraded intracellularly. In this particular canine VH-VK combination, the secretion of canine IgG2a using VK2-5 was similar when it was attached to V_κ (2105), C_{λ1} (2106) or C_{λ2} (2107).

[000342] The results in FIGs. 21A and 21B, indicate that the reduced secretion of Ig molecules bearing a hybrid canine V_λ-mouse C_κ was due to an inability to fold or to pair correctly with the γ2a HC. While not wishing to be bound by theory, it is believed that this results in retention of the incompletely assembled IgG2a molecule in the endoplasmic

reticulum (ER) by ER quality control mechanisms such as the Ig HC retention molecule BiP (Haas and Wabl (1983) Immunoglobulin Heavy Chain Binding Protein. Nature 306:387-389 PMID 6417546; Bole, et al. (1986) Posttranslational association of immunoglobulin heavy chain binding protein with nascent heavy chains in nonsecreting and secreting hybridomas. J. Cell Biology 102:1558-1566 PMID 3084497).

Example 10: Expression of Partly Canine Immunoglobulin with Mouse IgD

[000343] IgD is co-expressed with IgM on mature B cells in most mammals. However, the issue of whether dogs have a functional constant region gene to encode the δ HC is quite controversial. Early serological studies using a mAb identified an “IgD-like” molecule that was expressed on canine lymphocytes (Yang, et al. (1995) Identification of a dog IgD-like molecule by a monoclonal antibody. Vet. Immunol. and Immunopath. 47:215-224. PMID: 8571542). However, serum levels of this IgD increased upon immunization of dogs with ragweed extract. This is not typical of bona fide IgD, which is present in vanishingly small amounts in serum and is not boosted by immunization; IgD is primarily a BCR isotype, especially in mice. Later, Rogers, et al. ((2006) Molecular characterization of immunoglobulin D in mammals: immunoglobulin heavy constant delta genes in dogs, chimpanzees and four old world monkey species. Immunol. 118:88-100 (doi:10.1111/j.1365-2567.2006.02345.x)) cloned a cDNA by RT-PCR of RNA isolated from dog blood that, by sequence homology, encoded an authentic δ HC. However, the most recent annotation of the canine IgH locus by the international ImMunoGeneTics information system® /www.imgt.org, (IMGT) lists C δ as a non-functional open reading frame because of a non-canonical splice donor site, NGC instead of NGT, for the hinge 2 exon. It is possible that some low level of correct “leaky” splicing and IgD expression may occur in the dog, thus accounting for the ability of Rogers, et al. to isolate a C δ cDNA clone. However, the concern was that the canine V_H domains might not fold properly when linked to mouse C δ , since the dog V_H gene region has apparently been evolving with a partial or completely non-functional C δ gene. A problem with partial or absent assembly of the partly canine IgD could disturb normal B cell development.

[000344] To test whether canine V_H domains with a C δ backbone can assemble into an IgD molecule expressible on the cell membrane, transient transfection and flow cytometry analyses were conducting using methods similar to those described in Example 8.

[000345] 293T/17 cells were co-transfected with a human CD4 (hCD4) expression vector as a transfection control plus one of the HC constructs from Example 8, except that C μ was replaced with C δ , and one of the κ or λ LC constructs, along with a CD79a/b expression vector. As can be seen in FIGS. 22-24, the HC with canine V_H domains with a mouse IgD backbone were expressed on the cell surface when paired with a canine V κ -mouse C κ or a canine C λ -mouse C λ LC.

[000346] FIG. 22 shows expression of cell surface canine IGHV3-5 with a mouse IgD backbone and canine IGKV2-5/IGKJ1-C κ (column 2201) and canine IGLV3-28/IGLJ6 attached to mouse C λ 1 (2202), C λ 2 (2203) or C λ 3 (2204). In these studies, the top row (2205) shows staining for cell surface hCD4, the control for transfection efficiency. Row 2206 shows staining for CD79b, an obligate component of the BCR, which confirms cell surface IgD expression. Row 2207 shows IgD staining, 2208 shows κ LC, and 2209 shows λ LC. These particular canine V_H/V κ or V_H/V λ LC combinations were expressed well on the cell surface.

[000347] FIG. 23 shows expression of cell surface canine IGHV3-19 with a mouse IgD backbone and canine IGKV2-5/IGKJ1-C κ (column 2301) and canine IGLV3-28/IGLJ6 attached to mouse C λ 1 (2302), C λ 2 (2303) or C λ 3 (2304). (The cell surface staining data is arranged the same as in FIG. 22.) The cell surface expression of IgD with these particular canine V_H/V κ or V_H/V λ LC combinations was not as high as in FIG. 22. Recall that canine IGHV3-19 was also the most stringent V_H in terms of its ability to associate with a canine V κ -mouse C λ LC. (FIG. 19).

[000348] FIG. 24 shows expression of cell surface canine IGHV4-1 with a mouse IgD backbone and canine IGKV2-5/IGKJ1-C κ (column 2401) and canine IGLV3-28/IGLJ6 attached to mouse C λ 1 (2402), C λ 2 (2403) or C λ 3 (2404). (The cell surface staining data is arranged the same as in FIG. 22.) The cell surface expression of IgD with these particular canine V_H/V κ or V_H/V λ LC combinations was intermediate between that observed in FIG. 22 and FIG. 23.

[000349] This data demonstrates that canine V_H genes were expressed with a mouse IgD backbone, although the level of cell surface expression varied depending on the particular HC/LC combination. It is believed that HC/LC combinations that can be expressed as IgD on the cell surface are selected into the follicular B cell compartment during B cell development, generating an adequate BCR repertoire.

[000350] The preceding merely illustrates the principles of the methods described herein. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims. In the claims that follow, unless the term "means" is used, none of the features or elements recited therein should be construed as means-plus-function limitations pursuant to 35 U.S.C. §112 ¶6. All references cited herein are incorporated by reference in their entirety for all purposes.

SEQUENCE TABLES

Canine Ig

(NB, the sequence and annotation of the dog genome is still incomplete. These tables do not necessarily describe the complete canine VH, DH and JH, V κ AND J κ , or V λ and J λ gene segment repertoire.)

(F = Functional, ORF = open reading frame, P = pseudogene, *0X indicates the IMGT allele number)

Table 1. Canine IGH locus

Germline VH sequences

SEQ ID NO. 1 IGHV1-4-1 (P)

```
>IGHV1-4-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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tcaggaaataagggttgggtgtatgggatggattggtcccaaagatgggtgccacaagatat
tcacagaagttccacagcagagctctccctgatggcagacatgtccaaagcacagcctaca
tgctgctgagcagctcagaggcctgaggacacacctgcatattactgtgtgggacact
```

SEQ ID NO. 2 IGHV1-15 (P)

```
>IGHV1-15*01|Canis lupus familiaris_boxer|P|V-REGION|
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gcacagaagtttcagggcagagtcaccctgtcaacagacacatccacaagcacagcctac
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```

SEQ ID NO. 3 IGHV1-17 (P)

```
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ccctgcaagacatctggatacaccttcactgactacattttggaatgggtatgacaggct
ccaggaccagggccttgattggatgggacagattgatcctgaagatgggtgccacaaggtat
gtgcagaagttccaggcagagtcaccctgatggcagacacacaccacaagcacagccaaca
tgagctgaccagctctgagagctgaggacacagccatgtactactctgtgtga
```

SEQ ID NO. 4 IGHV1-30 (F)

```
>IGHV1-30*01|Canis lupus familiaris_boxer|F|V-REGION|
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ccaggagcagggccttgattggatgggacagattgatcctgaagatgggtgccacaaggtat
gcacagaagttccagggcagagtcaccctgacagcagacacatccacaagcacagcctac
atggagctgagcagctctgagagctggggacatagctgtgtactactgtgcgaga
```

SEQ ID NO. 5 IGHV3-2 (F)

```
>IGHV3-2*01|Canis lupus familiaris_boxer|F|V-REGION|
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tcctgtgtggcctctggattcaccttcagtagcaactacatgagctggatccgccaggct
ccagggaaggggctgcagtggtctcaaaattagcagtgatggaagtagcacaaagctac
gcagacgctgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagatgaggacacggcagtgattactgtgcaaggga
```

SEQ ID NO. 6 IGHV3-3 (F)

>IGHV3-3*01|Canis lupus familiaris_boxer|F|V-REGION|
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tcctgtgtggcctctggattaccttcagtagttactacatgtattggggcccgccaggt
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gcagacgctgtgaagggccgattcaccatctccagagacaacgcaagaatacgcgtgtat
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SEQ ID NO. 7 IGHV3-4 (P)

>IGHV3-4*01|Canis lupus familiaris_boxer|P|V-REGION|
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SEQ ID NO. 8 IGHV3-5 (F)

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SEQ ID NO. 9 IGHV3-5-1 (P)

>IMGT000001|IGHV3-5-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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SEQ ID NO. 10 IGHV3-6 (F)

>IGHV3-6*01|Canis lupus familiaris_boxer|F|V-REGION|
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gcagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacgcgtctat
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SEQ ID NO. 11 IGHV3-7 (F)

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caaaagaaggggctgcagtggtcgacatattagctatgatggaagtagtacatactac
gcagacactttgagggacagattcaccatctccagagacaacccaagaacatgctgtat
ctgcagatgaacagcctgagagccgaggacacagcgtgtattactgcatgaggaa

SEQ ID NO. 12 IGHV3-8 (F)

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gcagaagctgtaaagggccgattcaccatctccagagacaacgccaagaacatggcgtat
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SEQ ID NO. 13 IGHV3-9 (F)

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gcagacgctgtgaagggccgattcaccatctccagagacaacgccagaacacgctgtat
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SEQ ID NO. 14 IGHV3-10 (F)

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gcagacgctgtgaagggccaattcaccatctccagagacaacgccagaacacgctctat
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SEQ ID NO. 15 IGHV3-11 (P)

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cgctgtgaagggccgattcaccatctccagagacaatgccagaacacgctgtatctgca
gatgaacagcctgggagccgaggacacggctgtgtattattgtgtgaaacaga

SEQ ID NO. 16 IGHV3-12 (P)

>IGHV3-12*01|Canis lupus familiaris_boxer|P|V-REGION|
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cagacgctgtgaagggccgattcaccatctccagagacaatgccagaacacgctgtatc
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SEQ ID NO. 17 IGHV3-13 (F)

>IGHV3-13*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggagcaactggtggagtttggaggacacatggtgaatcctgggggttcctgggtctc
tcctgtcaggcctctggattcaccttcagtagctatggcatgagctgggtccgccaggct
caaaagaaggggctgcagtgggtcgacatatattagctatgatggaagtagcacatactac
acagacactgtgagggacagattcaccatctccagagacaacaccaagaacatgctgtat
ctgcagatgaacagcctgagagccgaggacacagccgtgtattactgcatgaggaa

SEQ ID NO. 18 IGHV3-14 (P)

>IGHV3-14*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagatggtggagctctgggggagacctggtgaagcctgggggatccctgagactc
tcctgtgtggcctctggattcaccttcagtaactacaaaatgtactgggtccaccaggct
ccagggaagggtggtgagtggtcgcaaggatttatgagagtggaagtagcacatactac
gcagaagctgtaaagggccgattcaccatctccagagacaacgccagaacatggtgtat
ctgcagatgaacagcctgagagccaggacacggccgtgtattactgtgtgagtga

SEQ ID NO. 19 IGHV3-16 (F)

>IGHV3-16*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtacagctggtggagctctggaggagacctggtgaagcctggggggtccctgagactc
tcctgtgtggcctctggattcacctttagtagttactacatgttttggtccgccaggca
ccagggaagggaatcagtggtcggtatattacaaagatggaagtagcacatactac
ccagacgctgtgaagggccgattcaccatctccagagacaacgccagaacacactgtat
ctgcagatgaacagcctgacagtggaggacacagccctttattactgtgagagaga

SEQ ID NO. 20 IGHV3-18 (F)

>IGHV3-18*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagaccttgtgaaacctgaggggtccctgagactc
tcctgtgtggtctctggcttcaccttcagtagctacgacatgagctgggtccgccaggct
ccagggaaggggctgcagtgggtcgcatatactagcagtgatggaaggagcacaaagttac
acagacgctgtgaagggccgattcaccatctccagagacaatgccagaacacgctgtat
ctgcagatgaacagcctgagaactgaggacacagccgtgtattactgtgcgaaggga

SEQ ID NO. 21 IGHV3-19 (F)

>IGHV3-19*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagtctgggggagacctggtgaagcctgcgggggtccctgagactg
tcctgtgtggcctctggattcaccttcagtagctacagcatgagctgggtccgccaggt
cctgagaaggggctgcagttggtcgcaggtattaacagcgggtggaagtagcacatactac
acagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacagtgat
ctgcagatgaacagcctgagagccgaggacacggccatgtattactgtgcaaagga

SEQ ID NO. 22 IGHV3-20 (P)

>IGHV3-20*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagtctgggggatacctggtgaagcctggagggtccctgagactct
cctctgtgtcctctggattcaccttcagtagctactgcatgtgatgggtctgccaggctc
caggaaaggggctgcagtgagtcgcatacagtaacagtggtggaagtagcactaggtaca
cagacgctgtgaagggctgattcaccacctccagagacaatgccaagaacacactgtatc
tgcagatgaacagcctgagagtgaggacacagcgggtgtattactgtgcagggtga

SEQ ID NO. 23 IGHV3-21 (P)

>IGHV3-21*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagtctgggggagacctggtgaagcctgggggggtccctgagactg
tcctgtgtggtctctggattcaccttcagtaagtagtgccatgagctgggtctgccaggct
ttgggggaaggggctacagttggtcgcagctattagctaagatggaaggagcacatactac
acagacactgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtac
ctgcagatgaacagcctgagagctgaggacacggccgtgtattactgtgagagtga

SEQ ID NO. 24 IGHV3-21-1 (P)

>IGHV3-21-1*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgaagctagtgaggtctgggggagacctggtgaagcctgggggatcaattagactc
tcctatgtgacctctggattcaccttcaggagctactggatgagctgggtcagccaggct
ccagggaaggggctgcagtggtcatatgggttaatactggtggaagcagaaaaagctat
gcagatgctgtgaaggggtgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcataatgaacagcctgagagccctgtattattatgtgagtga

SEQ ID NO. 25 IGHV3-22 (P)

>IGHV3-22*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagatgatggagtctgggggagaactgatgaagcctgcaggatccctgagacct
cctgtgtggcctctggattcaccttcagtagctactggatgtactggatccaccaaactc
cggggaaggggctgcagtggtcgcaggtattagcacagatggaagtagcacaagctacg
tagacgctctgaagggctgattcaccatctccagagacaacgccaagaacacgctctatc
tgagatgaacagcctgagagccgaggacatggccatgtattactgtgcaga

SEQ ID NO. 26 IGHV3-23 (F)

>IGHV3-23*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagtctgggggagacctggagaagcctgggggatccctgagactg
tcctgtgtggcctctggattcaccttcagtagctacggcatgagctgggtccgccaggt
ccagggaaggggctgcagggggtctcattgattaggtatgatggaagtagcacaaggtat
gcagacgctgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacagccgtgtattcctgtgcgaagga

SEQ ID NO. 27 IGHV3-24 (F)

>IGHV3-24*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagtctgggggagaccttggaagcctgaggggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagcttctacatgagctgggtctgccaggct
ccaaggaaggggctacagtggttcagaaattagcagtagtggaagtagcacaagctac
gcagacattgtgaagggccgattcaccatctccagagacaatgccaagaacatgctgtat
ctgcagatgaacagcctgagagccgaggacatggccgtatattattgtgcaaggta

SEQ ID NO. 28 IGHV3-25 (P)

>IGHV3-25*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagcctgggggagaactggtgaagcctggggcgctccctgagactc
tcctgtgtggtccttggtacaccttcagtagctacaacatgggctgggctcaccagcct
ccagggaaggggatgcagtggtgcaggttttaacagcgggtggaagtagcacaagctac
acagatgctgtgaaggggtgaattcaccatctccagagacaatgtcaagaacacgctgtat
ctgcagatgaacagcctgagatccgaggacacggccgtgtattactgtgtgaagga

SEQ ID NO. 29 IGHV3-26 (P)

>IGHV3-26*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgtagctggtggagtctgggggagacctggtgaagcctggggggtccctgagactc
tcctgtgtgggctctggattcaccttcagtagctactggatgagctgggtccgccaggt
ccagggaaggggtacagtggttcagaaattagcggtagtggaagtagcacaactat
gcagacgctgtgaagggccgattcatcatctccagagacaatgccaaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccatgtattactgtgcaagga

SEQ ID NO. 30 IGHV3-27 (P)

>IGHV3-27*01|Canis lupus familiaris_boxer|P|V-REGION|
aaggtgcatctggtggagtctgcgggagacgtggtgaagcctaggaggtccctgagactc
tcctgtgtgggctctggattcaccttcagtagctacagcatgtggtgggcccgtgaggct
cccggtatggggctacagggggtgcaggtattagatatgatggaagtagcacaagctac
gcagacgctctgaagggccgattcaccatctccagagacaatgccaaaacacactgtat
ctgtagaagaacagcctgagagccgaggaggacacggccgtgtattactgtgcaagga

SEQ ID NO. 31 IGHV3-28 (P)

>IGHV3-28*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctagtggagtctgggggagacctggtgaagtctggggggtccctgagagt
tcctgtgtgggctctggattcaccttcagtagctactggatgtactgggtccaccaggc
tcagggaaggggtccatgggtgcagtggtattaggtatgatggaagtagcacaagctac
gcagaagctgtgaagggccgattcactgtttctagagacaacgccaaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccgtgtattactgtgtgagga

SEQ ID NO. 32 IGHV3-29 (P)

>IGHV3-29*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagtctgggggagacctggtgaagactggagggttccctgagactc
tcctgtctcctgtgtggcttcgggtacaccttcagtaactacagcatgatctgggtccg
ccagggtccaaggaaggggctgcagtggtatcacaaactattagcaatagtggaagtagcac
aatcacgcagacacagtaaaagggccgatttaccatctccagagacaacaccaagaacac
gctgtatctacagatgagcagcctgggagccgatgacacggccctgtattactgtgtgag
gga

SEQ ID NO. 33 IGHV3-31 (P)

>IGHV3-31*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagtctgggggagaactggtgaagcctggggggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagctactacatgagctggatccgccaggt
cctgggaaggggtgcagtggtgcagatattagtgacagtgaggtagcacatactac
actgacgctgtgaagggccgattcaccatctccagagacaacgtcaagaactcgtgtat
ttgcagatgaacagcctgagagccgaggacacggccgtgtattactgtgcaagga

SEQ ID NO. 34 IGHV3-32 (ORF)

>IGHV3-32*01|Canis lupus familiaris_boxer|ORF|V-REGION|
ggggtgcagctggtggagtctgggggagacctggtgaagcctggggggtccctgacactc
tcctgtgtggcctatggattcaccttcagtagctacagcatgcaatgggtctgtcaggct
ccagggaagggggtgcagtggtgcatacattaacagtggtggaagtagcacaagctcc
gcagatgctgtgaagggctgattcatcatctccagagacaacgtcaagaacacgctatat
ctgcagatgaacagcctgagagccgaggacacggccgtgtattactgtgcggtga

SEQ ID NO. 35 IGHV3-33 (P)

>IGHV3-33*01|Canis lupus familiaris_boxer|P|V-REGION|
gagatgcagctggtggaggctgggggagacctggtgaagcctggggggtccctgagactc

ttctgtgtggcctctggatttaccttcagtagctattggatgagctgggtcggccaggct
ccagggaagggttgagtggttgcatatacattacagtggtggaagtagcacatactat
gcagacgctgtgaaggggcgattcaccatctccagagacaatgccagaacacgctgtat
ctgcagatgaactgcctgagagccgaggacacggccgtatattactgtgtggga

SEQ ID NO. 36 IGHV3-34 (F)

>IGHV3-34*01|Canis lupus familiaris_boxer|F|V-REGION|
cagacactgtgaaggggcgattcaccatctccagagacaacgccagaacacgctctatc
tgagatgaacagcctgagagctgaggacacggccgtgtattactgtgcgaagga
(Incomplete sequence in database)

SEQ ID NO. 37 IGHV3-35 (F)

>IGHV3-35*01|Canis lupus familiaris_boxer|F|V-REGION|| |
gaggtgcagctggtggagctctgggggagacctggtgaagcctgtgggatccctgagactc
tcctgtgtggcctctggattcaccttcagtagctatgacatgaactgggtccgcccaggct
ccagggaagggttgagtggttgcatatacattagcagtggtggaagtagcacatactat
gcagatgctgtgaaggggcggttcaccatctccagagacaacgccagaacacgctgtat
cttcagatgaacagcctgagagccgaggacacggccatgtattactgtgcgggtga

SEQ ID NO. 38 IGHV3-36 (P)

>IGHV3-36*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggggcagctggcgagctctgggggagacctggtgaagcctgagaggtccctgagactc
gcccggtgtggcctctggattcaccttcatttcctataccatgagctgggtccacaaggct
cctgggaaggggctgccgtgagtcgcatgaatttattctagtgggaagtaacatgagctat
gcagacgctgtgaaggggcgattcaccatctccagagacaatgccagaacatgctgtat
ctgcagatgaacagcctgagagctgaggacatggccatgtattactgtgtgaatga

SEQ ID NO. 39 IGHV3-37 (F)

>IGHV3-37*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtacagctggtggagctctggggaagatttggtgaagcctggagggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagcagtgaaatgagctgggtccaccaggct
ccagggcaggggctgcagtggtctcatggattaggtatgatggaagtatctcaaggat
gcagacactgtgaaggggcgattcaccatctccagagacaatgtcaagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccatatactactgtgcaga

SEQ ID NO. 40 IGHV3-38 (F)

>IGHV3-38*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagacctggtgaagcctggggggaccttgagactg
tcctgtgtggcctctggattcacctttagtagctatgacatgagctgggtccgtcagctc
ccagggaaggggctgcagtggttcaggtattttggaatgatggaagtagcacatactac
gcagacgctgtgaaggggcgattcaccatctccagagacaacgccagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccgtgtattactgtgcgaagga

SEQ ID NO. 41 IGHV3-39 (F)

>IGHV3-39*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtacagctggtggaatctgggggagacctcgtgaagcctgggggttcctgagactc
tcctgtgtggcctcgggattcaccttcagtagctactacatgagctggatccgcccaggct
cctgggaaggggctgcagtggttcagatattagttagtgaggtagcacaggctac
gcagacgctgtgaaggggcggttcaccatctccagagagaacgccagaacaagctgtat
cttcagatgaacagcctgagagccgaggacacagccgtgtattactgtgcgaagga

SEQ ID NO. 42 IGHV3-40 (P)

>IGHV3-40*01|Canis lupus familiaris_boxer|P|V-REGION|
atgcaatgggtccgtcaggctcctgggaagggggtgcagtggttcgcatatacattacag
ggtggaagtagcacagcttcgcagatgctgtgaagggcagtgagctggtttcgccaggct
ccagggaaggggctgcaatgggttacatggattgggtatgatggaagtagcacatactac
acagacactgtaaggggcgattcactatctccatagacaacgccagaacatgctgtat
ctgcagatgaacagcctgagagccgaggacatagccctgtattactgtgcgaggga

SEQ ID NO. 43 IGHV3-41 (F)

>IGHV3-41*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagacctggtgaagcctggggggtccctgagactc
tctgtgtagcctctggattcaccttcagtaactacgacatgagctgggtccgccaggct
cctgggaaggggctgcagtggtgcgagctattagctatgatggaagtagcacatactac
actgacgctgtgaagggccgattcaccatctccagagacaacgccaggaacacagtgat
ctgcagatgaacagcctgagagccgaggacacggctgtgtattactgtgcgaagga

SEQ ID NO. 44 IGHV3-42 (P)

IGHV3-42*01|Canis lupus familiaris_boxer|P|V-REGION|
gaagtgcagctggtggagctctgggggaagacctggtgaagccaggggggtccctgagact
ctcctgtgtgacctctggattcaccttcagtaggtatgccatgagctgggtccgccaggc
tccaggaaggggctgcagtggtgcagctattagcagtagtggaagtagcacatacta
cgtagatgctgtgaagggccgattcaccatctccatagacaacgccaagaacatggtgta
tctgcagatgaacagcctgagagctgaggatattgctgtgtattactgtgggaagga

SEQ ID NO. 45 IGHV3-43 (P)

>IGHV3-43*01|Canis lupus familiaris_boxer|P|V-REGION|
aaggtgtagctggtggagctctgggggagacctgatgaagcctggggggtccctgagactg
tctgtgtggcctctggattcaccttcaggagctatggcatgagctgggtctgccaggct
tcagggaaggggctgcagtggtgcgagctattagctatgatggaaggagcacatactac
acagacactgtgaagggccgattcaccatctccagagacaatggcaagaacacgctgtac
ctgcagatgaacagcctgagagctgaggacacggccgtgtattactgtgcgagtga

SEQ ID NO. 46 IGHV3-44 (ORF)

>IGHV3-44*01|Canis lupus familiaris_boxer|ORF|V-REGION|
gaggtgcagctggtggagctctgggggagacctggtgaagcctggggggtccctgagactc
tcatgtgtgacttctggattcaccttcagtagctattggatgagctgtgtccgccaggct
ccagggaaggagctgcagtggtgcgctacattaacagtgggtggaagtagcacatggtac
acagacgctgtgaagggctcgattcaccatctccagagacaacgccaagaacacgctgtat
ctgcagatgaacaacctgagagccgaagacacggccgtgtattactgtgcgaggga

SEQ ID NO. 47 IGHV3-45 (P)

>IGHV3-45*01|Canis lupus familiaris_boxer|P|V-REGION|
gaagtacagctgctggagctctgggggagaccgagtgaacctggggggtccagagactc
tctgtgtggcctcaagggtcaccttcagtagctacagcatgcattgtctccgtcagctct
cctgggatggggctacagtggtcacatacattagcagtaatggaagcagcacatactat
gcagacgctgtgaagggctcgattcaccatctccagagacaacgccaagaacatgctttat
ctacagatgaacagcctgagagctcaggacatagccctgtattactgtgcagatg

SEQ ID NO. 48 IGHV3-46 (F)

>IGHV3-46*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtacagctggtggagctctggggaagatttggtgaagcctggagggtccctgagactc
tctgtgtggcctctggattcaccttcagtagcagtgaatgagctgggtccaccaggct
ccagggcaggggctgcagtggtctcatggattaggtatgatggaagtagctcaaggat
gcagacactgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccatatattactgtgcaga

SEQ ID NO. 49 IGHV3-47 (F)

>IGHV3-47*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagacctggcgaagcctggggggtccctgagactc
tctgtgtggcctctggattaaccttcagtagctacagcatgagctgggtccgccaggct
cctgggaaggggctgcagtggtcacagctattagctatgatggaagtagcacatactac
actgacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacagtgat
ctgcagatgaacagcctgagagccgaggacacagctgtgtattactgtgtgga

SEQ ID NO. 50 IGHV3-47-1 (P)

>IGHV3-47-1*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgccactggtggaatctgggggagagctggtgaagcctggggggtccctgagactc
tcctttgtagcctctgcattcacttccagtagttactggataagctgggtccgccaaagct
ccagggaaggggctgcactgagctctcagtaattaacaaagatggaagtaccacataccac

gcagatgctgtgaagggccgattcaccatctccagagacaatgccagaacacgctgtat
ctgcagatgaacagcctgagagctgaggacacggctgtgtattactgtgcaca

SEQ ID NO. 51 IGHV3-48 (P)

>IGHV3-48*01|Canis lupus familiaris boxer|P|V-REGION|
gaggagcagttggtgaaatctaggggagacctggtgaagcctggcgggtccctgagactc
ttctgtgagtcctctacattcacctttcatagcaacagcatacattggctccaccagtct
cccggtagtggctacagtgggtcatatccaatagcagtaatggaagtagcatgtactatg
cagacgctgtaaagggctgattcaccatctccagagacagcaccaggaaacatgctgtatc
tgcagatgaacagcctgagagctgaggacacagcctgcattgctgtgcgagggga

SEQ ID NO. 52 IGHV3-49 (P)

>IGHV3-49*01|Canis lupus familiaris boxer|P|V-REGION|
gaggtgcagctggtggagtctgggggagacctcatgaagcctggggggtccctgagactc
tcctgtgtggcctctgggtttcaccttcagtagctacagcatgagctgggtccgccaggct
cccgggaaggggattcagtggtgcagtgatttaagctagtggaaatagcacaagctac
acagatgctgtgaagggccgattcaccatctccagagaacgccagaacacagtggtttct
gcagatgaacagcctgagagctgaggacaaggccatgtattactgtgcgagggga

SEQ ID NO. 53 IGHV3-50 (F)

>IGHV3-50*01|Canis lupus familiaris boxer|F|V-REGION|
gaggtgcagctggtggagtctgggggagacctggtgaagcctggggggtccctgagactc
tcctgtgtggcctctgggtttcaccttcagtagcaacgacatggactgggtccgccaggct
ccagggaaggggctgcagtggtgcagtgatttagcaatgatggaaggagcacaggctac
gcagatgctgtgaagggccgattcaccatctccagagacaacgccagaacacgctgtat
ctgcagatgaacagcctgagagctgaggacacagcctgtattactgtgcgaagga

SEQ ID NO. 54 IGHV3-51 (P)

>IGHV3-51*01|Canis lupus familiaris boxer|P|V-REGION|
gaggtgcagctggaggagtctgggggagacctggtgaagcctgggggtccctaagactgt
cctgtgtgacctccggattcactttcagtagctatgccatgcactgggtccgccaggctc
cagggaaggggctgcagtggtgcagttatttagcagggatggaagtagcacaactacg
cagacgctgtgaagggccgattcaccatctccagagacaacgccagaacatgctgtatc
tacagatgaacagcctgagagctgaggacacggccatgtattactgtgcgaagga

SEQ ID NO. 55 IGHV3-52 (P)

>IGHV3-52*01|Canis lupus familiaris boxer|P|V-REGION||
gaagtgcagctggtggagtatgggggagagctggtgaagcctggggggtccctgagactg
tcctgtgtggcctccggattcaccttcagtagctactacatgcactgggtccaccaggct
cagggaaggggctgcagtggttcgcatgaattaggagtgtggaagtagcacaactac
actgatgctgtgaagggccgattcaccatctccagagacaattccaagaacactctgtat
ctgcagatgaccagcctgagagccgaggacacggccctatattactgtgcgatgga

SEQ ID NO. 56 IGHV3-53 (P)

>IGHV3-53*01|Canis lupus familiaris boxer|P|V-REGION|
gagatgcagctggtggagtctagggaggcctggtgaagcctggggggtccctgagactct
cctgtgtggacctggattcaccttcagtagctactggatgtactgggtccaccaggctc
cagggatgggctgcagtggttcagaaattagcagtagtggaagtagcacaactatg
cagacgctgtgaggggcccattcaccatctccagagacaatgccagaacacgctgtacc
tgcagggtgaacagcctgagagccgaagacacggccctgtattactgtgtgagtga

SEQ ID NO. 57 IGHV3-54 (F)

>IGHV3-54*01|Canis lupus familiaris boxer|F|V-REGION|
gaggtgcagctggtggagtctgggggagacctgatgaagcctggggggtccctgagactc
tcctgtgtggcctccggattcactatcagtagcaactacatgaactgggtccgccaggct
ccagggaaggggctgcagtggttcggatacattagcagtgatggaagtagcacaagctat
gcagacgctgtgaagggccgattcaccatctccagagacaatgccagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggccctgtattactgtgtgaagggga

SEQ ID NO. 58 IGHV3-55 (P)

>IGHV3-55*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagctctggggaaacctggtgaagcctggggagctctctgagactct
cttgtgtggcctctggattcaccttcagtagctactggatgcattgggtctgccaggctc
cagggaaaggggttgggtgggttgaattattaacagtggtggaggtagcacatactatg
cagacacagtgaaggggccaattcaccatcttcagagacaatgccaaagaacatgctgtatc
tgcatgatgaacagcctgagagcccaggacatgaccgctattactgtgtgagtga

SEQ ID NO. 59 IGHV3-56 (P)

>IGHV3-56*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggaatctgggggagacctggtgaagcctgggggatccctgagactc
tcttgtgtggcctctggattcaccttcagtagctactatatggaatgggtctgccaggct
ccaggagggggtgaagtgggtcgacggattagcagtgacggaagtagcacatactaca
cagacgctgtgaaggggccgattcaccatctccagagacaatgccaaagacggccgtgtatt
actgtgcgaagga

SEQ ID NO. 60 IGHV3-57 (P)

>IGHV3-57*01|Canis lupus familiaris_boxer|P|V-REGION|
gaagtgcagcttgtggagctctgggggagagctggtgaagcctgggggtccctgagactg
tcttgtgtggcctctggattcaccttcagtagctactacatgcactgggtctgcaggctc
cagggaaaggggtcgagtggttgaagaattaggagtgtggaagtagcacaagctacc
cagacgctgtgaaggggcagattcaccatctccagagacaattccaagaacactctgtatc
tgcatgatgaacagcctgagagctgatgatacgccctatattactgtgcaagga

SEQ ID NO. 61 IGHV3-58 (F)

>IGHV3-58*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagacctggtgaagcctgggggatccctgagactc
tcttgtgtggcctccggattcaccttcagtagccatgccaaagagctgggtccgccaggct
ccagggaaggggctgaagtgggtagcagttattagcagtagtggaagtagcacaggctcc
gcagacactgtgaaggggccgattcaccatctccagagacaatgccaaagaacacgctgtat
ctgcagatgaacagcctgagagctgaggacacagccgtgtattactgtgcgaagga

SEQ ID NO. 62 IGHV3-59 (P)

>IGHV3-59*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtacagctggtggagctctggaggagaccttgtgaagactgagcgggtccctgagactc
tcttgtgtggcctctggattcaccttcagtagcttctacatgaggtgtctgccagactcc
agggaaagggaactacagtgggttcagaaattagcagtagtggaagtagcacaagctacac
agatgctctgaagggtgattctccatctccaaaaacaatgccaaagaacacgctgtatct
gcagatgaacagcctgagagccgaggtcacagccgtatattactgtgcaagga

SEQ ID NO. 63 IGHV3-60 (P)

>IGHV3-60*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgaagctggtggagctctgggggagacctggtgaagcctgggggatcaattaaactc
tcctatgtgacctctggattcaccttcaggagctactggatgagctgggtcagccaggct
ccagggaaggggctgcagtggttcacatgggttaatactggtggaagcagcaaaagctat
gcagatgctgtgaaggggcaattcaccatctccagagacaatgccaaagaacacgctgtat
ctgcatatgaacagcctgatagccctgtattattgtgtgagtga

SEQ ID NO. 64 IGHV3-61 (F)

>IGHV3-61*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctggtggaaacctggtgaagcctgggggtccctgagactg
tcttgtgtggcctctggattaaccttctatagctatgccatttactgggtccacgaggct
cctgggaaggggctgcagtggttcgcagctattaccactgatggaagtagcacatactac
actgacgctgtgaaggggccgattcaccatctccagagacaatgccaaagaacacgctgtat
ctgcagatgaacagcctgagagctgaggacatgcccgctgtattactgtgcgaggga

SEQ ID NO. 65 IGHV3-62 (P)

>IGHV3-62*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggagcagctggtggagctctggggagatctggtgaagtctgggggggtccctgagactc
tcttgtgtggcccttgattcaccttcagtaactgtgacatgagctgggtccattaggct

ccaggaaagggctgcagtggttgcatatgctatgatggaagtagcacaggttaca
aagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacatgctgtatc
ttcagatgaacagcctgagagctgaggacacggcctgtgtattactgtgcaga

SEQ ID NO. 66 IGHV3-63 (P)

IGHV3-63*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggagcagttggtgaaatctaggggagacctggtgaagcctggcggtccctgagactc
ttctgtgagtcctctacgttcacctttcatagctacagcatgcattggctccaccagtct
cccggtagtggctacagtggtcatatccaatagcagtaatggaagtagcatgtactatg
cagacgctgtaagggctgatacaccatctccagagacaacaccaggaaacatgctgtatc
tgcatatgaataacctgagagctgaggacacagcctgcattgctgtgcgagggga

SEQ ID NO. 67 IGHV3-64 (P)

>IGHV3-64*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtgagtgctgcgggagaccccgtagagcctggggggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagctacagcatgagctgggtccgcccaggct
cccgggaaggggatgcagtggtgcgcatggatataatgctagcgggaagtagcacaagctac
gcagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacactgttt
ctgcagatgcctgagagctgaggacacggccatgtattcctgtgcagggga

SEQ ID NO. 68 IGHV3-65 (P)

>IGHV3-65*01|Canis lupus familiaris_boxer|P|V-
REGION|gatgtacagctggtgagtgctgggggagacctggtgaagcctggggggtccctgagactg
tcctgtgtggcctctggattcaccttcagtagctactacatgtactagacccaccaaatt
ccagggaaggggatgcagggggttgcacggattagctatgatggaagtagcacaagctac
accgacgcaatgaaagggccgattcaccatctccagagacaacgccaagaacatgctgtat
ctgcaatgaacagcctgagagccgaggacacagcctgtgtattactgtgtgaagga

SEQ ID NO. 69 IGHV3-66 (P)

>IGHV3-66*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtgagtgctggcgagacctggtgaagcctggcggtccctgagactg
tcctgtatggcctctggattcaccttcagtagctacagcatgagctgtgtccgcccaggctc
ctgggaagggctgcagtggttcgcaaaaattagcaatagtgaagtagcacatactacac
agatgctgtgaagggccgattcaccatctccagagacaatgccaagaacacgctctatct
gcagatgaacagcctgagagccgaggacacggcctgtgtattactgtgcaga

SEQ ID NO. 70 IGHV3-67 (F)

>IGHV3-67*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtgagtgctgggggagacctggtgaagcctggggggtccctgagactg
tcctgtgtggcctctggattcaccttcagtagctactacatgtactgggtccgcccaggct
ccagggaaggggcttcagtggttcgcacggattagcagtgatggaagtagcacatactac
gcagacgctgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagccgaggacacggcctgtgtattactgtgcaaagga

SEQ ID NO. 71 IGHV3-68 (P)

>IGHV3-68*01|Canis lupus familiaris_boxer|P|V-REGION|
gaagtgcagctggtgagtgctgggggagagctggtgaagcctggggggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagctactacatgtactgggtccgcccaggct
ccagggaatggctgtgtgggtcacatgaattaggagtgtggaagtagcacatataca
ctgatgctgtgaaggaccgatacaccatctccaaagacaattccaagaacattctgtatc
tgcatatgaacagcctgagagccaaggacacggccctatatccctgtgcaatgga

SEQ ID NO. 72 IGHV3-69 (F)

>IGHV3-69*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtacagctggtgagtgctgggggagacctggtgaagcctgggggatccctgagactg
tcctgtgtggcctctggattcaccttcagtagctatgccatgagctgggtccgcccaggct
ccagggaaggggctgcagtggttcgcatacatgaacagtggtggaagtagcacatactac
gcagatgctgtgaagggccggttcaccatctccagagacaatgcagggaacacactgtat
ctgcagatgaacagcctgagatccgaggacacagcctgtgtattactgtccgaagga

SEQ ID NO. 73 IGHV3-70 (F)

>IGHV3-70*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgcagctggtggagctctggaggagaccttgtgaagcctgagcgggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagcttctacatgagctggttctgccaggct
ccagggaaggggctacagtggtgttcagaaattagcagtagtggaatagcacaaagctac
gcagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacgctgtat
ctacggatgcacagcctgagagccgaggacacggctgtatattactgtgcaaggta

SEQ ID NO. 74 IGHV3-71 (P)

>IGHV3-71*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgaagctggtggagtggtgggggagacctggtgaagcccgggggatcgattagactc
tcctttgtgacctctggattcaccttcaggagctattggatgggctgtgtcagccaggct
ccagggaaggggctgcagtggttcacatgggttaatactggtggaagcagcaaaagctat
gcagatgctatgaaggggctgattaccatctccaggcacaagccaagaacacactatct
gcatatgaacagcctgagagccgctgtattattgtgtgagtga

SEQ ID NO. 75 IGHV3-72 (P)

>IGHV3-72*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagctctggcggagacctggtgaagcctggggattccctgagactg
tcctgtgtggcctctggattcaccttcagtagctatgccatgagctgggtccgccaggct
cctaggaaggggctgcagtggttcgatacattagcagtgatggaagtagcacataatac
gcagacgctgtgaagggccgattcaccatttccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagctgaggatacggccctgtataactgtgcaaggga

SEQ ID NO. 76 IGHV3-73 (P)

>IGHV3-73*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctgatggagctctgggggagacctggtgaagcctggggggtccctgagactc
tcctgtgtggccctctggattcaccttcagtaactatgacatgagctcgggtccattagact
ccaggaaagggctgcagtgattgcatatattagctatgatggaagtagcacaggttaca
aagacgctgtgcagggccgattcaccatctccagagacaacgccaagaacacgctgtatc
ttcagatgaacagcctgagagctgagcacacggccctgtattactgtgcaga

SEQ ID NO. 77 IGHV3-74 (P)

>IGHV3-74*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggtgcagctggtggagctctgggggagaccttgggtgaagccttgtgggtcctgagactc
tcctgtgtggcctctggattcaccttcagtagctacatcatgagctgggtccgccaggct
ccagggaagtggctgcagtggttcgcatacattaacagtgggtggaagtagcacaaaggtac
acagatgctgtgaagggccgattcacctctccagagacaacgccaagaacatgctgtatc
tgcaagttgaacagcctgagagccgaggacaccgctgtgtattactgtgcgagga

SEQ ID NO. 78 IGHV3-75 (F)

>IGHV3-75*01|Canis lupus familiaris_boxer|F|V-REGION|
gaattgcagctggtggagcttgggggagatctggtgaagccaggggggtccctgagactc
tcctgtgtggcctctggattcaccttcagtagctatgccatgagttgggtctgccaggct
ccagggaaggggctgcagtggttgcagctattagcagtagtggaagtagcacataccat
gtagacgctgtgaagggccgattcaccatctccagagacaacgccaagaacacagtgat
ctgcagatgaacagcctgagagccgaggacacggccgtgtattactgtgcaga

SEQ ID NO. 79 IGHV3-76 (F)

>IGHV3-76*01|Canis lupus familiaris_boxer|F|V-REGION|
gaggtgccactggtggaatctgggggagagctggtgaagcctgaggggtccctgagattc
tcctgtgtagcctctggattcacttccagtagttactggataagctgggtccgccaagct
ccagggaaggggctgcactgggtctcagtaattaacaaagatggaagtaccacataccac
gcagatgctgtgaagggccgattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgagagctgagggcacgactgtgtattactgtgcaca

SEQ ID NO. 80 IGHV3-77 (P)

>IGHV3-77*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggagcagttggtgaagtctgggggagacctggtgaagcctggcaggtccctgagtcct
ctacattcaccttctcatagctacagcatgcattggctccaccagtctcccgtagtggt
acagtggtcatatccaatagcagtaaatggaagtagcatgtactatgcagacgctgtaaa

gggttgattcaccatctccagagacaacaccaggaacacgctgtatctgcagatgaacag
cctgagagccgacgacacggccgtgtgttgctgtgcgagga

SEQ ID NO. 81 IGHV3-78 (P)

>IGHV3-78*01|Canis lupus familiaris boxer|P|V-REGION|
gaggtgcagctggtggagctctgggggagaccttgtgaagccggaggggtccctgagactc
tcctgtgtggccgctggattcacctttagtagctacagcatgagctgggtccgccaggtc
cccgggaagggggtgcagtggtcacatagatttatgctagtgaagtagcacaagctac
acagatgctgtgaaggccgattcaccatctccagagacaacgccaagaacacagtggtt
ctgcagatgaacagcctgagagctgagaacacggccatgtattcctgtgcaaggga

SEQ ID NO. 82 IGHV3-79 (P)

>IGHV3-79*01|Canis lupus familiaris boxer|P|V-REGION|
tggggaattccctctggtgtggcctctggattcacctgcagtagctccctcacctccctc
tcctgtgtggccctctggattcacctcagtagctactacatactgtatccaccaagct
ccaggggaaggggctgcaggtggtcgcagtgattagctatgatggaagtagaacaagctac
gccgacgctatgtaggccaattcatctctccagagaaaacaccaagaacacgctgtat
ctgtagatgaacagcctgagtgccaaggacacggcactatatccctgtgcgaggaa

SEQ ID NO. 83 IGHV3-80 (F)

>IGHV3-80*01|Canis lupus familiaris boxer|F|V-REGION|
gaggtgcagctggtggagctctgggggagatctggtgaagcctgggggatccctgagactc
tcttgtgtggccctctggattcacctcagtagctactacatggaatgggtccgccaggtc
ccaggggaaggggctgcagtggtcgcacagattagcagtgatggaagtagcacatactac
ccagacgctgtgaagggtcaattcaccatctccagagacaatgccaagaacacgctgtat
ctgcagatgaacagcctgggagccgaggacacggccgtgtattactgtgcaaggga

SEQ ID NO. 84 IGHV3-81 (F)

>IGHV3-81*01|Canis lupus familiaris boxer|F|V-REGION|
gaggtgcagctggtggagctctggaggaaacctggtgaagcctggggggtccctgagactc
tcttgtgtggccctctggattcacctcagtagctactacatggactgggtccgccaggtc
ccaggggaaggggctgcagtggtcgcagggattagcagtgatggaagtagcacatactac
ccacaggtctgtgaaggccgattcaccatctccagagacaacgccaagaacacgctctat
ctgcagatgaacagcctgagagccgaggactctgctgtgtattactgtgcgatgga

SEQ ID NO. 85 IGHV3-82 (F)

>IGHV3-82*01|Canis lupus familiaris boxer|F|V-REGION|
gaggtgcagctggtggagctctggaggagacctggtgaagctctggggggtccctgagactc
tcttgtgtggccctctggattcacctcagtagctactacatgcactgggtccgccaggtc
acaggggaaggggctgcagtggtcacaaggattagcaatgatggaagtagcacaaggtac
gcagacgcatgaaggccaatttaccatctccagagacaattccaagaatacgtgtat
ctgcagatgaacagccagagagccgaggacatggccctatattactgtgcaaggga

SEQ ID NO. 86 IGHV3-83 (P)

>IGHV3-83*01|Canis lupus familiaris boxer|P|V-REGION|
gagttgcagctggttagagctctgggggagacctggtgaagcctggggggtctctgagactt
tcctgtgtgtcctctggattcacctcagtagctactggatgcactgggtccctccaggtc
ccaggggaaggggctggagtggtcgaattattaacagtggtggaggtagcatatactac
gcagacacagtggaaggccgattcaccatctccagagaaaacgccaagaacacgctctat
ctgcagatgaacagcctgagagctgaggacagggccatgcattactgtgcgaaggga

SEQ ID NO. 87 IGHV4-1 (F)

>IGHV4-1*01|Canis lupus familiaris boxer|F|V-REGION|
gaactcacactgcaggagtcagggccaggactggtgaagcctcacagaccctctctctc
acctgtgtgtgtccggaggctccgtcaccagcagttactactggaactggatccgccag
cgccctgggagggtggaatggatgggtactggacaggtagcacaactacaaccgcg
gcattccaggagcgcattctccatcactgctgacacggccaagaaccagttctccctgcag
ctgagctccatgaccaccgaggacacggccgtgtattactgtgcaagaga

SEQ ID NO. 88 IGHV(II) -1 (P)

>IGHV(II)-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 ctggcaccctgcaggagtctgtttctgggctggggaaaccaggcagatccttacactc
 acctgtcccttctctgggttcttattgagcatgtcagtatgggtgtcacatgggtccttt
 acccaccaggggaaggcactggagtcaatgccacatctggtgggagaaacgctaagtacca
 cagcctgtctctgaacagcagcaagatgtatagaaagtccaacacttggaagataaagg
 attatgtttcacaccagaagcacatctattcaacctgatgaacagccagcctgat

SEQ ID NO. 89 IGHV(II) -2 (P)

>IGHV(II)-2*01|Canis lupus familiaris_boxer|P|V-REGION|
 ctggcaccctgcaggagtctgtttctgggctggggaaaccaggcagacccttacactc
 acctgtcccttctctgggttcttattgagcatgtcagtggtgtcacatgggtccttt
 acccaccaggggaaggcactggagtcaatgccacgtctggtgggagaaactaagtacca
 cagcctgtctctgaacagcagcaagatgtatagaaagtccaacacttggaagataaagg
 attatgtttcacaccagaagcacatctattcaacctgatgaacaatcagcctgatgaga

Germline D sequences**SEQ ID NO. 90 IGHD1 (F)**

>IGHD1*01|Canis lupus familiaris_boxer|F|D-REGION|
 gtactactgtactgatgattactgtttcaac

SEQ ID NO. 91 IGHD2 (F)

>IGHD2*01|Canis lupus familiaris_boxer|F|D-REGION|
 ctactacggtagctactac

SEQ ID NO. 92 IGHD3 (F)

>IGHD3*01|Canis lupus familiaris_boxer|F|D-REGION|
 tatatatatatggatac

SEQ ID NO. 93 IGHD4 (F)

>IGHD4*01|Canis lupus familiaris_boxer|F|D-REGION|
 gtatagtagcagctggtac

SEQ ID NO. 94 IGHD5 (ORF)

>IGHD5*01|Canis lupus familiaris_boxer|ORF|D-REGION|
 agttctagtagttggggct

SEQ ID NO. 95 IGHD6 (F)

>IGHD6*01|Canis lupus familiaris_boxer|F|D-REGION|
 ctaactggggc

Germline JH sequences**SEQ ID NO. 96 IGHJ1 (ORF)**

>IGHJ1*01|Canis lupus familiaris_boxer|ORF|J-REGION|
 tgacatttactttgacctctggggcccgggcacctggtcaccatctcctcag

SEQ ID NO. 97 IGHJ2 (F)

>IGHJ2*01|Canis lupus familiaris_boxer|F|J-REGION|
 aacatgattacttagacctctggggccagggcacctggtcaccgtctcctcag

SEQ ID NO. 98 IGHJ3 (F)

>IGHJ3*01|Canis lupus familiaris_boxer|F|J-REGION|
 caatgcttttggttactggggccagggcacctggtcactgtctcctcag

SEQ ID NO. 99 IGHJ4 (F)

>IGHJ4*01|Canis lupus familiaris_boxer|F|J-REGION|
 ataattttgactactggggccagggaacctggtcaccgtctcctcag

SEQ ID NO. 100 IGHJ5 (F)

>IGHJ5*01|Canis lupus familiaris_boxer|F|J-REGION|
acaactggttctactactggggccaaggaccctggtcactgtgtcctcag

SEQ ID NO. 101 IGHJ6 (F)

>IGHJ6*01|Canis lupus familiaris_boxer|F|J-REGION|
attactatgggtatggactactggggccatggcacctcactcttcgtgtcctcag

Table 2. Canine Igk Sequence Information**Germline Vk sequences**

SEQ ID NO. 102 IGKV2-4 (F)

>IGKV2-4*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacgccaccgtccctgtctgtcagccctagagagacggcctcc
atctcctgcaaggccagtcagagcctcctgcacagtgtatggaaacacctatttgattgg
tacctgcaaaagccaggccagtcctccacagcttctgatctacttggtttccaaccgcttc
actggcggtgtcagacaggttcagtggcagcggtcagggacagatttcacctgagaatc
agcagagtggaggctaacgatactggagtttattactgcgggcaaggtaacacagcttcct
cc

SEQ ID NO. 103 IGKV2-5 (F)

>IGKV2-5*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacccccactgtccctgtccgtcagccctggagagacggcctcc
atctcctgcaaggccagtcagagcctcctgcacagtaatgggaacacctatttgattgg
ttccgacagaagccaggccagtcctccacagcggtttgatctataaggtctccaacagagac
cctgggggtcccagacaggttcagtggcagcggtcagggacagatttcacctgagaatc
agcagagtggaggctgatgatgtgagtttattactgcgggcaaggatatacaagatcct
cc

SEQ ID NO. 104 IGKV2-6 (F)

>IGKV2-6*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacccccactgtccctgtctgtcagccctggagagactgcctcc
atctcctgcaaggccagtcagagcctcctgcacagtgatggaaacagctatttgaaactgg
ttccgacagaagccaggccagtcctccacagcggtttaatctataaggtctccaacagagac
cctgggggtcccagacaggttcagtggcagcggtcagggacagatttcacctgagaatc
agcagagtggaggctgacgatactggagtttattactgcgggcaaggatatacaagatcct
cc

SEQ ID NO. 105 IGKV2-7 (F)

>IGKV2-7*01|Canis lupus familiaris_boxer|F|V-REGION||
gatattgtcatgacacagaaccactgtccctgtccgtcagccctggagagacggcctcc
atctcctgcaaggccagtcagagcctcctgcacagtaacgggaacacctatttgattgg
ttccgacagaagccaggccagtcctccacagggcctgatctataaggtctccaacagagac
cctgggggtcccagacaggttcagtggcagcggtcagggacagatttcacctgagaatc
agcagagtggaggctgacgatgtgagtttattactgcatgcaaggatatacaagtcct
cc

SEQ ID NO. 106 IGKV2-8 (F)

>IGKV2-8*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacccccaccgtccctgtccgtcagccctggagagacggcctcc
atctcctgcaaggccagtcagagcctcctgcacagtaacgggaacacctatttgattgg
ttccgacagaagccaggccagtcctccacagggcctgatctatagggtgtccaaccgctcc
actggcggtgtcagacaggttcagtggcagcggtcagggacagatttcacctgagaatc
agcagagtggaggctgacgatgtgagtttattactgcgggcaaggatatacaagatcct
cc

SEQ ID NO. 107 IGKV2-9 (F)

>IGKV2-9*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacccccactgtccctgtctgtcagccctggagagactgcctcc
atctcttgcaaggccagtcagagcctcctgcacagtgtatggaaacacgtatttgaattgg
ttccgacagaagccaggccagtcctccacagcggttgatctataaggtctccaacagagac
cctgggggtcccagacaggttcagtggcagcgggtcagggacagatttcacccctgagaatc
agcagagtggaggctgacgatactggagtttattactgcgggcaagttatacaagatcct
cc

SEQ ID NO. 108 IGKV2-10 (F)

>IGKV2-10*01|Canis lupus familiaris_boxer|F|V-REGION|
gatattgtcatgacacagacccccactgtccctgtccgtcagccctggagagactgcctcc
atctcctgcaaggccagtcagagcctcctgcacagtgtatggaaacacgtatttgaattgg
ttccgacagaagccaggccagtcctccacagcggttgatctataaggtctccaacagagac
cctgggggtcccagacaggttcagtggcagcgggtcagggacagatttcacccctgagaatc
agcagagtggaggctgacgatactggagtttattactgcatgcaaggtacacagtttcct
cg

SEQ ID NO. 109 IGKV2-11 (F)

>IGKV2-11*01|Canis lupus familiaris_boxer|F|V-REGION|
gatatcgatcatgacacagacccccactgtccctgtccgtcagccctggagagactgcctcc
atctcctgcaaggccagtcagagcctcctgcacagtaacgggaacacctatttgttttg
ttccgacagaagccaggccagtcctccacagcgcttgatcaacttggtttccaacagagac
cctgggggtcccacacaggttcagtggcagcgggtcagggacagatttcacccctgagaatc
agcagagtggaggctgacgatgctggagtttattactgcgggcaaggtatacaagtcct
cc

SEQ ID NO. 110 IGKV2S12 (P)

>IGKV2S12*01|Canis lupus familiaris_boxer|P|V-REGION|
gatatcgatgatgacacagacccccattgtccttgctcctgtcaccctggagagctagcctca
tcactgtgcaggaggccagtcagagcctcctgcacagtgtatggatatatttatttgaatt
ggacttttcagaaatcaggccagtcctcactactcttgatctatatgctttacaaccagac
ttctggaggtcccaggttggttcattggcagtggtatcagggacagatttcacccctgaggat
cagcagggtggaggctgaagatgctggagtttattattgccaacaaactctacaaaatcc
tcc

SEQ ID NO. 111 IGKV2S13 (F)

>IGKV2S13*01|Canis lupus familiaris_boxer|F|V-REGION|
gatatcgatcatgacgacagacccccactgtccctgtctgtcagccctggagagcggcctcc
atctcctgcaggccagtcagagcctcctgcacagtaatgggaacacctatttgtattgg
ttccgacagaagccaggccagtcctccacagggcctgatctacttggtttccaaccgtttc
tcttgggtcccagacaggttcagtggcagcgggtcagggacagatttcacccctgagaatc
agcagagtggaggctgacgatgctggagtttattactgcgggcaaaatttacagtttcct
tc

SEQ ID NO. 112 IGKV2S14 (P)

>IGKV2S14*01|Canis lupus familiaris_boxer|P|V-REGION|
gaggttgatgatgacacagacccccactgtccctgtctgtcagccctggagagcggcctcc
atctcctgcaggccagtcagagtcctcggcacagtaatggaaacacctatttgtattgg
tacctgcaaaagccaggccagtcctccacagcttctgatcgacttggtttccaaccatttc
actggggtgtcagacaggttcagtggcagcgggtctggcacagattttacccctgaggatc
agcagggtggaggctgaggatgttgagtttattactgcatgcaaagtacacatgatcct
cc

SEQ ID NO. 113 IGKV2S15 (P)

>IGKV2S15*01|Canis lupus familiaris_boxer|P|V-REGION|
gatatcatgatgacacagacccccactctccttgctgccaccctggggaattggctgcc
atcttctgcaggccagagtcctcctgcacaataatggaaacacttatttacttggttcc
tgagacatcaggccaggttccaaggcatctgaaccatttggcttccagctgttactctg
gggtctcagacaggttcagtggcaacgggtcagggacagatttcacactgaaaatcagca
gagtgaggctgaggatgttagtggtttattagtgctgcaagtacacaaccttccatc

SEQ ID NO. 114 IGKV2S16 (F)

>IGKV2S16*01|Canis lupus familiaris_boxer|F|V-REGION|
gagggcgtgatgacgcagacccccactgtccctggccgtcaccctggagagctggccact
atctcctgcagggccagtcagagctcctgcgcagtgatggaaaatcctatttgaattgg
tacctgcagaagccaggccagactcctcgccgctgatttatgaggttccaagcgtttc
tctggggtctcagacaggttcagtgccagcgggtcagggacagatttcaccctaaaaatc
agcaggggtggaggtgaggtgttgaggtttattactgccagcaaagtctacattttcct
cc

SEQ ID NO. 115 IGKV2S18 (P)

>IGKV2S18*01|Canis lupus familiaris_boxer|P|V-REGION|
gatatcgatcatgacacagacccccactgtccgtgtctgtcagccctggagagacggcctcc
atctcctgcagggccagtcagagcctcctgcacagtgatggaaacacctatttggattgg
tatctgcagaagccaggccagctcctcagagcctgatctataggggtgtccaactgcttc
actggggtgtcagacaggttcagtgccagcgggtcagggacagatttcaccctgagaatc
agcagagtgagggtgacaacgctggagttttattactgcatgcaaggatatacaagatcct
cc

SEQ ID NO. 116 IGKV2S19 (F)

>IGKV2S19*01|Canis lupus familiaris_boxer|F|V-REGION|
gatatcgatcatgacacagactccactgtccctgtctgtcagccctggagagacggcctcc
atctcctgcagggccaatcagagcctcctgcacagtaatgggaacacctatttggattgg
tatcatgcagaagccaggccagctcctcagggcctgatctataggggtgtccaaccacttc
actggcgtgtcagacaggttcagtgccagcgggtcagggacagatttcaccctgaagatc
agcagagtgagggtgacgatgctggagttttattactgcgggcaagggtacacactctcct
cc

SEQ ID NO. 117 IGKV3-3 (P)

>IGKV3-3*01|Canis lupus familiaris_boxer|P|V-REGION|
gaaatagtctttgacctagtctccagcctccctggctatttcccaaggggacagagtcaac
catcacctatgggaccagcaccagtaaaaagctccagcaacttaacctgggtaccaacagaa
ctctggagcttcttctaagctccttgtttacagcacagcaagcctggcttctgggatccc
agctggcttcattggcagtggtgtgggaactcttcctctctcacaatcaatggcatgga
ggctgaaggtgtcgcctactattactaccagcagtagggtagctatctgct

SEQ ID NO. 118 IGKV3S1 (F)

>IGKV3S1*01|Canis lupus familiaris_boxer|F|V-REGION|
gaaatcgatgatgacacagctctccagcctccctctccttgtctcaggaggaaaaagtcacc
atcacctgccgggccagtcagagtggttagcagctacttagcctgggtaccagcaaaaacct
gggcaggctcccaagctcctcatctatggtacatccaacaggggccactgggtgtcccatcc
cggttcagtggtgagtggtgtgggacagacttcagcttcaccatcagcagcctggagcct
gaagatggttgacgtttattactgtcagcagctataatagcggatata

SEQ ID NO. 119 IGKV3S2 (P)

>IGKV3S2*01|Canis lupus familiaris_boxer|P|V-REGION|
gagattgtgccaaacctagtctctagccttctaagactccagaagaaaaagtcaccatcag
ctgctgggcagtcagagtggttagcagctacttagcctgggtaccagcaaaaacctggacag
gtccccaggctcttcatctatggtgcatccaacaggggccactgggtgtcccagtcgcttc
agcggcagtggtgtgggacagatttcaccctcatcagcagcagctctggagtcagctctga
agatggttgcaacatattactgccagcagctataatagctaccacc

SEQ ID NO. 120 IGKV4S1 (F)

>IGKV4S1*01|Canis lupus familiaris_boxer|F|V-REGION|
gaaatcgatgatgacccagctctccaggctctctggctgggtctgcaggagagagcgtctcc
atcaactgcaagtccagccagagctctctgtacagcttcaaccagaagaactacttagcc
tggtaccagcagaaaccaggagagcgtcctaagctgctcatctacttagcctccagctgg
gcatctggggctccctgccgattcagcagcagtggtctgggacagatttcaccctcacc
atcaacaacctccaggctgaagatgtgggggattattactgtcagcagcattatagttct
cctcc

SEQ ID NO. 121 IGKV4-1 (ORF)

>IGKV4-1*01|Canis lupus familiaris_boxer|ORF|V-REGION|
 gacatcacgatgactcagtggtccaggtccctggctgtgtctccaggteagcaggtcacc
 acgaactgcaggggcagtcacaaagcggttagtggtacttagcctggtacctgcagaaacca
 ggacagcgtcctaagctgctcatctacttagcctccagctgggcatctggggtccttgcc
 cgattcagcagcagtggtatctgggacagatttcaccctcaccgtcaacaacctcgaggct
 gaagatgtgagggtattactgtcagcagcattatagttctcctct

SEQ ID NO. 122 IGKV7-2 (P)

>IGKV7-2*01|Canis lupus familiaris_boxer|P|V-REGION|
 gacattatgctgaccagtcctccagcctccttgacctgtgtctccaggagagagggcca
 ccatctcttgaggggcagtcagaaagccagtgatatttggggcattaccaccatatta
 ccttgtagcaaacagaaatcagaacagcatcctaaagtcctgattaatgaagcctcagtt
 gggctctggggtcctaggcaggttcagtggtgtgtgggtctgggactgatttcagcctcaca
 attgatcctgtggaggtggcgatgctgtcaactattactgccagcagagtaaggagtct
 cctcc

SEQ ID NO. 123 IGKV(II)-1 (P)

>IGKV(II)-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 gaaattgcagattgtcaaatggataataaccaggatgcgggtctctagcctccctgactccc
 aggggagagaaccatcattaccataaaataaatcctgatgacataataagtttgcttg
 tatcaatagaaaaccaggtgagattcctcgagtcctgggtatacgacacttccatccttaca
 ggtcccaactggttcagtggtcagtggtctccaagtcagatcttactctcatcatcagcaa
 tgtgggcacacctgatgctgctacttattactgttatgagcattcagga

Germline Jk sequences**SEQ ID NO. 124 IGKJ1 (F)**

>GKJ1*01|Canis lupus familiaris_boxer|F|J-REGION|
 gtggacgttcggagcaggaaccaaggtggagctcaaac

SEQ ID NO. 125 IGKJ2 (ORF)

>IGKJ2*01|Canis lupus familiaris_boxer|ORF|J-REGION|
 ttatactttcagccagggaaccaagctggagataaaac

SEQ ID NO. 126 IGKJ3 (F)

>IGKJ3*01|Canis lupus familiaris_boxer|F|J-REGION|
 gttcacttttggccaagggaacaaactggagatcaaac

SEQ ID NO. 127 IGKJ4 (F)

>IGKJ4*01|Canis lupus familiaris_boxer|F|J-REGION|
 gcttacgttcggccaagggaacaaactggagatcaaac

SEQ ID NO. 128 IGKJ5 (F)

>IGKJ5*01|Canis lupus familiaris_boxer|F|J-REGION|
 gatcacctttggcaaagggaacacatctggagattaaac

Table 3. Canine Igλ Sequence Information**Germline Vλ sequences****SEQ ID NO. 129 IGLV1-35 (P)**

>IGLV1-35*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagtctgtgctgactcagctggcctcggtgtctggggccctggggccacagggtcagcatc
 tcctggactggaagcagctccaacataagggttgattatcctttgagctgataccaacag
 ctcccagaatgaagaacgaacccaaactcctcatctatggtaacagcaattggctctcag
 gggttccagatccattctctagaggctccaagtctggcacctcaggctccctgaccaact
 ctggcctccaggctgaggacgaggtgattgttactgcgcagcgtgggacatggatctca

gtgctc

SEQ ID NO. 130 IGLV1-37 (ORF)

>IGLV1-37*01|Canis lupus familiaris_boxer|ORF|V-REGION|
caatctgtgctgactcagctggcctcagtgctctgggtccttgggccagaggggtcaccatc
tcctgctctggaagcacaatgacattgggtattattgggtgtaactgggtaccagcagctc
ccagggaaggccctaaactcctcatatacgataatgagaagcgaccctcaggtatcccc
gatcgattctctggctccaagtctggcaactcaggcacccctgaccatcactgggctccag
gctgaggacgaggtgattattactgccagtcctatggatttcagcctcggtggt

SEQ ID NO. 131 IGLV1-41 (ORF)

>IGLV1-41*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtgctgtgctgactcagccagcctccgtgctctgggtccctgggccagaggggtcaccatt
tcctgcaactggaagcagctccaacgttgggttatagcagtagtggtgggtgggtaccagcag
ttccagggaaggccctaaactcctcgtggacagtgatggggatcgaccctcgggggtccct
cccgatcgattctctggctccaagtctggcagcacagccacccctgaccatctctgggctc
caggtgaggatgaggtgattattactgctcattctgggacaacagtctcaaagtcc

SEQ ID NO. 132 IGLV1-44 (F)

>IGLV1-44*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgaatcagccggcctcagtgctctggggccctgggccagaaggtcaccatc
tcctgctctggaagcacaatgacattgatataatttgggtgtgagctgggtaccaacagctc
ccaggaaaggccctaaactcctcgtggacagtgatggggatcgaccctcaggggtccct
gacagattttctggtccagctctggcaactcaggcacccctgaccatcactgggctccag
gctgaggacgaggtgattattactgtcagtgctgttgattccagccttggtgctca

SEQ ID NO. 133 IGLV1-45 (P)

>IGLV1-45*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtgctgtactgactcaatcagcctcagcgtctgggtccttgggccagaggggtctccgtc
tcctgctctagcagcacaaacaacattgggtattattgggtgtaagtggtaccagcagatc
ccaagaaaggccctaaactcctcatatatgataatgagaagagaccctcaggtgtcccc
aattgattctctgggtccaagtctggcaacttaggcacccctaacctcaatgggcttcag
gctgaggggcgaggtgattattactgccagtcctatggatttcagcctcggtggt

SEQ ID NO. 134 IGLV1-46 (F)

>IGLV1-46*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtgctgtgctgactcaaccagcctcagtgctccgggtctctgggccagaggggtcaccatc
tcctgcaactggaagcagctccaacattggtagagattatgtgggtgggtaccaacagctc
ccgggaacacgccccagaacctcatctatggtaataagtaaccgaccctcgggggtcccc
gatcgattctctgggtccaagttaggcagcacagccacccctgaccatctctgggctccag
gctgaggacgaggtgattattactgctctacatgggacaacagtctcactgttcc

SEQ ID NO. 135 IGLV1-48 (F)

>IGLV1-48*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtgctatgctgactcagccagcctcagtgctctgggtccctgggccagaaggtcaccatc
tcctgcaactggaagcagctccaacatcggtggtaattatgtgggtgggtaccaacagctc
ccagggaatagccctagaacctcatctatggtaataattaccgaccttcaggggtcccc
gatcgattctctgggtccaagttaggcaggttcagccacccctgaccatctctgggctccag
gctgaggacgaggtgagtgattactgctcatcatgggatgatagtgctcagaggtca

SEQ ID NO. 136 IGLV1-49 (F)

>IGLV1-49*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgactcagccggcctcagtgctctgggtccctgggacagaggggtcaccatc
tcctgcaactggaagcagcaccaacattggcagtggttatgatgtacaatgggtaccagcag
ctcccaggaaagtccttaaaactatcatctatggtaataagcaatcgaccctcaggggtc
ccggatcgcttctctgggtccaagttaggcagcacagccctctctgaccatcactgggctc
caggctgaggacgaggtgattattactgccagtcctctgatgacaacctcgatgatca

SEQ ID NO. 137 IGLV1-50 (P)

>IGLV1-50*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtgctgtgctgactcagccggcctca...gtgtccgggtctctgggccagagaggtcacc

atctcctgcaactggaagcagctccaacatc.....gatagaaaatat
gttggtctggtaccaacagctc...ccgggaacaggccccagaaccgtcatctatgataat
.....agtaaccgaccctcgggggtccct...gatcgattctct
ggctccaag.....tcaggcagcacagccaccctgaccatctctgggctccaggctgag
gacgaggctgat...tattactgctcaacatacgacagcagctctcagtagtgg

SEQ ID NO. 138 IGLV1-52 (P)

>IGLV1-52*01|Canis lupus familiaris boxer|P|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggccagagggtcaccatc
tcctgcactggaagcagctccaacatcagtagatataatgtgaactggtaccaacagctc
ctgggaacaggccccagaaccctcatctatggtagtagtaaccgaccctcgggggtcccc
gattgattctctggctccaagtcaggcagccagctaccctgaccatctctgggctccag
gctgaggatgaggctgattattactgctcaacatacgacaggggtctcagtgctcg

SEQ ID NO. 139 IGLV1-54 (P)

>IGLV1-54*01|Canis lupus familiaris boxer|P|V-REGION|
cagcctgtgctgactcagccgcctcaggggtctggggcctgggccagaggttcagcatc
tcctgttctggaagcacaacaacatcagtgattattatgtgaactggtactaacagctc
ccagggaacagccctaaaaccattatctatttggatgataccagaccctcgggggtcccg
gattgattctctgtctccaagtcagcagctcagctaccctgaccatctctgggctccag
gctgaggatgaagctgattattactgctcatcctgggggtgatagtctcaatgctcc

SEQ ID NO. 140 IGLV1-55 (F)

>IGLV1-55*01|Canis lupus familiaris boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggccagaggatcaccatc
tcctgcactggaagcagctccaacattggaggttaataatgtgggttggtaccagcagctc
ccagggaagaggccccagaactgtcatctatagtacaaatagtcgaccctcgggggtgccc
gatcgattctctggctccaagtcctggcagcacagccaccctgaccatctctgggctccag
gctgaggatgaggctgattattactgctcaacgtgggatgatagtctcagtgctcc

SEQ ID NO. 141 IGLV1-56 (ORF)

>IGLV1-56*01|Canis lupus familiaris boxer|ORF|V-REGION|
cggctctgtgctgactcagccgcctcagtgtcgggatctgtgggccagagaatcaccatc
tcccgctctggaagcacaacagcattgggtatacttggtgtgaactggtaccaagagctc
ccaggaaaggccccaaactcctcgtagatggtagtggaatagaccctcaggggtccct
gaccgattttctggctccaaactctggcaactcaggcactctgaccatcactgggcttcag
cctgaggacgaggctgattattattgtcagtcattgaaccatgcttgggtgctcc

SEQ ID NO. 142 IGLV1-57 (F)

>IGLV1-57*01|Canis lupus familiaris boxer|F|V-REGION|
caggctgtgctgactccgctgcctcagtgtctcgccctgggacagacgggtcaccatc
tcttgtagtggaaatagcaccctcagcagtggttatgtgtacaatggtaccagcag
ctcccaggaaagtccctgaaactatcatctatggtgatagcaatcgaccctcgggggtc
ccagatcgattctctggcttcagctctggcaattcagccacactggccatcactgggctc
caggatgaggacgaggctgattattactgccagtccttagatgacaacctcaatggtca

SEQ ID NO. 143 IGLV1-58 (F)

>IGLV1-58*01|Canis lupus familiaris boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggccagagggtcaccatc
tcctgcactggaagcagctccaacatcggttagatatagtgttggtggttcagcagctc
ccgggaaaaggccccagaaccgtcatctatagtagtagtaaccgaccctcaggggtccct
gatcgattctctggctccaagtcaggcagcacagccaccctgaccatctctgggctccag
gctgaggacgaggctgattattactgctcaacatacgacagcagctctcagtagtag

SEQ ID NO. 144 IGLV1-61 (P)

>IGLV1-61*01|Canis lupus familiaris boxer|P|V-REGION|
cagtctgtgctgacatagccaccctcagtgtctggggcctgggccagagggtcaccatc
tcctgcactggaagcagctcaagcatgggttagttattatgtgagctggcacaagcagctc
ccaggaaacaggccccagaaccatcatgtgttgtaaaaacatcgacctcgggaatctcca
atcaagctctctggctcccattctggcaacacagccaccctgaccatcactgggctcctgg
ctgaggatgaggctgattattactgttcaacatgggatgacaatctcaatgcacc

SEQ ID NO. 145 IGLV1-63 (P)

>IGLV1-63*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagctgccctcagtgctctggggccctgggccagagggtcaccatc
tctgtctctggaagcagctctaaacttggggcttatgctctgaactagaaccaacaattc
ccaggaacagattccaatttctcatctatgatgataagtaattgatctttctggatgcct
gatttaattctgtggctccacatccagcagttcaggctccctgaccatcactgggctctgg
gatgaggacaaggctgattattactgccagtgccattaccatagcctccgtgct

SEQ ID NO. 146 IGLV1-65 (P)

>IGLV1-65*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccagcctcagtgctctggatccctgggccaaagggtcaccatc
tctgcaactggaagcacaacaacatcggtgggtgataattatgtgcaactgggtaccaacag
ctcccaggaaaggcaccagctctcctcatctatggatgataacagagaatctggggctc
ccggaacgattctctggctccaagtccagcagctcagccactctgaccatcactgggctc
catgctgaggacgaggctgatattattgccagtcctacgatgacagcctcaatactca

SEQ ID NO. 147 IGLV1-66 (F)

>IGLV1-66*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccgccctcagtgctcaggatctgtggggccagagaatcaccatc
tctgtctctggaagcacaacagcattgggtatacttgggtgtgaactgggtaccaactgtc
tcaggaaaggccctaaactcctcgtagatggtagtgaaatcgaccctcaggggtccct
gaccgattttctggctccaaatctggcaactcaggcactctgaccatcactgggcttcag
cctgaggacgaggctgattattattgtcagtccttgaaacccatgcttgggtgctcc

SEQ ID NO. 148 IGLV1-67 (F)

>IGLV1-67*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtcctgactcagccggcctcagtgctctggggtctggggccagagggtcaccatc
tctgcaactggaagcagctccaacattgggtgaaattatgtgagctggcaccagcaggctc
ccagaaacaggccccagaaacatcatctatgctgataactaccgagcctcgggggtccct
gatcgattctctggctccaagtccagcagcacagccacctgaccatctctgtgctccag
gctgaggatgaggctgattattactgctcagtgggggatgatagctctcaaagcacc

SEQ ID NO. 149 IGLV1-68 (P)

>IGLV1-68*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcacatcctgactcagcagccctcagtcctctgggtcactggggccagagggtcaccatc
tcttgcaactggattccctagcaacaatgattatgatgcaatgaaaattcatacttaagt
ggctgggtaccaacagtcctccaggaaagtcaccagctcctcatttatgatgaaaccaga
aactctgggggtccctgatcgattctctggctccagaaactggtagctcagcctccctgccc
atctctggactccaggctgaggacaagactgagttactgctcagcatgggatgatcgt
cttgatgctca

SEQ ID NO. 150 IGLV1-69 (P)

>IGLV1-69*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctaaactcagccaccctcagtgctcggggctcgctggggccagagggtcaccatc
tctgtctctggaagcacaacaacatcagttattgttggtgagctgggtaccaacagctc
ccaggaaaggccctaaactcctcgtggacagtgatggggatcgaccgtcaggggtccct
gaccgattttctggctctaaagtctggcaaatcagccacctgaccatcactgggcttcag
gctgaggacgaggctgattattactgtatatttggtccacgctttgtgctca

SEQ ID NO. 151 IGLV1-69-1 (P)

>IGLV1-69-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccactgttagggcctggggccctgggccagagggtcaccctct
cctgacctggaagagtccagttattggtgattatggtatgaaatggtacaagcagcttgc
aaggacagacccagactcgtcatctatggcaatagcaattgatcctcgggtcccaatc
aattttctggctctgggttttggcatcactggctccttgaccacctctgggctccagactg
aaaaataggctgattactagtgttctccagtgatccaggcctgt

SEQ ID NO. 152 IGLV1-70 (F)

>IGLV1-70*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcaaccggcctccgtgtctgggtccctggggccagagagtcaccatc

tcttgcaactagaagcagctcgaacgttggtatggcaatgatgtgggatgggtaccagcag
ctcccaggaacaggccccagaaccatcatctataataccaatactcgaccctctgggggtt
cctgatcgattctctggctccaaatcaggcagcacagccaccctgaccatctctggactc
caggetgaggacgaggetgattattactgctcttccatgacagcagctctcaatgtc

SEQ ID NO. 153 IGLV1-72 (ORF)

>IGLV1-72*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtctgtgctaactcagccggcctcagtgctgtggtccctgggtcagagggtcaccatc
tgcaactggaagcagctccaacattggtacatatagtgtaggctggtaccaacagctccca
ggatcaggccccagaaccatcatctatggtagtagtaaccgaccgttgggggtccctgat
cgattctctggctccagggtcaggcagcacagccaccctgaccatctctgggtccaggct
gaggacgaagctgattattactgcttcacatacgacagtagtctcaaagctcc

SEQ ID NO. 154 IGLV1-73 (F)

>IGLV1-73*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgaatcagccaccctcagtgctgtggtccctgggccagagaatcaccatc
tcctgctctggaagcagcaatgacatcggtatgcttggtgtgaactggtaccaacagctc
ccaggaaatgccctaaactcctttagatggtagtgggaatcgaccctcaggggtccct
gaccaatctctggctccaaatctggcaattcaggcactctgaccatcactgggtccag
gctgaggacgaggetgattattattgtcagtcctatgatctcacgcttggtgctcc

SEQ ID NO. 155 IGLV1-74 (P)

>IGLV1-74*01|Canis lupus familiaris_boxer|P|V-REGION||
cagtcctatgatgactcagccaccctcagtgctgtggtcactgggccagagggtcaccatc
tactgcaactggaatccctagcaacactgattatagtggttggaatttatacttatgtg
agctgggtaccaacagtataaggaaaggcaccagtcctcctcatctatgggatgataccg
gaaactctgaggtccctgatcaattctctggctccagggtctggtagctcaacctccctga
ccatctctggactccagggtgaggatagtccttaatgtc

SEQ ID NO. 156 IGLV1-75 (F)

>IGLV1-75*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgactgggtccctgggccagagggtcaccatc
tcctgcaactggaagcagctccaacatcggtggatataatgttggtggttcagcagctc
ccgggaacaggccccagaaccgtcatctatagtagtagtaaccgaccctcgggggtcccg
gatcgattctctggctccagggtcaggcagcacagccaccctgaccatctctgggtccag
gctgaggacgaggetgagttactgctcaacatgggacagcagctctcaaagctcc

SEQ ID NO. 157 IGLV1-78 (P)

>IGLV1-78*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccggcctcagtgctccagggtccctgggccagatagtcaccatc
tcttgctggaagcagctccaacatcggtacaaaatgttggtggttccagcagctc
ccgagaacaggccccagaaccgtcatctatggtaatagtaactgaccctcgggggtccctc
gatcaattctctggctccaaagtcaggcagcatagccaccctgaccatctctgtgctccag
gctgaggacgaggettattattactgctcaacatagacagcagctctcagtgctct

SEQ ID NO. 158 IGLV1-79 (P)

>IGLV1-79*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccggcctctgtgtctggggccctgggccagaggtcaccatct
cctgcaactaggagcagctccaatgttggttatagcagttatgtgggtggtaccagcagc
tcccaggaacaggccccaaaaccatcatctataataccaatactcgaccctctgggggttc
ctgatcgattctctggctccaaatcaggcagcacagccacccttaccattgctggactcc
aggctgaggacgaggetgattattactgctcatcctatgacagcagctctcaaagctcc

SEQ ID NO. 159 IGLV1-79-1 (P)

>IGLV1-79-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctatgctgactcaccctggccagaggatcaccctctcctgacctggaagagtccca
gtattggtgattatggtgtgaaatggtacaggcagctagcaagaacagaccccagactcc
tcatttatagcaatagcaatcgatccttgagtcccaatcaattttccgctctggtttt
gacattactggctccttgaccacctccagggtccagactgaaaaataggctgattactag
tgcttatcagtgatccaggcttggtgggctg

SEQ ID NO. 160 IGLV1-80 (F)

>IGLV1-80*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccgacctcagtgctcgtgggtccctgggccagaggggtcacaatc
tcatgctctagaagcacgaataacatcgggtattgtcggggcgagctgggtaccaacagctc
ccaggaaaggccctaaactcctcgtggacagtgatggggatcaactgtcaggggtccct
gaccgattttctggtccaaagtctggcaactcagccaacctgaccatcactgggtccag
gctgaggacaaggctgattattactgccagtcctttgatcacacgcttggtgctcg

SEQ ID NO. 161 IGLV1-81 (P)

>IGLV1-81*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgttgagtcagccagcctcagtgctcgtgggttctgggccagaggggtcaccatc
tcttgcaactggaagcagctccaacatcgggtggaattacgtgagctggcaccagcaggtc
ccagaaacaggccccagaaacatcatctatgctgataactactgagcctcgggggtccct
gatggattctctggtccaaagtaaggcagcacagccaccccgaccatctctgtgctccag
gctgaggatgaggctgattattactgctcagtgggggataatagtctcaaagcacc

SEQ ID NO. 162 IGLV1-82 (F)

>IGLV1-82*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccagcctcagtgctcgggggtccctgggccagagagtcaccatc
tcttgcctctggaaggacaaacatcggtaggtttggtgctagctgggtaccaacagctcca
ggaaaggccctaaactcctcgtggacagtgatggggatcgaccgtcaggggtccctgac
cgattttccggctccaagtctggcaactcggccactctgaccatcactggtctccatgct
gaggacgaggctgattattactgtctgtctatttggtcccacgcttggtgctca

SEQ ID NO. 163 IGLV1-82-1 (P)

>IGLV1-82-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccactgttagggcctggggcctgggccagagggtcactctct
cctgcccctggaagagtcaccagttatggtgattatgatgtgaagtgttacaggcagctcac
aagaacagaccctagactcctcatccatgggtgatagcaattgatcctcgggtccccaatc
acttttctggctctggttttggcatcactggctgcttgaccacctctgggtccagactg
aaaaataggctgattactagtgttatccagtgatccag

SEQ ID NO. 164 IGLV1-83 (P)

>IGLV1-83*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccggcctctgtgtctggggcctgggccagaggtcaccatct
cctgcactaggagcagctccaatgttggttatagcagttatgtgggtcgtggtaccagcagc
tcccaggaacaggccccaaaaacatcatctataataccaatactcgaccctctgggggtcc
ctgatcgattctctgggtccaaatcaggcaggacagccacccttaccattgctggactcc
aggctgaggacgaggctgattattactgctcatcctatgacagcagtcctcaaagctcc

SEQ ID NO. 165 IGLV1-84 (F)

>IGLV1-84*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgactcagccggcctcagtgctcgtgggtccctgggccagaggggtcaccatc
tcttgcaactggaagcagctccaatgttggttatggcaattatgtgggtcgtggtaccagcag
ctcccaggaacaggccccagaaacctcatctatggtagtagttaccgaccctcgggggtc
cctgatcgattctctgggtccagttcaggcagctcagccacactgaccatctctgggtc
caggctgaggatgaagctgattattactgctcatcctatgacagcagtcctcagtggtg

SEQ ID NO. 166 IGLV1-84-1 (ORF)

>IGLV1-84-1*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtctgtgctgactcagccagcctcagcgtcgtgggtccttgggccagaggggtcactgtc
tcttgcctctagcagcacaacaacatcgggtattattggtgtgaagtgtggtaccagcagatc
ccaggaaaggccataaactcctcatatatgataatgagaagcgaccctcaggtgtcccc
aatcgattctctgggtccaaagtctggcgacttaagcaccctgaccatcaatgggttcag
ggtgaggacgaggctgattattattgcccagtcctatggatttcagcctcgggtggtca

SEQ ID NO. 167 IGLV1-86 (ORF)

>IGLV1-86*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtctgtgctgactcagccagcctcagtgctcgtgggtccctgggccagaggggtcaccatc
tcttgcaactggaatccccagcaacacagattttgatggaatagaatttgatacttctgtg
agctgggtaccaacagctcccagaaaagccccctaaaacatcatctatggtagtactctt

tcattctcgggggtccccgatcgattctctggtccagggtctggcagcacagccaccctg
accatctctggggtccagggtgaggacgagggtgattattactgctcatcctgggatgat
agtctcaaatcata

SEQ ID NO. 168 IGLV1-87 (F)

>IGLV1-87*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtcgtgctgactcagccagcctcagtgctctggatccctgggccaaagggtcaccatc
tctgcaactggaagcacaacaacatcggtggtgataattatgtgcactggtaccaacag
ctcccaggaaaggcaccagtcctcatctatggtgatgataacagagaatctggggtc
cctgaacgattctctggtccaagtcaggcagctcagccactctgaccatcactggggtc
cagggtgaggacgagggtgattattattgccagtcctacgatgacagcctcaataactca

SEQ ID NO. 169 IGLV1-88 (P)

>IGLV1-88*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcgtgctgactcagccgcccctcagtgctcgggatctgtgggccagagaatcaccatc
tctgctctggaagcacaacagctaccaacagctctcaggaaaggcctctaaactctc
gtagatggtactgggaaccgacctcaggggtccccgaccgattttctgggtccaaatct
ggcaactcaggcactctgaccatcactgggcttgggacgagggtgaggacgagggtgagg
acgagggtgattattattgttagtcactgatctcacgcttggtgctcc

SEQ ID NO. 170 IGLV1-88-2 (P)

>IGLV1-88-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggccgcccctgggcaatgagttcgtgcagggtcaaggctgagacagacctgcagaattca
ggtttgtctgagacacagctcatcagatgtgtgcagtggtgtcctgggtaccaacggctc
ccatgaatgggtcctaaatccttatctagaaataacatttagatcactttgtggccccga
tccattctctgggtccatgtctggcaactctggcctcatgaacatcactgggctatggtc
tgaagatggagctgctcttcacaggccctcttgggacaaaattcttggggct

SEQ ID NO. 171 IGLV1-88-3 (P)

>IGLV1-88-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcctatcctgactcagccgcccctcagtcctctgggtcactgggccagagggtcaccatc
tctgcaatggaatccctgcacgcaatgattatgatgcatgaaaattcatacttacgtga
gctggtaccaacagttcccaagaaagtcaccagtcctcatctacgatgataccagaaa
ctctggggaccctgatcaattctctgggtccagatctggtaactcagcctccctgcccat
ctctggactccaggctgaggacgagggtgagtattactgctcagcatgggatgatcgtct
tgatgctca

SEQ ID NO. 172 IGLV1-89 (P)

>IGLV1-89*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcgtgactgactcagccgcccctcagtgctctgggtccctgggccagagggtcaccatc
tctgcaactggaagcagctccaacatcggtggtatattatgtgagctggctctagcagctc
ccgggaacaggccccagaacctcatctatagtagtagtaaccgaccttcaggggtccct
gatcgattctctggtccagggtcaggcagcacagccaccctgaccatctctggggtccag
gctgaggatgagggtgattattactgttcaacatacgacagcagctctcaaagctcc

SEQ ID NO. 173 IGLV1-89-2 (P)

>IGLV1-89-2*01|Canis lupus familiaris_boxer|P|V-REGION|
cttccctgtgctgaccagccaccctcaagggtctgggggtctggttcagaagatcaccatc
ttctgttctggaagcacaacaacatgggtgataattatgttaactggtacaaacagctt
ccagggaacggccccctaaaacctcatctaagtggatcatatcagaccctcaggggtcctg
gagagattctctgtctccaattctggcagctcagccaacctgaccatctctggggtccag
gatgaggactagggtgattattattgctcatcctggcatgatagtcagtgctcc

SEQ ID NO. 174 IGLV1-91 (P)

>IGLV1-91*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgctgactcagctgccctcagtgctctgcagccctgggacagagggtcaccatc
tgcaactggaagcagcaccacatcggcagtggttattatacactatggtaccagcagctg
caggaaagtcctcctaaaactatcatctatggtaatagcaatcgaccttgaggggtcccg
atcgattctctggtccaagtatggcaattcagccaacctgaccatcactggggtccagg
ctgaggacgaggatgattattactgccagtcctctgatgacaacctcgatgggtca

SEQ ID NO. 175 IGLV1-92 (F)

>IGLV1-92*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcgggtgtctgggtccctgggccagaggggtcaccatc
tcttgcaactggaagcagctccaatgttggttatggcaattatgtgggtcgtgaccagcag
cttccaggaacaggccccagaaccattatctgttataccaatactcgaccctctgggggt
cctgatcgatactctggctccaagtcaggcagcacagccaccctgaccatctctgggtc
caggctgaagacgagactgattattactgtactacgtgtgacagcagctctcaatgctag

SEQ ID NO. 176 IGLV1-94 (F)

>IGLV1-94*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagcctccctcagtgtccgggtccctgggccagaggggtcaccatc
tcttgcaactggaagcagctccaacatcggttagaggttatgtgcaactggtaccaacagctc
ccaggaacaggccccagaaccctcatctatggtattagtaaccgaccctcaggggtcccc
gatcgattctctggctccaggtcaggcagcacagccactctgacaatctctgggtccag
gctgaggatgaggctgattattactgtctcatcctgggacagcagctctcagtgtctct

SEQ ID NO. 177 IGLV1-95-1 (P)

>IGLV1-95-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccactgttagggcctgggtccctgggccagaggggtcaccctct
cctgcccctggaagagtctcagttttggtgattatggtgtgaaacggtacaggaagctcgc
atggacagaccccagactcctcatctatggcaatagcaattgattctcgggtccccagtc
tattttctggctctggttttggcatcactggctccttgaccacctccgggtccagactg
aaaaataggctgatttctagtgtctctccagtgtaccaggccttt

SEQ ID NO. 178 IGLV1-96 (F)

>IGLV1-96*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgcgctgactcaaacggcctccatgtctgggtctctgggccagaggggtcacctgc
tcttgcaactggaagcagttccaacgttggttatagaagttatgtgggtcgtgaccagcag
ctcccaggaacaggccccagaaccatcatctataataaccaatactcgaccctctgggggt
cctgatcgattctctggctccatatcaggcagcacagccaccctgactattgctggactc
caggctgaggacgaggtgattattactgtctcatcctatgacagcagctctcaaagctcc

SEQ ID NO. 179 IGLV1-97 (P)

>IGLV1-97*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgaatcagctgccttcagtgttaggatccctgggccagagaatcaccatc
tctgtctctggaagcagcaatgacatcggtatgcttggtgtgaactggtaccaagagccg
ccaggaaaggccccctaaactcctcgtagatggtagtggaatcgaccctcaggggtccctg
ccgattttctggctccaaactctggcaactcaggcactctgaccatcactgggtccaggc
tgaggacgaggctgattattattgtcagtcactgatctcacgcttggtgctcc

SEQ ID NO. 180 IGLV1-97-4 (F)

>IGLV1-97-4*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagcctccctcagtgttcagggtccctgggccagaggggtcactata
tcttgcaactggaagcagctccaacgtcggttagaggttatgtgatctggtaccaacagctc
ctgggaacacgcccagaaccctcatatatggtatagtaaccaaccctcaggggtcccc
aatcaattctctggctccaggtcaggcagcacagacactctgacaatctctgggtccag
gctgaggatgaggctgattattactgtctcatcctgggacagcagctctcagtgtctct

SEQ ID NO. 181 IGLV1-98 (P)

>IGLV1-98*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccagtctcagtgtctggggccctgtgcccagaggggtcaccatc
tcttgcaactggaacagctccaacattgggttatagcagttgtgtgagctgatatcagcag
ctcccaggaacaggccccagaaccatcatctatagtatgaataactcaaccctctgggggt
cctgatcgattctctggctccaggtcaggcaactcagccaccctaaccatctctgggtc
caggctgaggacaaggctgactattactgtctcaacatatgacagcagctctcagtgtctca

SEQ ID NO. 182 IGLV1-100 (F)

>IGLV1-100*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccgacctcagtgtcgggggtccctgggccagaggggtcaccatc
tctgtctctggaagcagcaacaacatcggtattgttggtgcgagctggtaccaacagctc
ccaggaaaggccccctaaactcctcgtagcagtgatggggatcgaccgtcaggggtccct

gaccgggttttccggctccaagtctggcaactcagccacctgaccatcactgggcttcag
gctgaggacgaggctgattattactgccagtcctttgataccagcttgatgtca

SEQ ID NO. 183 IGLV1-100-1 (P)

>IGLV1-100-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtactgactcagcagccgttagtgcttggggccctggccagagggtcagcttct
cctgccttgggaagagtcceagttatggtaattatgggtgtgaaatggtaacagcagctcaa
aaggacagacccccagacttctcatctatggcaatagcaattgatcctcgggtcccaatc
aatcttctggctctggttttggcatcactggctccttgaccacctatgggtccagactg
aaaaataggctgattactagtgtctttccagtgtccagtcctgaggggc

SEQ ID NO. 184 IGLV1-101 (P)

>IGLV1-101*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccggcctccgtgtctggggccttgggcccagagggtcaccatc
tcctgcactggaagcagctccaatgttgggttatagcagctatgtgggttgtagccagcag
ctcccaggaagtcctccaaaccatcatctataataccaatactcgacctctggggtt
cctgatcaattctctggctccaaatcaggcagcagcagccacctgaccattgctggacttc
aggctgaggacgaggctgattattactgctcatcctatgacagcagctctcaaagctcc

SEQ ID NO. 185 IGLV1-103 (F)

>IGLV1-103*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgactcagccacctctgtgtctgcagccctggggcagagggtcaccatc
tcctgcactggaagtaacaccaacatcggcagtggttatgatgtacaatggtaccagcag
ctcccaggaagtccctaaaaactatcatttatggtaatagcaatcgacctcgggggtc
ccggttcgattctctggctccaagttaggcagcagcagccacctgaccatcactgggatc
caggctgaggatgaggctgattattactgccagtcctatgatgacaacctcgatggtca

SEQ ID NO. 186 IGLV1-104 (P)

>IGLV1-104*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccagcttcagtgtctgggtccctgggcccagaggatcaccatc
tcctgcactaaaagcagctccaacatcggtaggtattatgtgagctgacaacagctccca
ggaacaggcccccagaaacgctcatctatgataataataactgacctcgggggtccctgat
caattttctggctctaaatcaggcagcagcagccacctgaccatctctaggctccaggct
gaggacgatgctgattattactgctcgccatatgccagcagctctcagtgtctgg

SEQ ID NO. 187 IGLV1-106 (F)

>IGLV1-106*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgttgactcaaccggcctcagtgtctgggtccctgggcccagagggtcatcatc
tcctgcactggaagcagctccagcattggcagagggttatgtgggttgtagcaacagctc
ccagggaacaggcccccagaaacctcatctatggtattagtaacctacccccgggagtcctc
aatagattctctggttcgagggtcaggcagcagcagccacctgaccatcgctgagctccag
gctgaggacgaggctgattattactgctcatcgtgggacagaagtctcagtgtctcc

SEQ ID NO. 188 IGLV1-107 (P)

> IGLV1-107*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgctgactcagcccgccctcagtgtctgcggccttgggacagagggtcaccat
ctcctgcactggaagcagcaccacatcagcagtggttacggtgtacaatggtaccagca
gtcccaggaagtccctaaaaaatctatggtactagcaagtgaccttggggatccc
ggttcaattctctggctccaagttaggcagcagcagccacctgaccatcactggtatcta
ggctgaggacgaggctgattattactgccaatcctatgatgacaacctcgatggtca

SEQ ID NO. 189 IGLV1-110 (P)

> IGLV1-110*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtacggaatcaaccggcctcagagtctgcagccctgggacagagagtcaccatc
tcctgcacgggaagcagatccaacattggcagtggttatgtgtacaatggtaccaacgg
ctcacaggaaagtctccttaaaactatcatctatggttaatagcaatcaacctcgggggt
cctggatcaattctctggctccaagttaggcagcagcagccacctgaccatcactgggat
ccagtctgaggacgaggctgattattactgccagtcctatgatagaagtctctgtgtctca

SEQ ID NO. 190 IGLV1-111 (ORF)

>IGLV1-111*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggctgaggggtcaccatc
tgctgcactggaagcagctccaacatcagtagttattatgtgggctggtaccaaccactc
gcgggaacaggccccagaactgtcatctatgataatagtaaccgtccctcggggtccct
gatcaattctctggctccaagtcaggcagcacagccacctgaccatctctcggtccag
gctgaggacgaggtgattattacggctcatcatatgacagcagctctcaatgctgg

SEQ ID NO. 191 IGLV1-112 (P)

>IGLV1-112*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccagcctcagtgtctcagtcctgggtcagaggggtcaccatc
tctgtactggaagcagctccaatgttggttataacagttatgtgagctggtaccagcag
ctcccaggaaacagtccccagaacctcatctattataccaatactcgacctatggggtt
cctgatcgattctctggctccaatcaggcaactcagccacctgaccattgctggactc
caggctgaggacgaggtgattattattgctcaacatatgacagcagctctcagtggtgc

SEQ ID NO. 192 IGLV1-113 (P)

>IGLV1-113-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgaatcagacgccctcagtgtcgggtccctgggcccagagagtcgccatc
tctgtctctggaagcacaacatcagtaggttgggtgcgagctggttaacaacagctcctg
ggaaaggcttcaaaactcctcctagacagtgatgggatcaacctcagtggtccctgac
tgattttccggctccaagtcctggcaactcagggtgccctgaccatcactgggtccaggct
gaggacgaggtgattattactgccagtcctttgatccacacttggtgctca

SEQ ID NO. 193 IGLV1-114 (P)

>IGLV1-114*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctttgctgactcagccacctcagtgtctgaggccctgggacagaggggtcaccatc
tctgtcactggaagcagcaccaacatcggcagtggttatgatgtacaatggtaccagcag
ctcccaggaaagtccccctcaactatcgtatacggtaatatagcaattgacctcgggggtc
ccagatcaattctctggctccaagtcctcacaattcagccacctgaccatcactgggtc
cagactgaggacgaggtgattattactgccagtcctctgatgacaacctcga

SEQ ID NO. 194 IGLV1-115 (P)

>IGLV1-115*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccagcctcagtgtctgggtccctgggcccagaggggtcaccatc
tctgtcactggaagcagctccaacatcggtagatatagtgtaggctgataccagcagctc
ccgggaacaggccccagaactgtcatctatggtagtagtagccgacctcgggggtcccc
gatcgattctctggctccaagtcaggcagcacagccacctgaccatctcagggtccag
gctgaggacgaggtgattattactgttcaacatacgacagcagctctcaaagctcc

SEQ ID NO. 195 IGLV1-116 (F)

>IGLV1-116*01|Canis lupus familiaris_boxer|F|V-REGION|
cagcctgtgctcactcagccgcctcagtgtctgggtccctgggacagaggggtcactatc
tctgtcactggaagcagctccaacatccttggttaattctgtgaactggtaccagcagctc
acaggaagaggccccagaacctcatctattatgataacaaccgacctctgggggtccct
gatcaattctctggctccaagtcaggcaactcagccacctgaccatctctgggtccag
gctgaggacgagactgattattactgctcaacgtgggacagcaggtcagagctcc

SEQ ID NO. 196 IGLV1-118 (P)

GLV1-118*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggcccagaggggtcaccatc
tctgtcactgaaagcagctccaacatcgggtgatattatgtgggctggtaccaacagctc
ccaggaacaggccccagaacctcatctatagtagtagtaaccgacctcaggggtccct
gattgattctctggctccaggtcaggcagcacagccacctgaccatctctgggtccag
gctgaggacgaggtgattattactgctctacatgggacagcagctctcaaagctcc

SEQ ID NO. 197 IGLV1-118-2 (P)

>IGLV1-118-2*01|Canis lupus familiaris_boxer|P|V-REGION|
ctgcctgtgctgaccagccgcctcaaggctctgggggtctggttcagaggttcaccatc
ttctgttctggaagcacaacaacataggtgataattattttaactggtacaaacagctt
ccaggaacggccccataaacatcatctaagtggatcatatcagacctcaggggtcctg

gagagattctctgtctccaattctggcagctcagccaacctgaccatctctgggctccag
gctgaggactaggctgattattattgtctcatcctgggatgatagtctcaatgctcc

SEQ ID NO. 198 IGLV1-122 (P)

>IGLV1-122*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgctgactcagctgcctcagtgctctgcagccctgggacagaggggtcaccatc
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caggaaagtccttaaaactatcatctatggtaatagcaatcgacccttgaggggtcccg
atcgattctctggctccaagtatggcaattcagccacgctgaccatcactgggctccagg
ctgaggacgaggatgattattactgccagtcctctgatgacaacctcgatgggtca

SEQ ID NO. 199 IGLV1-123 (P)

>IGLV1-123*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccggcctcagtgctctgggtccctgggtcagaggggtcaccatc
tcctgcaactggaagcagctccaacatcggtgaatattatgtgagttggctccagcagctc
ccgggaacacagcccccagaacctcatctatagtagtagtaaccgacctcaggggtccct
gatcgattctctggctccaagtcaggtagcatagccacctatctctgggctccaggctg
aagacgaggctgattattactgtactacgtgggacagcagctctcaatgctgg

SEQ ID NO. 200 IGLV1-125 (F)

>IGLV1-125*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgctccgggtccctgggcccagaggggtcaccatc
tcctgcaactggaagcagctccaacatcggttagaggttatgtgggctggtaccaacagctc
ccgggaacagggcccccagaacctcatctatggtaatagtaaccgacctcaggggtcccc
gatcggttctctggctccaggtcaggcagcacagccacctgaccatctctgggctccag
gctgaggatgaggctgattattactgtctcatcgtgggacagcagctctcagtgctct

SEQ ID NO. 201 IGLV1-127 (P)

>IGLV1-127*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagcctccctcagtgctctgggtccctgggcccagaggtcaccgtct
cctgcaactggaagctgcttcaacattggtagatatagtgtagctggctccagcagctcc
ccgggaacagggcccccagaacctcatctattatgatcgtagccgacctcaggggttcccg
atcgattctctggctccaagtcaggcagcacagccacctgaccatctctgggctccagg
ctgaggacgaggctgattattactgtctcatcctatgacagcagctctcaaaggtca

SEQ ID NO. 202 IGLV1-129 (P)

>IGLV1-129*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccagctctcagtgctctgggtccctgtgccagaggggtcaccatc
tcctgcaactggaagcagctccaacattgggtatagcagctgtgtgagctgatatcagcag
tcccaggaacagggcccccagaacctcatctatagtagtaataactctacctctggggtt
cctgatcgattgtctggctccaggtcaggcaactcagccaccttaaccatctctgggctc
caggctgaggacaaggctgactattactgtctcaacatattgacagcagctctcaatgctca

SEQ ID NO. 203 IGLV1-130 (P)

>IGLV1-130*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgacctcagctggcctcagtgctctgggtccctgggcccagaggggtcaccatc
acctgcaactggaagcagctccaacattggtagtattatgtgggctggttccaacagctc
ccagggaacagggccctagaacctcatctaaggcaatagtaaccgacctcgggggtccct
gatcaattctctggctccaagtcaggcagcacagccacctgaccatctctgggctccag
gctgaggatgatgctgattattactgcacatcatgggatagcagctctcaaggctcc

SEQ ID NO. 204 IGLV1-132 (ORF)

>IGLV1-132*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagtctgtgctgactcagcctccctcagtgctctgggacctggggcaaaggggtcatcatc
tcctgcaactggaatccccagcaacataaatttagaagaattgggaatcgctactaagggtg
aactgggtaccaacagctcccaggaaggcaccagctctcctcatctatgatgatagc
agagggttctgggattcctgatcgattctctggctccaagtcaggcaactcaggcacctg
accatcactgggctccaggctgaggatgaggctgattattattgccaatcctatgatgaa
agccttggtgtt

SEQ ID NO. 205 IGLV1-133 (P)

>IGLV1-133*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagcctccctcagtggttcagggtccctgggcccagaggggtcaccatc
tcttgcaactggaagcagctccaacgtcggtagaggttatgtgatctggtaccaaggtcc
tggaacacgcccagaacctcatatatggttagtagtaaccaacctcaggggtcccca
atcgattctctggctccaggtcaggcagcacagacactctgacaatctctgtgttccagg
ctgaggatgaggctgattattactgctcatcctgggacagcagtcctcagtgctct

SEQ ID NO. 206 IGLV1-135 (F)

>IGLV1-135*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgaatcagctgcctcagtggttaggatccctgggcccagagaatcaccatc
tctgtctctggaagcagcaatgacatcggtatgcttggtgtgaactggtaccaagagctc
ccaggaaaggccctaaactcctcgtagatggtagtggaatcgacctcaggggtccct
gaccgattttctggctccaaatctggcaactcaggcactctgaccatcactggggtccag
gctgaggacgaggctgattattatgtcagtcactgatctcacgcttggtgctcc

SEQ ID NO. 207 IGLV1-136 (F)

>IGLV1-136*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtggtctgggtccctgggcccagaggggtcaccatc
tcttgcaactggaagcagctccaacatcggttagaggttatgtgggctggtaccagcagctc
ccaggaaacagggcccagaacctcatctatgatagtagtagccgacctcgggggtccct
gatcgattctctggctccaggtcaggcagcacagcaacctgaccatctctggggtccag
gctgaggacgaggctgattattactgctcagcatatgacagcagtcctcagtggtg

SEQ ID NO. 208 IGLV1-138 (F)

>IGLV1-138*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtggtctgggtccctgggcccagaggggtcaccatc
tcttgcaactggaagcagctccaatgttggttatggcaattatgtgggctggtaccagcag
ctcccaggaacaagccccagaacctcatctatgatagtagtagccgacctcgggggtc
cctgatcgattctctggctccaggtcaggcagcacagcaacctgaccatctctggggtc
caggctgaggatgaagccgattattactgctcatcctatgacagcagtcctcagtggtg

SEQ ID NO. 209 IGLV1-139 (F)

>IGLV1-139*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgactccgctgcctcagtggtctgcggccctgggacagacgggtcaccatc
tcttgtaactggaatatgaccccaatcagcagtggttatgctgtacaatggtaccagcag
ctcccaggaaggtcccctgaaactatcatctatggtgatagcaatcgacctcgggggtc
ccagatcgattctctggcttcagctctggcaattcagccacactggccatcactggggtc
caggatgaggacgaggctgattattactgctcagtccttagatgacaacctcaatggtca

SEQ ID NO. 210 IGLV1-140 (P)

>IGLV1-140*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccggcctccgtgtctgggacttgggcccagaggggtcaccatc
tcttgcaactggaagcagctccaatttgggttatagcagctatgtgggcttgtaaccagcag
ctcccaggaacagggcccagaacctcatctataataccaatactcgacctctgggggtt
cctgatcgattctctggctccaaatcaggcagcacagccacctgaccattgctggacttc
aagctgaggacgaggctgattattactgctcatcctatgacagcagtcctcaaagctcc

SEQ ID NO. 211 IGLV1-140-1 (P)

>IGLV1-140-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtactgactcagccgccattagtgcttggggccctggccagaggggtcaccttct
cctgccttggaagagtccagatttggtgattatggtgtgaaatggtacaagcagctcaa
aaggacagaccccagacttctcatctatggcaatagcaattgatcctcggggtccccaatc
aatcttctggctctggttttggcatcactggctccttgaccacctatggggtccagactg
aaaaataggctgattactagtgcttctccgggtgatccag

SEQ ID NO. 212 IGLV1-141 (F)

>IGLV1-141*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccgacctcagtgctcggggtcccttgggcccagaggggtcaccatc
tctgtctctggaagcagcaacaacatcggtattgttggtgcgagctggtaccaacagctc
ccaggaaaggccctaaactcctcggtacagtggttggggatcgacctcaggggtccct

gaccgggttttccggctccaactctggcaactcagccacctgaccatcactggggttcag
gctgaggacgaggctgattattactgccagtcctttgataccagcttggtgtca

SEQ ID NO. 213 IGLV1-143 (P)

>IGLV1-143*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccagtcctcagtgctctggggccctgtgccagaggggtcaccatc
tcctgcactggaagcagctccaacattgggttatagcagctgtgtgagctgatatcagcag
ctcccaggaacaggccccagaacctcatctatagtatgaatactctaccctctggggtt
cctgatcgattgtctggctccaggtcaggcaactcagccaccttaacctctctgggctc
caggctgaggacaaggctgactattactgctcaacatatgacagcagctctcaatgtca

SEQ ID NO. 214 IGLV1-144 (F)

> IGLV1-144*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagcctccctcagtggttcaggtccctgggccagaggggtcaccatc
tcctgcactggaagcagctgcaacgtcggttagaggttatgtgatctggtaccaacagctc
ctgggaacacgcccagaacctcatatatggtagtagtaaccaacctcaggggtcccc
aatcgattctctggctccaggtcaggcagcacagccactctgacaatctctgggttccag
gctgaggatgaggctgattattactgctcatcctgggacagcagctctcagtgctct

SEQ ID NO. 215 IGLV1-146 (P)

> IGLV1-146*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgaatcagctgccttcagtggttaggatccctgggccagagaatcaccatc
tcctgctctggaagcagctgaacatcggttagaggttatgtggtgtgaactggtaccaagagctc
ccaggaaaggccccataaactcctcgtagatggtactgggaatcgacctcaggggtccct
gactgattttctggctccaaatctggcaactcaggcactctgaccatcactggggtccag
gctgaggacgaggctgattattattgtcagtcactgatctcacgcttggtgtcc

SEQ ID NO. 216 IGLV1-147 (F)

>IGLV1-147*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgctctgggtccctgggccagaggggtcaccatc
tcctgcactggaagcagctccaacatcggttagaggttatgtgggctggtaccagcagctc
ccaggaaacaggccccagaaacctcatctatgataatagtaaccgacctcggggtccct
gatcgattctctggctccaaagtccaggcagcacagccacctgaccatctctggggtccag
gctgaggacgaggctgattattactgctcaacatacgacagcagctctcagtggtg

SEQ ID NO. 217 IGLV1-149 (F)

>IGLV1-149*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgctctgggtccctgggccagaggggtcaccatc
tcctgcactggaagcagctccaatgttggttatggcaattatgtgggctggtaccagcag
ctcccaggaacaggccccagaaacctcatctatcgtagtagtagccgacctcggggtc
cctgatcgattctctggctccaggtcaggcagcacagcaacctgaccatctctggggtc
caggctgaggatgaagccgattattactgctcatcctatgacagcagctctcagtggtg

SEQ ID NO. 218 IGLV1-150 (F)

>IGLV1-150*01|Canis lupus familiaris_boxer|F|V-REGION|
caggctgtgctgactccgctgcctcagtgctctgcggccctgggacagcgggtcaccatc
tcctgtactggaatagcaccaaatcggcagtggttatgctgtacaatggtaccagcag
ctcccaggaagtccccgaaactatcatctatggtgatagcaatcgacctcggggtc
ccagatcgattctctggcttcagctctggcaattcagccacactggccatcactggggtc
caggatgaggacgaggctgattattactgccagtccttagatgacaacctcgatggtca

SEQ ID NO. 219 IGLV1-151 (F)

> IGLV1-151*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgcgctgactcaaacggcctccatgtctgggtctctgggccagaggggtcaccgtc
tcctgcactggaagcagttccaacgttggttatagaagttagtggtggtggtaccagcag
ctcccaggaacaggccccagaaacctcatctataataactcgacctctggggtt
cctgatcgattctctggctccatcaggcagcacagccacctgactattgctggactc
caggctgaggacgaggctgattattactgctcatcctatgacagcagctctcaaagctcc

SEQ ID NO. 220 IGLV1-151-1 (P)

>IGLV1-151-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcagccactgttagggcctgggttcctggccagagggtcaccctct
cctgccctggaagagtctcagttttggtgattatggtgtgaaacggtacaggaagctcgc
atggacagaccccagactcctcatctatggcaatagcaattgattctcggtccccagtc
tattttctggctctgggttttggcatcactggctccttgaccacctccgggtccagactg
aaaaataggtgatttctagtgttc

SEQ ID NO. 221 IGLV1-152 (P)

>IGLV1-152*01|Canis lupus familiaris_boxer|P|V-REGION|
caatctgtgctgatccagccggcctcagtgtcgggatccctgggcccagagagtcaccatc
tctgtctctggaaggacaaacaacatcggttaggtttggtgagctggtaccaacagctc
ccaggaaaggccctaaactcctcgtggacagtgtggtggtgattgaccgtcaggggtccct
gaccggttttccggctccaggtctggcagctcagccacctgaccatcactgggtccag
gctgaggatgaggtgattattactgccagtcctttgatccacgcttggtgtca

SEQ ID NO. 222 IGLV1-154 (P)

>IGLV1-154*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccgtcctcagtgtccgggtccctgggcccagagggtcactgtc
cctgcactggaagcagctccaacattggttagatatagtgtgagctggtatatactgtg
gtccagcagctcccgggaacaggccccagaaccatcatctattatgattgtagccgacc
ctcaggggttcccgatcgattctctggctccaagtcaggcagcacagccacctgaccat
ctctgggtccaggctgaggacgaggtgattattactgctcatcctatgacagcagtct
caaaggtca

SEQ ID NO. 223 IGLV1-155 (F)

>IGLV1-155*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccctccctcagtgtccgggtccctgggcccagagggtcaccatc
tctgcactggaagcagctccaacatcggttagaggttatgtgcactggtaccaacagctc
ccaggaaacaggccccagaaccctcatctatggtattagtaaccgacctcaggggtcccc
gatcgattctctgggtccaggtcaggcagcacagccactctgacaatctctgggtccag
gctgaggatgaggtgattattactgctcatcctgggacagcagtctcagtgtct

SEQ ID NO. 224 IGLV1-157 (F)

>IGLV1-157*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccggcctcagtgtctgggtccctgggcccagagggtcaccatc
tctgcactggaagcagctccaacatcggttagaggttatgtgggtggtaccagcagctc
ccaggaaacaggccccagaaccctcatctatgataatagtaaccgacctcgggggtccct
gatcgattctctgggtccaggtcaggcagcacagccacctgaccatctctgggtccag
gctgaggacgaggtgattattactgctcaacatacgacagcagtctcagtgtgtg

SEQ ID NO. 225 IGLV1-158 (F)

>IGLV1-158*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgaatcagctgccttcagtgttaggatccctgggcccagagaatcaccatc
tctgtctctggaagcacgaatgacatcggtatgcttggtgtgaactggtaccaagagctc
ccaggaaaggccctaaactcctcgtagatggtactgggaatcgacctcaggggtccct
gaccgattttctgggtccaaatctggcaactcaggcactctgaccatcactgggtccag
gctgaggacgaggtgattattattgtcagtcactgatctcacgcttggtgtcc

SEQ ID NO. 226 IGLV1-159 (F)

>IGLV1-159*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtctgtgctgactcagccctccctcagtgttcagggtccctgggcccagagggtcaccatc
tctgcactggaagcagctgcaacgtcggttagaggttatgtgatctggtaccaacagctc
ctgggaacacgcccagaaccctcatatattggtagtagtaaccaaccctcaggggtcccc
aatcgattctctgggtccaggtcaggcagcacagccactctgacaatctctgggtccag
gctgaggatgaggtgattattactgctcatcctgggacagcagtctcagtgtct

SEQ ID NO. 227 IGLV1-160 (P)

>IGLV1-160*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtctgtgctgactcaaccagtctcagtgtctgggtccctgtgcccagagggtcaccatc
tctgcactggaagcagctccaacattggttatagcagctgtgtgagctgatatacagcag

ctcccaggaacaggccccagaaccatcatctatagtatgaatactctacccctctgggggtt
cctgatcgattgtctggctccaggtcagggaactcagccaccctaaccatctctggggtc
caggctgaggacaaggtgactattactgctcaacatatgacagcagctctcaatgtctca

SEQ ID NO. 228 IGLV1-161 (P)

>IGLV1-161-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caaggctcagctgccctgaggacagagtcacatgacaggtcagggcagaaacagggactctg
aatccagctctgagtcaggacacatcaggagtgccaatatgtgtcctgctaccaacagc
tccatgagtgggcagtcacaaatcctcatgtattatgatggcttgacctctgtggaccctg
gtccattctctgacctcatgtctggcagctctggctctctggccattgctgggctgagcc
aggaggtatgaggtcatgcttcactgccccctccagtgcagcatttcaaggat

SEQ ID NO. 229 IGLV1-162 (F)

> IGLV1-162*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtcctgtgctgactcaacccttcctcggtgtctgggactttgggccagaggggtcaccatc
tctgtctctggaagcagcaacaacatcggtattgttggtgagagctggtaccaacagctc
ccaggaaaggccccctaaactcctcgtgtacagtgatggggatcgaccgtcaggggtccct
gaccgggttttcggctccaactctggcaactcagacacctgaccatcactgggcttcag
gctgaggacgaggtgattattactgccagtcctttgataccacgcttgatgctca

SEQ ID NO. 230 IGLV2-31 (F)

> IGLV2-31*01|Canis lupus familiaris_boxer|F|V-REGION|
cagtcctgcctgactcaacccttcctcggtgtctgggactttgggccagactgtcaccatc
tctgtgatggaagcagcagtaacattggcagtagtaattatatcgaatggtaccaacag
tcccaggcacctccccaaaactcctgatttactataccaataatcgccatcagggatc
cctgctcgcttctctggctccaagtctgggaacacggcctccttgaccatctctgggctc
caggctgaagatgaggtgattattactgcagcgcatatactggtagtaatactttc

SEQ ID NO. 231 IGLV2-31-1 (P)

>IGLV2-31-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcctaaccctaattgagcccccttttgtccaggattctaggatggactgtcactgtc
tctgtgtttttaagcagctgtgacatcaggagtgataatgaaatatcctggtagcaatag
caccggagcatgactcagaaattcctgatttactataccagttcttgggcatcagatatc
cctgattgctttcctggctcccagctctggaaacatggcctgtctgaccatttccaggctc
caggctaatgatgacgctgattatcattgttacttatatgatggtagtggcgctttt

SEQ ID NO. 232 IGLV2-32 (P)

>IGLV2-32*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcctgcctgactcagcctccctcgatgtctgggacactgggacagaccatcatcatt
tctgtactggaagcggcagtgacattgggaggtatagttatgtctcctggtagcaagag
ctcccaagcagctccccacactcctgatttatggtaccaataatcgccattagagatc
cctgctcgcttctctggctccaagtctggaaacacagccccatgaccatctctgggctt
caggctgaagatgaggtcaattattactgttgctcatatacaaccagtggcacaca

SEQ ID NO. 233 IGLV2-32-1 (P)

>IGLV2-32-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagtcctgccttgaccacaactcctttgtgtctgggactttgagacaaactgtcacatct
cttgcaatggaagcagcagccacactggaaacttataacctacctctggcaccagcaatg
tctggaaaggccccacactccagatagatgctgtgagttctttgccttcagggttcca
gctctgtcctcaggctctgagctagcaacacagcctccagtcatttttgactgcacc
ctgaggacaaggctgattattactgattgtccaggacagccagag

SEQ ID NO. 234 IGLV3-1 (P)

>IGLV3-1*01|Canis lupus familiaris_boxer|P|V-REGION|
gccacaagctgactcaatccctgtttatgtcagtgccctgggacagatggccaggatc
acctgtgggagagacaaactctggaagaaaaagtgctcactggtagcagcagaagccaagc
caggctcccgtgatgcttatcgatgatgattgcttccagccctcaggattctctgagcaa
ttctcaggcactaaactcggggaacacagccacctgaccattagtgggccccccagcgagg
acgcggtattactgtgccaccagccatggcagttggagcacct

SEQ ID NO. 235 IGLV3-1-1 (P)

>IGLV3-1-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tccaatgtactgaacacagccacccttggtgtcagtgaaacctgggacagaaggccagcctc
acctgtggaagaaacagcattgaagataaatatgtttcatgtgcccagcaggagccaggc
caggcccccatgctggtcatctattatagtagacacaagaaacctgagcgattttctgcct
ccagctctagctcgggtacatgatcacctgaccaacagtggggcctaggacaaggacg
aggatggctattactgtcagtcctatgacagtagtggtactcct

SEQ ID NO. 236 IGLV3-2 (F)

>IGLV3-2*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgactcagtcaccctcagtggtcagtgaccctgggacagacggccagcatc
acctgtaggggaaacagcattggaaggaaagatgttcattggtaccagcagaagccgggc
caagccccctgctgattatctataatgataacagccagccctcagggatccctgagcga
ttctctgggaccaactcaggggagcacggccaccctgaccatcagtgaggcccaaccaac
gatgaggctgactattactgccaggtgtgggaaagtagcgctgatgct

SEQ ID NO. 237 IGLV3-3 (F)

>IGLV3-3*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgacacagctgccatccaaaaatgtgaccctgaagcagccggcccatc
acctgtgggggagacaacattggaagtaaaagtgttcactggtaccagcagaagctgggc
caggccccctgtactgattatctattatgatagcagcagggcgacagggatccctgagcga
ttctccggcgccaactcggggaacacggccaccctgaccatcagcggggccctggccgag
gacgaggtgactattactgccaggtgtgggacagcagtgctaaggct

SEQ ID NO. 238 IGLV3-4 (F)

>IGLV3-4*01|Canis lupus familiaris_boxer|F|V-REGION|
tccactgggttgaaatcaggctccctccatgttggtggccctgggacagatggaaacaatc
acctgtccggagatatcttagggaaaagatatgcataattggtaccagcagaaagccaaagc
caagccccctgtgctcctaatacaataaaaaataatgagcgggcttctgggatccctcactgg
ttctctggttccaaactcgggcaacatggccaccctgaccatcagtggggcccgggtgag
gacgaggtgactattactgccagtcctatgacagcagtggaatgct

SEQ ID NO. 239 IGLV3-7 (P)

>IGLV3-7*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatgtgctgactctgctgctatcagtgaccgtgaacctgggacagaccaccagcatc
acctgtggtggagacagcattggagggagaactgtttactggtaccagcagaagcctggc
cagcgccccctgctgattatctataatgatagcaattgaccctcagggatccctgctga
ttctctggctccaactcagggaaacagggcctccctaaccatcattggggcctgggcctaa
gacgagctgtagtattacggagaggtgtgggacagcagtgctaaggct

SEQ ID NO. 240 IGLV3-7-1 (P)

>IGLV3-7-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatatgtgctgactcagcagccattggcaagtgtaaacctcagccagtgggccagcacc
acctgtggtggagataacattggagaaaaaccgtccaatggaaccagcagaagcctggc
taagctcccattacggctatctataaaggtagtgatctgcctcagggatccctgagcaa
ttccctggccccaatgtggggaacggggcctccctgaacatcagcggggctaagccgacg
acgaggtattactgccagtcagcagacattagtgtgaaggct

SEQ ID NO. 241 IGLV3-8 (F)

>IGLV3-8*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgacacagctgccatccgtgagtgtagccctgaggcagacggccccgcac
acctgtgggggagacagcattggaagtaaaagtgtttactggtaccagcagaagctgggc
caggccccctgtactgattatctatagatagcaacagggcgacagggatccctgagcga
ttctctggcgccaactcggggaacacggccaccctgaccatcagcggggcctggccgag
gacgaggtgactattactgccaggtgtgggacagcagtgactaaggct

SEQ ID NO. 242 IGLV3-9 (P)

>IGLV3-9*01|Canis lupus familiaris_boxer|P|V-REGION|
tccactgggttgaaatcaggctccctccgtgttgctggcactgggacagatggcaacaatc
acctgatccagagatgtctttgggaaaaatatgcataattggtaccagcagaagccaagcc
aagccccctgtgctcctaatacaataaaaaataatgagcaggattctgggatccctgaccggt

tctctggctccaactcgggcaacacggccaccctgaccatcagtggggccccgggcccagag
acgaggctgactattactgcccagtcctatgacagcagtggaatgtt

SEQ ID NO. 243 IGLV3-11 (F)

>IGLV3-11*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgtctcagccgccatcagcgactgtgactctgaggcagacggccccgcctc
acctgtgggggagacagcattggaaagtaaaagtgtgaatggtagcagcagaagccgggc
cagcccccgctgctcattatctatggtgatagcagcagccgctcagggatccctgagcga
ttctccggcgccaactcggggaacacggccaccctgaccatcagcggggccctggccgag
gacgaggctgactattactgccaggtgtgggacagcagtactaaggct

SEQ ID NO. 244 IGLV3-13 (P)

>IGLV3-13*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatgtactgactcagctgccatcagtgactgtgaacctgggacagaccaccagcatc
acctgtgggtggagacagcattggaggagaactgtttactggtagcagcagaagcctggc
cagcgcccccgctgctgattatctataatgatagcaattggccctcagagatccctgcctga
ttctctggctccaactcaggggaacagggcctccctaaccatcattggggcctgggcctaa
gatgagctctgagtattacggagaggtgtgggacagcagtgtctaaggct

SEQ ID NO. 245 IGLV3-13-1 (P)

>IGLV3-13-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatatgtgactcagcagccattggcaagtgtaaacctcagccagtgggccagcacc
acctgtgggtggagataacattggagagaaaactgtccaatggaaccagcagaagcctggc
taagctctcattatggctatctataaaggtagtgatctaccctcagggatccctgagcaa
ttccctggcccccaactcgggtcggggcctccctgaacatcagcggggctacgccgacgac
taggctattactgccagtcagcagacattagtgttaaggct

SEQ ID NO. 246 IGLV3-14 (F)

>IGLV3-14*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgacacagctgccatccatgagtgtagccctgaggcagacggccccgcac
acctgtgaggggagacagcattggaaagtaaaagagttactggtagcagcagaagctgggc
caggctccctgtactgattatctatgatgatagcagcagccgctcagggatccctgagcga
ttctccggcgccaactcggggaacacagccaccctgaccatcagcggggccctggccgag
gacgaggctgactattactgccaggtgtgggacagcagtactaaggct

SEQ ID NO. 247 IGLV3-15 (P)

>IGLV3-15*01|Canis lupus familiaris_boxer|P|V-REGION|
tccactgggttgatcaggctccctccgtgttggtggccctgggacagatggaaacaatc
acctgtctgagagatgtcttagggaaaagatatgcataaggtaccagcataagccaagc
caagccccgtgtctcctaatacaataaaaataatgagcaggattctgggatccctgaccgg
ttctctggctccaactcgggcaacacggccaccctgaccatcagtggggccccgggctgag
gacgaggctgagtattactgccagtcctatgacagcagtggaatgtt

SEQ ID NO. 248 IGLV3-18 (P)

>IGLV3-18*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatgtgctgacacagctgccatccgtgaatgtgacccagaggcagacggccccgcac
acctgtgggggagacagcattggaaagtaaaagtgtttactggtagcagcagaagctgggc
caggccccgtgttgattatctatagagacagcaacagggcagggatccctgagcgatt
ctctggcgccaacacggggaacatggccaccctgactatcagcggggccctggccgtgga
cgaggctgactattactgccaggtgtgggacagcagtgtctaaggct

SEQ ID NO. 249 IGLV3-19 (ORF)

>IGLV3-19*01|Canis lupus familiaris_boxer|ORF|V-REGION|
tccccctgggctgaatcagcctccctccgtgttggtggccctgggacagatggcaacaaac
acctgtctcggagatgtcttagggaaaagatatgcataatggtagcagcataagccaagc
caagccccgtgtgtcctaatacaataaaaataatgagctgggttctgggatccctgaccga
ttctctggctccaactcgggcaacacggccaccctgaccatcagtggggccccgggcccag
gacgaggctgactattactgccagtcctatgacagcagtggaatgtt

SEQ ID NO. 250 IGLV3-21 (F)

>IGLV3-21*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgagctgactcagccaccatccgtgaatgtgacctgagggagacggcccacatc
acctgtgggggagacagcattggaagtaaatatgttcaatggatccagcagaatccaggc
cagggccccgtggtgattatctataaagatagcaacaggccgacagggatccctgagcga
ttctctggcgccaactcagggaaacacgggtaccctgaccatcagtggggccctggccgaa
gacgaggtgactattactgccaggtgggggacagtgggtactaaggct

SEQ ID NO. 251 IGLV3-23 (P)

>IGLV3-23*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatgtactgactcagctgccatcagtgactgtgaacctgggacagaccaccagcatc
acctgtgggtggagacagcattggagggagaactgtttactgggtaccagcagaagcctggc
cagcgccccctgctgattatctataatgatagcaattggccctcagagatccctgectga
ttctctggctccaactcagggaaacagggcctccctaaccatcattggggcctgggcctaa
gacgagctctgagattacggagaggtgtgggacagcagtgctaaggct

SEQ ID NO. 252 IGLV3-23-1 (P)

>IGLV3-23-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tcctatatgtctgactcagcagccattggcaagtgtaaacctcagccagtgggccagcacc
acctgtgggtggagataacattggagaaaaactgtccaatggaaccagcagaagcctggc
taagctcccattacggtatctataaaggtagtgatctgccctcagggatccctgagcaa
ttccctggcccccaactcgggaaacggggcctccctgaacatcagcggggcctaagccgacg
actaggctattactgccagtcagcagacattagtggttaaggct

SEQ ID NO. 253 IGLV3-24 (F)

>IGLV3-24*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgacacagctgccatccgtgagtgtagacctgaggcagacggcccgcacatc
acctgtgggggagacagcattggaagtaaaaatgtttactgggtaccagcagaagctgggc
cagggccccctgtactgattatctatgatgatagcagcagggcgtcagggatccctgagcga
ttctccggcgccaactcggggaaacacggccaccctgaccatcagcggggccctggccgag
gatgaggtgactattactgccaggtgtgggacagcagtgactaagcct

SEQ ID NO. 254 IGLV3-25 (ORF)

>IGLV3-25*01|Canis lupus familiaris_boxer|ORF|V-REGION|
tccactgggttgaaatcaggcttccctccgtgttggtggccctgggacagatggaaacaatc
acctgtctcgagagatgtcttagggaaaagatatgcataataggtaccagcataagccaagc
caagccccctgtgctcctaatacaataaaaaataatgagcaggattctgggatccctgaccgg
ttctctggctccaactcggggcaacacggccaccctgaccatcagtggggcccggtgag
gacgaggtgagattactgccagtcctatgacagcagtggaatgtt

SEQ ID NO. 255 IGLV3-26 (F)

>IGLV3-26*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgctgacacagctgccatccgtgaatgtgacctgaggcagccggcccacatc
acctgtgggggagacagcattggaagtaaaagtgttcaactgggtaccaacagaagctgggc
cagggccccctgtactgattatctatgggtgatagcaacaggccgtcagggatccctgagcga
ttctctgggtgacaactcggggaaacacggccaccctgaccatcagtggggccctggccgag
gacgaggttactattactgccaggtgtgggacagcagtgctcaggct

SEQ ID NO. 256 IGLV3-27 (F)

>IGLV3-27*01|Canis lupus familiaris_boxer|F|V-REGION|
tccagtgtgctgactcagcctccttcagtatcagtgtctctgggacagacagcaaccatc
tctgtctctggagagagctctgagtaaatattatgcacaatgggtccagcagaaggcaggc
caagtccctgtgttggtcatatataaggacactgagcgccctctgggatccctgaccga
ttctccggctccagttcagggaaacacacacccctgaccatcagcggggctcgggccgag
gacgaggtgactattactgcgagtcagaagtcagtactgggtactgct

SEQ ID NO. 257 IGLV3-28 (F)

>IGLV3-28*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctatgtgttgactcagctgccttcagtgtcagtgaacctgggaaagacagccagcatc
acctgtgagggaaataacataggagataaatatgcttattgggtaccagcagaagcctggc
cagggccccctgctgattatctatgaggatagcaagcgccctcagggatccctgagcga

ttctctggctccaactcggggaacacggccaccctgaccatcagcggggccagggccgag
gatgaggctgactattactgtcaggtgtgggacaacagtgtctaaggct

SEQ ID NO. 258 IGLV3-29 (F)

>IGLV3-29*01|Canis lupus familiaris_boxer|F|V-REGION|
tccagtgtgctgactcagcctccctcggtgtcagtgctccctgggacagacgggcgaccatc
acctgctctggagagagtctgagcagatactatgcacaatgggtatcagcagaagccaggc
caagcccccatgacagtcataatggtgggacagagagcgaccctcagggatccctgaccga
ttctccagctccagttcagagaacacacacaccttgacaatcagtgaggccaggtgag
gatgaggctgaatattactgtgagatatgggacgccagtgctgatgat

SEQ ID NO. 259 IGLV3-30 (F)

>IGLV3-30*01|Canis lupus familiaris_boxer|F|V-REGION|
tcctacgtggtgacccagccaccctcagtgctcagtgaaacctgggacagacggccagcatc
acctgtgggggagacaacattgcaagcacatatgtttcctggcagcagcagaagtcgggt
caagccccctgtgagcagattatctatcgtgatagcaaccggccctcagggatccctgagcga
ttctctggctccaactcggggaacacggccaccctgaccatcagcagggccagggccgag
gatgaggctgactattactgccaggtgtggaagagtggtaataaggct

SEQ ID NO. 260 IGLV4-5 (F)

>IGLV4-5*01|Canis lupus familiaris_boxer|F|V-REGION|
ttgcccgtgctgacccagcctacaaatgcactctgcctccctggaagagtcgggtcaagctg
acctgcacttttgagcagtgagcacagcaattacattgttcagtggtatcaacaacaacca
gggaaggccccctcggtatctgatgtatgtcaggagtgtatggaagctacaaaaggggggac
gggatccccagtcgcttctcaggctccagctctggggtgaccgctatttaaccatctcc
aacatcaagtcgtgaagatgaggatgactattattactgtggtgcagactatacaatcagt
ggccaatacggttaagc

SEQ ID NO. 261 IGLV4-6 (P)

>IGLV4-6*01|Canis lupus familiaris_boxer|P|V-REGION|
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acatgcactctgagcagtgagcacagcagttactatatttactggtatgaacaacaacca
ccagggaaggccccctcggtatctgatgaggggttaacagtgatggaagccacagcaggggg
gacgggatccccagtcgcttctcaggctccagctctggggtgaccgctatttaaccatc
tccaacatccagtcgtgaggatgaggcagattattactgtggtgcaccgctggttagcagt
agc

SEQ ID NO. 262 IGLV4-10 (F)

>IGLV4-10*01|Canis lupus familiaris_boxer|F|V-REGION|
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acctgcacttttgagcagtgagcacagcaattacattgttcattggtatcaacaacaacca
gggaaggccccctcggtatctgatgtatgtcaggagtgtatggaagctacaaaaggggggac
gggatccccagtcgcttctcaggctccagctctggggtgaccgctatttaaccatctcc
aacatcaagtcgtgaagatgaggatgactattattactgtggtgcagactatacaatcagt
ggccaatacggttaagc

SEQ ID NO. 263 IGLV4-12 (P)

>IGLV4-12*01|Canis lupus familiaris_boxer|P|V-REGION|
ttgcccgtgctgacccagcctccaagtgcatctgcctccctggaagcctcggtcaagctc
acatgcactctgagcagtgagcacagcagttactatatttactggtatcaacaacaacca
gggaaggccccctcggtatctgatgaagggttaacagtgatggaagccacagcaggggggac
gggatccccagtcgcttctcaggctccagctctggggtgaccgctatttaaccatctcc
aacatccagtcgtgaggatgaggcaggttattactatggtgtaccctggttagcagtagc

SEQ ID NO. 264 IGLV4-16 (ORF)

>IGLV4-16*01|Canis lupus familiaris_boxer|ORF|V-REGION|
ttgcccgtgctgacccagcctacaaatgcactctgcctccctggaagagtcgggtcaagctc
acatgcacttttgagcagtgagcacagcaattacattgttcaatggtatcaacaacaacca
gggaaggccccctcggtatctgatgcagtgatgtcaggagtgtatggaagctacaacaggggggac
gggatccccagtcgcttctcaggctccagctctggggtgaccgctatttaaccatctcc
aacatcaagtcgtgaagatgaggatgactattattacagtggtgcatactatacaatcagt

ggccaatacggttaagc

SEQ ID NO. 265 IGLV4-17 (P)

>IGLV4-17*01|Canis lupus familiaris_boxer|P|V-REGION|
ttgcccatgctgacccagcctccaagtgcacatctgcctccctggaagcctcggtcaagctc
acatgcactctgagcagtgagcaaacaggttactatatttactgggtatcaacaacaacaa
ccagggaaggccctcggtatctgatgaagggttaacagtgatggaagccacagcagggcg
tcgggatccccagtcgcttctcaggtccagctctggggtgaccgctatttaaccatct
ccaacatccagctctgaggatgaggcagattattactgtggtgtaccactggtagcagta
gc

SEQ ID NO. 266 IGLV4-20 (ORF)

>IGLV4-20*01|Canis lupus familiaris_boxer|ORF|V-REGION|
ttgcccatgctgaccgagcctacaaatgcacatctgcctccctggaagagtcagtcagctc
actgcactcttgagcagtgagcacagcaattacattgttcgatgggtatcaacaacaacaa
gggaaggccctcggtatctgatgtatgtcaggagtgatggaagctacaacagggggac
gggatccccagtcgcttttcaggtccagctctggggtgaccgctatttaaccatctcc
aacatcaagctctgaagatgaggctgagtattattacggtggtgcagactataaaatcagt
gaccaatatggttaaga

SEQ ID NO. 267 IGLV4-22 (F)

>IGLV4-22*01|Canis lupus familiaris_boxer|F|V-REGION|
ttgcccgctgctgacccagcctccaagtgcacatctgcctgctggaacctcggtcaagctc
acatgcactctgagcagtgagcacagcagttactatatttactgggtatcaacaacaacaa
ccagggaaggccctcggtatctgatgaagggttaacagtgatggaagccacagcaggggg
gacgggatccccagtcgcttctcaggtccagctctggggtgaccgctatttaaccatc
tccaacatccagctctgaagatgaggcagattattactgtggtgtaccgctggtagcagt
agc

SEQ ID NO. 268 IGLV5-34 (P)

>IGLV5-34*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgctgacccagcgcgcctccctctctgcacccctgggatcaacagccagactc
acctgcacctgagcagtggttctcagtggtggcagctactacataactggtagcagtag
aagccaggagccctccccgggtatctcctgtactaactactactcaagtacacagctggg
ccccgggggtccccagccatttctctggatccaaagacaactcggccaatgcagggtcct
gtcacctctgggtgcagcctgaggacgaggctgactactactgtgctacaggttattg
ggatgggagcaactatgcttacc

SEQ ID NO. 269 IGLV5-38 (P)

>IGLV5-38*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagcgcgcctccctctctgcacccctgggaacagcggccagaaat
acctgcactctgagcagtgacctcagtggtggcagctgtgctataagctgatccagcag
aagccaggagccctccctgggtatctcctgaactactaaacacacccatgcaagcaccag
gactcacatctgtagccgcttctctggatttgaggatgcctctgccagtgccagggctctg
ctcatctctggaggctgaccatcactgtgctaagatcatggcagtgggggcagctagtgt
taca

SEQ ID NO. 270 IGLV5-38-1 (P)

>IGLV5-38-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagcgcgcctccctctctgcacccctgggaacaacagccagactca
cctgcacccctgagcagtggttcaatatgtggggctaccatatattctggtaccagcaga
agccaggagccctccccgggtatctgctgaacttctactcagataagcaccagggctcca
aggacacctcggccaatgcagggatcctgctcatctctgggctccagcctgaggacgagg
ctgactactactgtaaaatctggtacagtggtctggt

SEQ ID NO. 271 IGLV5-40-1 (P)

>IGLV5-40-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctctgctaccagccaccccccttctctgcgtctccaggtactacagccagacccac
ctgcacccctgagcagtggtgcaacagtggtggcagctgttcttataacgggtcccacaaag
acagagggccctccctgggtatctgctgaggttcccccttaatagacacccatgtctctgga
tccacacataccttgggccaatgcagggtcctgctcat

SEQ ID NO. 272 IGLV5-42 (P)

>IGLV5-42*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagcctgtgctgaccaagtgccctctctttctgcatctcctggaacaacagtcagactca
 ctgtcacctggagcagtggtccagcactggcagctactatatacactgggtccagagcc
 acagagccagagccacagagctctccctgggtatctcctgtactactactcagactcagat
 aagcaccagggtctctgggttctcagctctgtctcctgatccaaggatgcctcagttatt
 ggagggctctctcatctctgggtgcagcctgaggattagactgaccttcactgtctaata
 cagaaacaataatgcttct

SEQ ID NO. 273 IGLV5-47 (P)

>IGLV5-47*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagcctgtgctgaccagctgccctccctctctgcataccggggaacaaactccagatgt
 acctacaccctgagcagtggtcgcaactactaaacatacttctcaagagaatacagggc
 accttccacagtacatcctgtactactactcagactcaagtgcagtgattgggatttggg
 tccagggcacttctctggatccaaagatgcctcagccaatgcagggatcctgctgatctc
 tgggtgcagccagaggacaagtctgactgtcactgtgctacagatcatggcagtgaggag
 cagcttccgatact

SEQ ID NO. 274 IGLV5-47-1 (P)

>IGLV5-47-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagccagggtgacccagccacactccctctctgcatacaggggagaacagccacacat
 acctgcaccctgagcgggtggtcctcagtggtggcagctgccatatactggatccagaag
 aagccagagagccctccctgatgtctcctgaactactactaagactcagataaggcctcg
 acgtccccagccctactctgaatccaaagacaccttggccaagtggaatcctgctcat
 ctctgggtgcagccggaggacaaggctgtctcttactgtataatatggcacagtggttc
 tggtcacagggaca

SEQ ID NO. 275 IGLV5-48-1 (P)

>IGLV5-48-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 caccctgtgctgaccagctgccctccctctctgcatacctgggaacaacagccagactc
 atgtgcaccctgagcagtggtgctgcagtggtggccatacgtggttccagcagccaggagg
 cctcctgagtacctgctgatggtctactgagactcaccagggccccgggtggccccagccg
 cttctctgggtccaaaggacacctcgccaatgcagggtcctgctcatctctaggctgca
 gcctgaggacgaggtgactgtcactgtgttacagaccatggcagtgaggagcagctcccg
 aaactca

SEQ ID NO. 276 IGLV5-49-1 (P)

>IGLV5-49-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagccagggtggtgccagcttccccccacctccctctgcatctccaggaacaacagccag
 actcacatgaaccatgagcagtggttcatcggtggcgtgctacatatactgggtccaa
 cagaagccaggagcaccgccccagtgatctcctgaggttctactcagactcagataagca
 ctagggtcaacgacccagccctgttctggatctgaagacacctccgccaagcagggc
 ctctgctcatctctgggtgcagcgtgaggacaaggctgactcttatgggacaatctggc
 acagtggtcctggtcacagggacaca

SEQ ID NO. 277 IGLV5-51 (P)

>IGLV5-51*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagcctgtgctgaccagctgccctccctttctgcatcctgggaacaacagccagactc
 acatgcaccctgagcagcgggtgcagcgggtggccacacattggttccagcagccaggagg
 cctcctgagtacctgctgatggtctactgagactcaccagggccccgggtggttgcagcct
 cttctctgggtccaaaggacacctcgccaatgcaggactcctgctcatctctgggtgca
 gcctgaggatgaggtgactgtcactgtgctacagaccatggcagtgaggagcagctccgg
 atact

SEQ ID NO. 278 IGLV5-53 (P)

>IGLV5-53*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagcctgtgctgaccagctgccctccctttctgcatcctggagaacaacagccagactc
 acctgcaccctgagcagtggtgctgagtggtggccatctgctggttccagcagccagggaag
 cctcctgagtatctgctgacggtcttctgagactcaccagggccccgaggtccccagcct
 cttctctgggtccaaaggacacctcagccaatgcaggactcctgctcatctctgggtgca

gcctgaggatgaggctgactgtcactgtgctacagaccatggcagtgaggagcagctcccg
atact

SEQ ID NO. 279 IGLV5-53-1 (P)

>IGLV5-53-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caccctgggctgaccagtcgtcctccctctctgcacccctgggaacaacagccagactc
acctgcaccctgagcagtggttcagaaatgacaggtatgtaataagttggttccagcag
aatcagggagcccttcctgggtgtcctgtattattactcgaactcaagtacacatttg
ggctctgaggttcccagctgcttctctggatccaagacaaggccaccccacactgagta
gacctctctctgggtgggtctagagctccagctccacctgaggctgatgcacaattgcag

SEQ ID NO. 280 IGLV5-57-1 (P)

>IGLV5-57-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagggtggcccagctgcctccctctctgcacccaggaacaacagccagactc
acatgaaccctgagcagtggttcattggtgggtgctacatatactggttccaaacag
agccagggagcatgccccagtatctcctgaggttctactcagactcagataagcacc
aggtctcaacatccccagccggctctggatctgaagacactcagccgaagcagggcctc
tgctcatctctgggtgcagcatgaggacaaggctgactcttactgtacaatctggcaca
tggtcctgggtcacagggaca

SEQ ID NO. 281 IGLV5-58-1 (P)

>IGLV5-58-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccattgccctccctctctgcacccctgggaataacaaccagactca
cttgactctgagcagcggctgcagcgggtggccatacagtggttccagcagcaaggaaagc
ctcctgagtacctgctgacgttctactgagactcaccagggctctagggtccccagccac
ttctctgggtttcaaggacaccagggccaatgcagggcact

SEQ ID NO. 282 IGLV5-59 (P)

>IGLV5-59*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagtcgcctccctctctcggtatcttgggaacaacagtcagactca
cctgtaccctgatcagtggtccagtggtggcagctattacatcaactggttccagaaga
agccaaggagccctcccgatctcctgtactactacttagactcagataagcaccagg
gctctgggttccccagctgcttctcctgatccaaggatgcctcagtcattggaggacacc
ctcatctctgaactgcagcctgaggactagactgaccttcgctgtctaatacagaacaat
aatgcttct

SEQ ID NO. 283 IGLV5-62 (P)

>IGLV5-62*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagcctccctctctctctgcacccctgggaacaatagccagacaa
acatgcagcctgagcaggggtacagtatggggacttatgtcatacgtggttccagcag
tagcaagaaactctcctgagtatctgctgaggttatactgagcctcagcaggtctctggg
gacccagctgagtccttagatccaagatgcctcagccaattcagggctcctgcttatct
ctgtgctgcagcctgaggacaagggttactattactgttctgtacatcatggaattgtga
gcagctatacttacc

SEQ ID NO. 284 IGLV5-64 (F)

>IGLV5-64*01|Canis lupus familiaris_boxer|F|V-REGION|
cagcttggtgagccagcgcctccctctctgcacccctgggatcatccgcccagactc
acctgcacctgagcagtggttcagtggtggcagttattctgtaacttggttccagcag
aagccagggagccctctctgggtacctcctgtactaccactcagactcagataagcaccag
ggctccaggggtccccagcgttctctggatccaaggacacctcgccaatgcagggtc
ctgctcatctctgggtgcagcctgaggatgaggctgactactactgtgcctccgctcat
ggcagtgaggagcaactaccattact

SEQ ID NO. 285 IGLV5-67-1 (P)

>IGLV5-67-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagtgtgacccagctgccctccttctctgtatctctgggaacaacagtcagactc
acctgcaccctgagcagtggttggcagctactaaacatccttttcaaggagaaaccaagga
gccccccaccccggtatctctatactactattcagactcagataaaacccaggtctctg
gggtccccagccacttctctgcacccaagactcctaggccaatgcagggtcctgctcg
cctctgggctgcagcctgaggacgaggtgactatcactgtgctataaatcatgacagtg
ggagtagttcctgatact

SEQ ID NO. 286 IGLV5-70-1 (P)

>IGLV5-70-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttggtgacccagcgccctcctctctgcacatctcctgaaacaacagtcagactca
catgcaccctgagcagtggtggccagctactacatacactggttccagtgga
agccacgggtgcccgcccggtatctcctgtactactactcagactcagatgagcaccagg
gtcctgagtacctgctgatggtctactgagactcaccaggctatgggtccccagcatct
ctcatctctgggtacagtgctgaggtctacactgaccttcactgtctaatacggaacaat
aatgtttct

SEQ ID NO. 287 IGLV5-72-1 (P)

>IGLV5-72-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagcgacctccctctctgcacccctgggaacaacagccagactca
cctgcaccctgagcagcggtgaagcggtggccatacgtggttccagcagccaggaagc
ctcctgagtacctgctgatggtctactgagactcaccaggctatgggtccccagcatct
tctctgggtccaaggacacctcggtccaatgcagggtcctgctcatctctgggtgcagc
ctgaggtcgaggctgactgtcactgtgctacagaccatggcagtgaggagcagctcccgat
act

SEQ ID NO. 288 IGLV5-76 (P)

>IGLV5-76*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagtcgccctccctctcagcatctttggaacaacagtcagactca
cctgtacccctgagcagtggtccagtggttggcagctattacatcaactggttccagaaga
agccacggagccctccccagtatctcctatactactacttagactcagataagcaccagg
gtcctgggggtccccagctgcttctcctgatccaaggatgcctcagtcattggagggcacc
ctcatctctgagctgcagcctgaggactagactgaccttcgctgtctaatacggaacaat
aatgcttct

SEQ ID NO. 289 IGLV5-77 (P)

>IGLV5-77*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagccacctccctctctgcacccccgggaacaacagccagactc
acctgcaccctgagcagtggttccagtggttgggtgactatgacatgtactggtaccagaag
aagccaggaagccccaccccggtatctcctgtactactactcagactcatataaacacc
agggtccgggggtctccagcagcttctctggatccaaggatacctcagccaatacagggc
tctgtctcatctctgggccacagcctgaggacgaggtgactactactgtgctacagatc
atggcagtgagagcaggtactcttacc

SEQ ID NO. 290 IGLV5-77-1 (P)

>IGLV5-77-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctctgctacccagcacccttctcgtgcgtttccaggtactacagccagaatcacc
tgcaccttgagcaggggcatcagtggttgggagctgttcttataacgggtcccgagagg
cagggagccctgctgggtatctgctgaggttccctctaatagacaccacatctctggat
ccaaagaaacctcggtccaatgcagggtcctgctcattgttgtgctgccacctgacaact
agtctatcagtggtggttgaggactaggactattactgggatgctttggttt

SEQ ID NO. 291 IGLV5-78-1 (P)

>IGLV5-78-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttgctgatccagcgccctccctctctgcacatctcctggaacaacagtcagactca
cctgcacccagagcagtggttggcagctactacatacactggttccagtgga
agccatggagccctccctggtatcttctgtactactaatcagactcagatgagcaccagg
gtcctgggggtccccagcgcttctcctgatccaaggatgcctcagccagagcaggggtcc
ctcatctctggactgcagcctgaggactagactgaccttcactgtctaatacagaacaat
aatgttt

SEQ ID NO. 292 IGLV5-83-1 (P)

>IGLV5-83-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tgcagggtccctgtcccagcctttgcccctccctctttgcatctcctggaagaacagtcaga
tccacctgcacccagagcagtggtgcccctgtgttggtgagctactacatacaccggttccag
tggaagccacggagccgtctccatatctcctgtactactactcagactcagatgagcacc
agagctctggagtccccaaactgcttctcctgatccaaggatgcctcaggaaggcagggc
tccctcatctctgggtacaggtgaggacaagactgacctttactgtctaataccaaaac
aataatgtttct

SEQ ID NO. 293 IGLV5-85 (F)

>IGLV5-85*01|Canis lupus familiaris_boxer|F|V-REGION|
cagcctgtgctgacccagccaccctccctctctgcatccctgggatcaacagccagaccc
acctgcacccctgagcagtggttccagtgttggaagctaccatatactctggttccagcag
aagtcagagagccctcccgggtatctcctgaggttctactcagattctaataaacaccag
ggtcccgggtcccagccgttctctggatccaaggacacctcaacctatgcagggtc
ttgtctcatctctgggtgcagcctgaggacgaggctgactactactgtgtctacagaccat
ggcagtgaggagcagctacacttacc

SEQ ID NO. 294 IGLV5-86-1 (P)

>IGLV5-86-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttgctgacccagcgcctccctctctgcatctcctggaacaaaagtcagactca
cctgcatccagagcagtggtggtggcagctactacatacactggttccagtaga
agccatggagccctcccagtatctcctgtactactacttagactcagataagcactagg
cctatggggaacccagatccttcccctgatccaaggatgcctcagtcagtgcagggtcaa
agagaggggattatttagagtggacaattggggcctttggccaggag

SEQ ID NO. 295 IGLV5-88-1 (P)

>IGLV5-88-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagtgcagaccagctgcctccttctctgtacctctgggaacaacagccagactc
acctgcacccctgagcagtggttggcggccagtaaacatccttttcaaggagaaaccaagga
gccccccagctctcctgtactattaccagactcagataaacccccaggtctctggggtc
cccagccacttctctgaatccaaagactcctaggccaatgcagggtcctgtctgcctct
gggctgcagcctgaggacgaggctgactatcactgtgtgtgtaaatcatgacagtgggagc
agctccgatact

SEQ ID NO. 296 IGLV5-89-1 (P)

>IGLV5-89-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtggtgacccagcttcccttctctgcatccctgggaacaacagccagactcacat
gcacctgagctgtggttccagtattgatagatatgctataaactggttccagcagaagg
cagagagccttcccgtgtactactgtgtattactgtgtactcaagtacacagttgggt
tcagcgtcccagctgcatctctggatccaagacaaggccacattcacaacagtagac
ccatctctggttgggtctagagctccagccccacctgagactgatgcacaattgcagc

SEQ ID NO. 297 IGLV5-92-2 (P)

>IGLV5-92-2*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtatagaccagtcacccctcccttctgcatctttggaacaacagtcagagtca
cctgtacccctgagcagtggttccagtgttggtgagctactacatactggttccaggaga
agccatggagcaatccccgggtatctcctgtactactcagggtcagatgagcaccagggt
ctgggatccgtagctgttctcctgatacaatgatgcctcagccaaggcagagctcccta
atctctgggctgcagcctgaggactatactgacctcactgtctaatacagaacaataat
cctttt

SEQ ID NO. 298 IGLV5-94-1 (P)

>IGLV5-94-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tagcctgtgctgacccagcgcctcccactctgcatccctgggaacaacagccagactca
cctgcgcctgagcagcgggtgcagcagtgaccatacgtgtggttccagcagccagaaggc
ctcctgagtacctgctgacggtctactgagactcaccagcgcctccgggtcctcagcctc
ttctctgggtccaaggacacctcgccaatgcagggcactcagatgg

SEQ ID NO. 299 IGLV5-95 (P)

>IGLV5-95*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgatgacccagctgtcctccctctctgcatccctggaaacaacaaccagacac
acctgcaccctgagcagtggttcagaaataacagctgtgtaataagttgattccagcag
aagtcagggagccctccctgggtgtcctctgtactattactcagactcaagtatacatttg
ggctctgaggttcccagctgttctctggatccaagacaaggccaccccactgagta
gacccatccctgggtgggtctagagctccagccccactggaggctgatgcacaattgcag
c

SEQ ID NO. 300 IGLV5-96-1 (P)

>IGLV5-96-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caacctttgcggaaccagcgcactccctctgcatctcctggaaacaacagttagactcatc
tgacccagagcagtggtccctggtggcagctactacaaacactggttccagcagaag
ccacggagccctcccggtacttctgtactacttctcagactcagatgagcaccagggc
tctggggagccgcagccaattctcctgatccaaggatgactcaggaaaggcagggtccct
catctctgggtacagcctgaggactagactgaccttactgtctaatcagaaacaataa
tgcttct

SEQ ID NO. 301 IGLV5-97-1 (P)

>IGLV5-97-1*01|Canis lupus familiaris_boxer|P|V-REGION|
ttaaacaaccaaccaaccaaccaaccaaccaaccaaccaaccaataacagccagattc
acctgtccctgagcagtggttcagtggtgggtggtataacacactggtaccagcagaa
gccagggagccctccctgttacctcctgtactactactcagaatcagataaacaccatgg
ctccgggatcaccagctgttccctggccctatggacacctcgcccaatgcagggtccct
gctcatctcagggtgcagcctgaggacgaggctgactactactgcggtatactccacag
cagtgaggagcagctactcttacc

SEQ ID NO. 302 IGLV5-97-2 (P)

>IGLV5-97-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgaggacacactcctcctcctctctgcatccctgggatcatcaaccagactc
acctgcateccttcccagggcctgaatggtggcaggtactgaacatactggacaaggagaa
tcaaggagacatcaggagttccctcagatccagataagtgccagggcacggggttctcag
ccacttctatggatctaataatgatgcctcaggcaatgcagggtcctcctgctcatgtctgggt
gcagcctgaggacgaggtgactatgactatgctgcacattgtgggtgggagcagctcc
cgatact

SEQ ID NO. 303 IGLV5-97-3 (P)

>IGLV5-97-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagcgcctccctctctgcatccctgggaacaacagccagactc
acctgcaccctgagcagcagctgcagcgggtggccatagctggttccagcatgcaagagg
cctcctgagtacctgtgatggtctactgagactcaccagggccctggggtccccagcct
cttctctggtcccaaggaagcctcgcccaatgcagggtcctgctcatctctgggtgca
gctgagaatgaggtgactgtcactgtgctacagaccatggcagtgggaaacagctccca
atact

SEQ ID NO. 304 IGLV5-101-1 (P)

>IGLV5-101-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttgctgacccagcgtcctccctctctgcatctcctggaaacaacagtcagactca
catgtaccctgagcagtggtcccggtgctggcagctactacacacactggttccagcaga
ggccacagagtcctccccgggtatctcctgtactactactcagactcagatgatctccagg
gtccgggttccccagccactcctcctgatccaaggatgcctcagccagggcagggtcc
catctctgggtacagcctgaggactacactgaccttactgtctaatcggaacaataa
tgtttct

SEQ ID NO. 305 IGLV5-103-1 (P)

>IGLV5-103-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagggtggtggccagctgccccccacctccctctgcatctccaggaacaacagccag
actcacatgaacctgagcagtggttcattgttggcagctgctacatatactggtcca
acagaagccaggaggccccccctcccccaatatctcttgagggttgattcagaatcagata
aacaccagggtcfaatgtccccagccctgctctggatctgaagacacctccgccaagca
gggcctctgctcatctctgtgggtgcagcgtgaggacaaggctgactcttactgtacaatc
tgg

SEQ ID NO. 306 IGLV5-105 (P)

>IGLV5-105*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagcgcgcctccctctctgcatccctgggaacaacagccagactc
acctgcacctgagcagcagctacagtggtggccataactggttcagcagccaggagg
cctcctgagtacctgctgatggtctactgagatttaccaggggcccggtccccagccg
cttctctggctccaaggacatctcgccaatgcagggtcctgctcatctctgggtgta
gcctgaggacgaggctgactgtcactgtgctacagaacatggcagcgggagcagctccca
atact

SEQ ID NO. 307 IGLV5-105-1 (P)

>IGLV5-105-1*01|Canis lupus familiaris_boxer|P|V-REGION|
ctgcctctgctaccagccacgccttctctgcatctccaggtactacagccagaccac
ctgcacctgaacagtggtcagcagcttctccttataatggctcccgcaaag
gcaggagccctgctggtatctgctaagggtgtactctaataaataccatggcttagg
gtcccaagccacatctctggatccaaagaacctc

SEQ ID NO. 308 IGLV5-106-1 (P)

>IGLV5-106-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttgctgaccagcgtccctccctctctgcatctcctgggaacaacagtcagactca
cctgtatccagagcagtggtggccagtggtggcagctactacatacaccggttcagcgga
aaccacggagccctccctgtatctcctgtactactactcagactcagataagcactagg
cctacagggtccccagctgcttctcctgatccatggatgcctcagccagtgagtgctcc
ctcatctctgggtacagcctgaggactagactgaccttactgtctaatecgaaacaat
aatgcttct

SEQ ID NO. 309 IGLV5-109 (F)

>IGLV5-109*01|Canis lupus familiaris_boxer|F|V-REGION|
cagcttgtgctgaccagcgcgcctccctctctgcatccctgggatcaacaaccagactc
acctgcacctgagcagtggttcagtggtgggtgctatagcatatactggcaccagcag
aagccaggagcactccctggtagcctcctgtactactactcaagtaacagagttgggacct
ggggtccccagctgcttctctggatccaaagacacctcagccaatgtagggtcctgctc
atctcagggtgcagcctgaggatgagactgactactactgtgctatagggtcacggcagt
ggagcagctacacttacc

SEQ ID NO. 310 IGLV5-110-1 (P)

>IGLV5-110-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagggtggtggccagctgccccccacctccctctgcatctccaggaataacagcca
gactcacatgaacctgagcagtggttcattgttggcgcgtgctacatatactgattcc
aacagaagccaaggagccccgcctccaccagtatctcctgatattctactcagactcaga
taagcaccagggtcfaatgtccccagccctgctctgaatctgaagacacctccgccaagc
agggtctctgctcatctctgggtcagcgtgaggacaaggctgactcttactgtacaatc
tgg

SEQ ID NO. 311 IGLV5-111-1 (P)

>IGLV5-111-1*01|Canis lupus familiaris_boxer|P|V-REGION|
tagcctgtgctgaccagtgctctccctctctgcatccctgggaacaacagccagactcc
cctgcacctgagcagcggtgcagcggtgtccatacgcaggttcagcagccaggaggc
ctcctgaataacctgctgatggtctacgggtgactcaccaggggccccgggtccccagccgc
ttctctgggtccgaggacacctcgccaatgcagggtcctgctcatctctgggtgcag
cctgaggacaagactgactgtcactgtgctacagaccatggcagtaggagcagttcccaa
tact

SEQ ID NO. 312 IGLV5-111-2 (P)

>IGLV5-111-2*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagctgcccttctctctgcatccctggagacaacaagcagatgt
acctacaccagagcgggtgtcggcagctactacacatactcatcaaggacaatccaggga
gacctccctgggtatttctgtactactactcagactcaactacatggttgggatttgggtg
tccccaaaccttctctgtatccaaagatgcctcagccaatgcagggtcctgctcatct
ctgggctgcagccagaggacaaggatgactgtcactgtgctgcattcagatcatggcagt
gggagcagctcccatact

SEQ ID NO. 313 IGLV5-113-2 (P)

>IGLV5-113-2*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctttgtgatccagtgccctccctctctgcatctcctggaacaagagtcagactca
cctgcacccagagcagtggtggccccagggttggcagctactacatactggttcagcgga
aaccacggagccctcctcagtatctcctgtactactactcagaatcagatgagcaccagg
gctctgggggtccccagccacttctcctgatccaaggatgcctcaggcaaggcagggtcc
ctcatccctgggtacagcctgagggtagactgaccttactgtctaataccgaaacaat
aatgtttct

SEQ ID NO. 314 IGLV5-114-1 (P)

>IGLV5-114-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagccagggtggtggccagctgccctccctctctgcatctccaggaacaacagccagactc
acatgaacctgaacagtggttcttcttggcggtgatacatatacttgttccaacag
aaaccagggaacccccgctccccgtattgctgaggttctactcagactcagataagcac
cagggtcacaatccccagccctgctctggatctgaagacacctcaactgaagcagggtcc
tctgctcatctctggatgtccagcgtgaggacaagggttgattcttactgtacaatctggc
acagtggctcctggt

SEQ ID NO. 315 IGLV5-115-1 (P)

>IGLV5-115-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctctgctgaccagccacctccctctctgcatccctgggaacaagaccagagtc
acctgcacctgagcaacaactgcagtggtggccatacgtggttccagcagccagggaag
cctcctgaatacctattgatggtttactgagacttaccagggcccccggggccccagctg
cttctctgggtccaaggacaccttgccaatgcaggactcctgctcatctctgggtgta
gctgaggatgaggtgactgtcactgtgctacagaccatggcagtgaggagcagctcccg
atact

SEQ ID NO. 316 IGLV5-118-1 (P)

>IGLV5-118-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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gcacctgagctatggcttcagtattgatagatatgttataagctggttccagcagaagg
cagagagccttccctggtacctactgtactattactgatactcaagtacacagttgggt
tcggcattcccagctgcgtctctggatccaagacaaggccacattcacaatgagtagac
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cattgtcttgatatccgaaa

SEQ ID NO. 317 IGLV5-124-1 (P)

>IGLV5-124-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtatagaccagtcacctccctttctgcatctttggaacaacagtcagactca
cctgtaccttgagcagtggttccagtgttggcagctactacatactggttccaggaga
agccatggagcaatccccgggtatctcctgtactattcaggctcagatgagcaccagggt
ctgggatccctagctgcttctcctgatccaaggatgcctcagccaaggcagagctccctc
atctctgggtgctgcagcctgaggactagactgaccttactgtctaatacagaacaataat
gcttct

SEQ ID NO. 318 IGLV5-125-1 (P)

>IGLV5-125-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagcgcctccctctctgcatccctgggaacaacagccagactca
cctgcaccttgagcagcgggtgcagcgggtggccatatgctggttccagcagccagaaggc
ctcctgagtacctgctgacggtctactgagactcaccagggccccctgggtcctcagcctc
ttctctgactccaaagacacctcgccaatgcagggcactcagatggctgtgaagttcat
acaacagggtcctcatgggggtcatgggtaccacttcacgttt

SEQ ID NO. 319 IGLV5-126 (P)

>IGLV5-126*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgatgacccagctgtcctccctctcagcatccctggaaacaacaacaagactc
acctgaaccctgagcagtggttcagaaatgacagatgtgtaataagttggttcagcag
aagtcaggaggccctccctggtgtcctgtactattactcggactcaagtacacatttg
ggctctgagggttccagctgttctctggatccaagacaaggccaccccacactgagta
gacccatccccgggtgggtctagagctccagcccactggaggctgatgcacaattgcag
c

SEQ ID NO. 320 IGLV5-128-1 (P)

>IGLV5-128-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caacctttgcggaaccagcgccctccctctctgcattcctggaaacaacagttagactca
tctgcacccagagcagtggtggccctggtggcagctactacaaacactggttcagcaga
agccacggagccctcccggtacctcctgtactactactcagactcagatgagcaccagg
gctctggggaccacagccacttctcctgatccaaggatgcctcaggaaaggcagggtcc
ctcatctctgggtacagcctgaggactagactgaccttcactgtctaatacagaacaat
aatgcttct

SEQ ID NO. 321 IGLV5-129-1 (P)

>IGLV5-129-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagctgcctctctgcattcctggaaacaacaggcagatgtactta
cacctgagcagttttggcagctactacacatactcgtcaaggagaatacaggagagact
ccctggtatttctgtactactactcagactcaactacatggttgggatttgggggtccc
aaccatttctctggatccaaagatgcctcagccaatgcagggtcctgctcatctctggg
ctgcagccagaggacaaggatgactgtcactgtgctgcatacatatcaaggcagtggaag
cagctcccaatact

SEQ ID NO. 322 IGLV5-129-2 (P)

>IGLV5-129-2*01|Canis lupus familiaris_boxer|P|V-REGION|
ctgctgtgctgacccagtgccctccctctctgcattcctggaaacaacagccagactca
cctgcacccctgagcagtggtgctgcagcggtggccatatgctggttcagcagccaggaggc
ctcctaagtacctgctgatggtctactgagactcatcacgggtcctgggtccctagcctc
ttctctgggtccaaggacacctcgccaatgcagggtcctgctcatctctgggtgcag
cctgaggacgaggctgactgtcattgtgctacagaccatggcagtgaggagcagctcctga
tact

SEQ ID NO. 323 IGLV5-131 (F)

>IGLV5-131*01|Canis lupus familiaris_boxer|F|V-REGION|
cagcctgtgctgacccagccacccctccctctctgcattcctggaaacaacagccagactc
acctgcacccctgagcagtggttcagtggttggtgactatgacatgtactggtaccagcag
aagccaggaggccctccccgggatctcctgtactactactcggactcatataaaaaccag
ggctctgggtctccaaaagcttctctggatccaaggatacctcagccaatgcagggtc
ctgctcatctctgggtgcagcctgaggacgaggctgactactactgtgctacagatcat
ggcagtgagagcagctactcttacc

SEQ ID NO. 324 IGLV5-132-1 (P)

>IGLV5-132-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtatagaccagtcacccctccctttctgcattcctggaaacaacagtcagactca
cctgtaccctgagcagtggttcagtggtggcagctactacataactggttcaggaga
agccatggagcaatccccgggtatctcctgtactactcaggctcagatgagcaccagggt
ctggggtccctagctgtttctcctgatccaaggatgcctcagccaaggcagagctccctc
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gcttct

SEQ ID NO. 325 IGLV5-134 (P)

>IGLV5-134*01|Canis lupus familiaris_boxer|P|V-REGION|
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 acctgcaccatgagcagcagctgcagcgggtggccatatgctgggtaccagcatgcaagagg
 cctcctgagtacctgctgatgggtctactgagactcaccagggccctgggggtccccagcct
 ctctctgggtccaaggacaccttgccaatgcagggtcctgctcatctctgggtgca
 gctgagaatgagggtgactgtcactgtgctacagaccatggcagtgaggaaacagctccca
 atact

SEQ ID NO. 326 IGLV5-134-1 (P)

>IGLV5-134-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 taaaaccaaaccacaaaccaaaccacaaacacaaacacaaacacaaataacagccagattc
 acctgctccctgagcagtggtgttcagtggtgggtggtataacacactgggtaccagcagaa
 gccaggagccctccctgttacctcctgtactactactcagaatcagataaacaccatgg
 ctctgagtacctgctgatgggtctactgagactcaccaggctatgggggtccccagcatct
 gtcataccttgggtgcagcctgaggacgagggtgactactactgcggtatactccacag
 cagtgggagcagctactcttacc

SEQ ID NO. 327 IGLV5-135-1 (P)

>IGLV5-135-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 aagcctgtgctgacccagcgcgcctccctctctgcatccctgggaacaacagccagactca
 cctgcaccctgagcagcgggtgagtggtgggtataggctgggtccagcagccagggaagc
 ctctgagtacctgctgatgggtctactgagactcaccaggctatgggggtccccagcatct
 tctctgggtccaaggaagcctcggccaatgcagggtcctgctcatctctggcctgcagc
 ctgagggtcagggtgactgtcactgtgctacagaccatggcagtgaggagcagctcccgat
 ac

SEQ ID NO. 328 IGLV5-137-1 (P)

>IGLV5-137-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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 cctgtaccgtgaacagtggtccagtggtggcagctattacatcaactgggtccagcata
 agccatggagctctccctagtatcacctgtactactacttagactcagataagcaccagg
 gctctgggggtccccagctgcttctcctgatccaaggatgcctcagtcattggagggcacc
 ctcatctctgggtgcagcctgaggactagactgaccttcacgtctaatacagaacaata
 atgcttct

SEQ ID NO. 329 IGLV5-137-2 (P)

>IGLV5-137-2*01|Canis lupus familiaris_boxer|P|V-REGION|
 ctgcctgtgctgacccagcgcgcctccctctctgcatccctgggatcaacagccagactc
 acctgcacactgagcagtggtgcagcgggtggccatatgctgggtccagcagccaggagg
 cctcctgtgtacctgctgatgggtctactgagactcaccagggccccagtggtccccagcca
 ctactctgggtttcaaagacacctcggccaatgcagggtcactcagatagctgcgaaattca
 tacaacaagggtcctcatggggactcatgggcaccccttcagattttctgctgcatga
 acag

SEQ ID NO. 330 IGLV5-138-1 (P)

>IGLV5-138-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagggatggcccagctgttccccacctccctctgcatctccaggaaacaacagccagact
 cacatgaaccatgagcagtggttcatgttggtggcgtgtacataactgggttccaaca
 gaagccagggtgagtcctctcccccatatctcctgagtttctactcagactcagataagc
 accaggggtcaaaatccccagcctgttctggatctgaagacacctcagccaaagcagcg
 cctctgctcatctctgggtgcagggtgaggataagaatgactcttactctacaatctgg

SEQ ID NO. 331 IGLV5-139-1 (P)

>IGLV5-139-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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 tctgcacccagagcagtggtggcctcagtggtggcagctactacaaacactgggtccagcaga
 agccacggagccctccccagctacctcctgtactacttctcagactcagatgagcaccagg
 gctctggggactgcagccacttccctgatccaaggatgcctcaggaagcaggggtccc
 tcatctctgggtacagcctgaggactagactgaccttcactgtctaatacagaacaata
 atgcttcttacagt

SEQ ID NO. 332 IGLV5-145 (P)

>IGLV5-145*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgacccagcgccctccctctctgcatccctgggaacaacattcagactc
acctgcacccctgagcagcagctgcagcgggtggccatatgctgggtccagcatgcaagagg
cctcctgagtacctactgatggctactgagactcaccagggccctgggggtccccagcct
cttctccggctccaaggacaccttgcccaatgcagggtcctgctcatctctgggctgca
gctgagaatgaggctgactgtcactgtgctacagaccatggcagtggggaacagctccca
atact

SEQ ID NO. 333 IGLV5-145-1 (P)

>IGLV5-145-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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acctgcatccttcccagggcctgaatgttggcaggtactgaacatactggacaaggagaa
tcaaggaggcatcaggagttccctcagatccagataagtgccagggcacgggttctcag
ccacttctatggatctaataatgatgcctcaggcaatgcagggtcctgctcatgtctgggt
gcagcctgaggacgaggtgactatgactatgctgcacattgtgggtgggagcagctcc
cgatact

SEQ ID NO. 334 IGLV5-146-1 (P)

>IGLV5-146-1*01|Canis lupus familiaris_boxer|P|V-REGION|
aagcctgtgctgacccagcgcccttctctctgcatccctgggaacaacagccagactca
cctgcacccctgagcagcgggtgagtggtggctataggctgggtccagcagccaggaagc
ctcctgagtacctgctgatggctactgagactcaccaggtatgggggtccccagcatat
tctctgggtccaaggaagcctcggccaatgcagggtcctgctcatctctgggtgcagc
ctgagggtcagggtgactgtcactgtgctacagaccatggcagtgaggagcagctccgat
act

SEQ ID NO. 335 IGLV5-148 (P)

>IGLV5-148*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtgggtaccaaggatccatcactctcagtgtttccaggaggacagtcacattc
acatgtggcctcagctctgggtcagctctttacaagtaactacccagctgggtaccagcag
acccatggccgggtcctcaccatgcttatctacagcacaagcagctgccccccgggggtc
cctgatcgcttctctggatccatctctgggaacaaagttgcctcaccatcacaggagcc
cagcctgaggatgagactattattgttcaactgcgtatgggtagtagcattta

SEQ ID NO. 336 IGLV5-148-1 (P)

>IGLV5-148-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctaaccagctcgccctccctcttgacatctttggaacaacagtcagactca
cctgtaccgtgaacagtggtccagttattggcagctattacatcaactgggtccaggaga
agccatggagctctccctgggtatcacctatactacttcttagactcagataagcaccagg
gctctgggggtccccagctgcttctcctgatccaaggatgcctcagtcattggagggcacc
ctcatctctgggtgcagcctgaggactagactgaccttcaactgtctaatacagaacaat
aatgcttct

SEQ ID NO. 337 IGLV5-148-2 (P)

>IGLV5-148-2*01|Canis lupus familiaris_boxer|P|V-REGION|
ctgcctgtgctgacccagcgccctccctctctgcatccctgggatcaacagccagactc
acctgcacactgagcagtggtgcagcggtagccatatgctgggtccagcagccaggagg
cctcctgggtacctgctgatggctactgagactcaccagggccccagtggtccccagcca
ctactctggatgcaaagacacctcgccaatgcagggt

SEQ ID NO. 338 IGLV5-149-1 (P)

>IGLV5-149-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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cacatgaaccatgagcagtggtcttattgttggcggtgctacataactgggtccaaca
gaagccaggagggtccccctcccccatatctcctgagtttctactcagactcagataagc
accaggggtcaaaatccccagccctgttctggatctgaagacacctcagccaaagcagcg
cctctgctcatctctgggtgcagggtgaggataagaatgactcttactctacaatctgg

SEQ ID NO. 339 IGLV5-150-2 (P)

>IGLV5-150-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caacctttgcggaaccagcgcaactccctctgcatctcctggaacaacagttagactcatc
tgacccagagcagtggtggccagtggtggcagctactacaaacactgggtccagcagaag
ccacggagccctccccggtacttcctgtactacttctcagactcagatgagcaccagggc
tctggggaccgcagccacttctcctgatccaaggatgactcaggaaaggcagggtccct
catctctgggtacagcctgaggactagactgaccttcactgtctaatcagaaacaataa
tgcttct

SEQ ID NO. 340 IGLV5-154-1 (P)

>IGLV5-154-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgatgaccagctgtcctccctctctgcatccctggaacaacaaccagacac
acctgcaccctgagcagtggtgttcagaaataacagctgtgtaataagttgattccagcag
aagtcaggagccctccctgggtgtcctgtactattactcagactcaagtatacatttg
ggctctgaggttcccagctgcttctctggatccaagacaaggccaccccacactgagta
gacccatccctgggtgggtctagagctccagccccactggaggctgatgcacaattgcag
c

SEQ ID NO. 341 IGLV5-155-1 (P)

>IGLV5-155-1*01|Canis lupus familiaris_boxer|P|V-REGION|
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cctgtaccgtgaacagtggtccagtggtggcagctattacatcaactgggtccagtata
agccatggagctctccctagtatcacctgtactactacttagactcagataagcaccagg
gctctgggttcccagctgcttctcctgatccaaggatgcctcagtcattggaggggcacc
ctcatctcggtgtgcagcctgaggactagactgaccttcactgtctaatcagaaacaat
aatgcttctaacagtga

SEQ ID NO. 342 IGLV5-157-1 (P)

>IGLV5-157-1*01|Canis lupus familiaris_boxer|P|V-REGION||
cccagcgccctttctctctgcatccctgggaacaacagccagactcacctgcaccctgag
cagcggtagagtgggtggctataggctgggtccagcagccaggaagcctcctgagtacct
gctgatgggtctactgagactcaccaggtatgggttcccagcatcttctctgggtccaa
ggacacctcggtcaatgcagggtcctgctcatctctgggtgcagcctgaggtcgaggc
tgactgtcactgtgctacagaccatggcagtgaggagcagctcccgata

SEQ ID NO. 343 IGLV5-158-1 (P)

>IGLV5-158-1*01|Canis lupus familiaris_boxer|P|V-REGION|
ataacagccagattcacctgtccctgagcagtggttcagtgttggtggctataacaca
ctgggtaccagcagaagccaggagccctccctgttacctcctgtactactactcagaatc
agataaacaccatgggtccgggatcaccagctgcttccctggccctatggacacctcggc
caatgcagggtcctgctcatctcagggtgcagcctgaggacgaggctgactactactg
cgtatactccacagcagtgaggagcagctactcttacc

SEQ ID NO. 344 IGLV5-158-2 (P)

>IGLV5-158-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgacgacacactcctcctcctctctgacaccttgggatcatcaaccagactc
acctgcacccctccagggtcctgaatggtggcaggtactgaacatactggacaaggagaa
tcaaggaggcatcaggagttccctcagatccagataagtgccaggggcaggggttctcag
ccacttctatggatctaataatgatgcctcaggcaatgcagggttccctgctcatgtctgggt
gcagcctgaggacgaggtgactatgactatgctgcacattgtgggtgggagcagctcc
cgatact

SEQ ID NO. 345 IGLV5-158-3 (P)

>IGLV5-158-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagcctgtgctgaccagcgccctcctcctctctgcatccctgggaacaacattcagactc
acctgcaccctgagcagcagctgcagcggtggccatagctgggtccagcatgcaaggag
cctcctgagtacctactgatggtctactgagactcaccagggccctgggggtcccagcct
cttctctgggtccaaggacaccttggccaatgcagggtcctgctcatctctgggtgca
gctgagaatgaggtgactgtcactgtgctacagaccatggcagtggggaacagctccca
atact

SEQ ID NO. 346 IGLV7-32-2 (P)

>IGLV7-32-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtggtgactccagagcccttctgaccatcccaggagtgacagtcacttttacc
tgtgactccagcactggagagtcattaatagtgactatccacgttagttccagcagaagc
ctagacaaactcgaccacacacacacacaaacactcacggactccccccagttctcagg
ctccctccaggctcaaaactgcctcacctttttggggtcccagcctgagaaagaagggtg
agtactaccatatgctgggtctatcttggttcttgg

SEQ ID NO. 347 IGLV7-33 (P)

>IGLV7-33*01|Canis lupus familiaris_boxer|P|V-REGION||
caggctgtggtgactcaggaaccctcactgaccgtgtccctggaggagacagtcactctca
cctgtgcctccagcactggcgaggtcaccaatggacactatccatactggttccagcaga
agcctggccaagtccccaggacattgatttataatacacacataataactcctggaccct
accggttctcaggctgcctctttgggggcaaagctgccttgaccatcacaggggccag
cccaggatgaagctgaggactactgctggctagtatatatggtaatagg

SEQ ID NO. 348 IGLV7-36-1 (P)

>IGLV7-36-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtggtgattcaggaatcctcactaacagtgtccccaggagggaacactctcacct
gtgcctcgaaactggcacagtcaccaatgtcagtatccttactggtttcagcagaaccc
tagtcaagtcccccagggcattgacttaggatacaagcaataaacacttctggatccctac
caagctttcagtttccctccttggtgtaaaactccctgaccttctctggttccctagc
ctgaggccaaggctgattaccactggtgggtactcatagtggtgctgca

SEQ ID NO. 349 IGLV7-38-2 (P)

>IGLV7-38-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctcatggtgactcaggagccttcatggccatgtcccaggaggagacagtcactctca
cctatgcctccagcacaggacactatccatactggatccaagaaaatattggccaagtca
gggccattttatttataataaaaaacaacaaatactgatttctcatgctcccttcttgggag
caaactctgacatgaccatctcctagtgtcccagcctgaggacgaggatgagtaccatggg
ggtacactatagtgggtgctggg

SEQ ID NO. 350 IGLV7-43-1 (P)

>IGLV7-43-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtggtgactcaggagccttcatggctcgtgtcccaggaggagacagtcactctca
ctatgcctccagcacagaacactatccatactggatccaggaaaatattggccaagtcta
gagcattttatttataaaaagaaacaataaatactgatttctaggtcccttcttgggaata
aatctgacttgaccatctgctagtgtgcgcagcctgaggacgaggctgagtaccctagggg
ttacac

SEQ ID NO. 351 IGLV7-44-1 (P)

>IGLV7-44-1*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgatgactcaggagtcctcactaacagtgtcccaggaggagacattcactctc
acctgtgcctccagccactggcatagtaacaatgtcagtatccttctcgtgtttaccag
aagcctggccaagttcccagggcattgatttaggatacaagcaatgaaattcctggacc
cccaccaagtgtcagggttcccttctgtggagcaatattctcctgaccctctacagtgcct
tggtgagaacatagctgagtggaactgggtggtgctgttttattgtgatgctgggtgc

SEQ ID NO. 352 IGLV7-84-2 (P)

>IGLV7-84-2*01|Canis lupus familiaris_boxer|P|V-REGION|
caggctgtgatgactcaagagtcctcactaacagtgtcccaggaggagacattcactctc
acctgcgcctccagctactggcatagtaacaatgtcagtatccttactgggttttagcag
aatcctggccaagttcccagggcattgatttaggatacaagcaatgaacacacctggacc
cccaccatgtgtcagggttcccttctgtggagcaatattctcctgaccctctacagtgcct
tggtgagaacatagctgagtggaactgggtggtgctgttttattgtgatg

SEQ ID NO. 353 IGLV7-90-2 (P)

>IGLV7-90-2*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggtggcataggagccttcatggccatattcccaggaggagacagtcactctca
cctatccctccagcacaggacactatctatactggatctagtagcatactggccaagtct
aggtcattttatttataataaaaaacaataaatactcatagacctccactcatttctcaggc

tcccatcttgggggcaaactctgactggattgtcccctagtgccagcctgaggatgaggc
tgagtaccgctggggtacacatatggtggtggtggg

SEQ ID NO. 354 IGLV7-120-1 (P)

>IGLV7-120-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggtggcataggagccttcatggccatatcccagggaggacagtcactctca
cctatccctccagcacaggacactatctatactggatctagtagcatactggccaagtct
aggtcattttatttataataaaaaacaataaatactcatagacctccactcatttctcaggc
tcccatcttgggggcaaactctgactggattgtcccctagtgccagcctgaggatgaggc
tgagtaccgctggggtacacatatggtggtggtggg

SEQ ID NO. 355 IGLV8-36 (F)

>IGLV8-36*01|Canis lupus familiaris_boxer|F|V-REGION|
cagactgtggtgacccaggagccatcactctcagtgctctctgggagggacagtcaccctc
acatgtggcctcagctctcggtcagtcctctacaagtaactaccccaactgggtcccagcag
acccagggcaggctcctcgcatgattatctacaacacaaacagccgccctctggggtc
cctaatacgcttctcagtgatccatctctgggaacaaagccgcctcaccatcacaggagcc
cagcctgaggacgaggctgactactactgtgctctgggattaagtagtagtagtagtta

SEQ ID NO. 356 IGLV8-39 (F)

>IGLV8-39*01|Canis lupus familiaris_boxer|F|V-REGION|
cagactgtggttaacccaggagccatcactctcagtgctctccaggagggacagtcacactc
acatgtggcctcagctctcggtcagtcctctacaagtaaccacccctagctgggtaccagcag
acccaagggaaggctcctcgcatgcttctctacaacacaaacagccgccctctgggatc
cctaattgcttctctggatccatctctgggaacaaagccgcctcaccatcacaggagcc
cagcctgaggacgagactgactattactgtttattgtatatgggtagtaacattta

SEQ ID NO. 357 IGLV8-40 (P)

>IGLV8-40*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtggtgacccaggagccatcactctaagtttctccaggagggacagtcacactc
acatgtggcctcagctctcggtcagtcctctacaagtaactacccagctgggttccagcag
acccaggccgggtcctctagaacagttatctacaacacaaacagctgccctctggggtc
cctaatacgcttctcagtgatccatctctgggaacaaagccgcctcaccatcacagagcc
cagcctgaggatgaggctgactcctgctgtgctgaatatcaaagcagtgaggagcagctac
acttacc

SEQ ID NO. 358 IGLV8-43 (P)

>IGLV8-43*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggttaacccagggaaccatcactctcagtgctctccatgagggacagtcacactc
acatgtggcctcagctctcggtcagtcctctacaagtaactaccccaactgggtaccagcag
acccaaggccgggtcctctacagggttattctacaacacaaacagccgccctctggggtc
cctgatcgcttctctggatccatctctgggaacaaagccgcctcaccatcacagctgcc
cagcctgaggacgaggctgactattactgttcattgtatatgggtagtaacatttg

SEQ ID NO. 359 IGLV8-60 (P)

>IGLV8-60*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtgatcacccaagatacatcactctcagtgctctccaggagggacagtcacactc
acatgtggcctcagctctcggtcagtcctctacaagtaactacccagctgggtaccagcag
acccaaggccgggtcctctcgcatgcttattctacagcacaacagccacccctctggggtc
cctaattgcttctcagtagatccatctctgggaagaaagctgcctcaccatcacaggagcc
cagcctgaggatgagactattattgttccactaaatatgggtagtacatgta

SEQ ID NO. 360 IGLV8-71 (P)

>IGLV8-71*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtggtgacccaggacccatcactgtcagtgctctagaggagggacagtcacactc
acttggtggcctcagctctcggtcagtcactacaataaataacccagctgggtcccagcaga
ccccagggcaggctcctcgcatgattatctatgacacaaacagccgccctctgggggtcc
ctgatcgcttctctggatccatctctgggaacaaagctgcctcaccatcacaggagccc
atcctgaggatgagactgactactactgtggtataacaacatggcagtgaggagcagcctca
cttacc

SEQ ID NO. 361 IGLV8-74-1 (ORF)

>IGLV8-74-1*01|Canis lupus familiaris_boxer|ORF|V-REGION|
cagattgtggtgacccaggagccatcactgtcagtggtctccaggaggaaacagttacactc
acatgtggcctaagctctgtgggtcagtcactataagtaactaccctgattggtaccagcag
actccaggcagggtctcctcgcatgcttatctacaacacaaaacacgccccctctggggtc
cctaatactctctgtgatccatctctgggaacaaaagccgccccctaccatcacaggagcc
cagcctgaggatgaggettactactgtgtgtgtatcaaggcagtgaggagcagctac
acttacc

SEQ ID NO. 362 IGLV8-76-1 (P)

>IGLV8-76-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggtcaccaggatccatcactctcagtggtctccaggaggaaacagtcacactc
acatgtggcctcagctctgtgggtcagtcctctacaagtaactaccccggtggtaccagcag
acccaagtgaagctccttgcatgcttatctacagcacaacagctacccccctctggggtt
cctaattgcttcactggatccatctctgggaagaaaagctgcctcaccatcacaggagac
cagcctgaggatgagactattattgttctactgcatatgggtagtacactta

SEQ ID NO. 363 IGLV8-88-4 (P)

>IGLV8-88-4*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggtgggtcaggagtcacagtcctcagtggtctccaggagggaacagtcacactc
acttgtggcctcagctctgtgggtcagtgactacaagtaactaccacagctggtaccagcgg
acccaaggccggtctcctcacatgcttatctatgacacaagcagccgctccttctgaggtc
ctgatcgcttccctgggtccatctctgggaacaaaagctgcctcactgtcagaggagccc
agcctgaggacgaggtgactactactgtggcatgcatgatgtcagtgaggaggaattaca
attacc

SEQ ID NO. 364 IGLV8-89-3 (P)

>IGLV8-89-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtggtggccaggaggcattgtgtgctcagtggtctccaggagggaagagtcacactca
cttgtggcctcagctctgtgggtcagtcactacaagtaactaccccaactgggtccagcaga
cccaggggcgggtcctggcacgattatctacagcacaagactgccccctctgggggtcc
ctgactgcttctctagatccatctctgggaacaaaagccgccccctaccatcacaggagccc
agtctgaggacgaggtattactgttttacacgacatggtagtgaggagctgctacactta
cc

SEQ ID NO. 365 IGLV8-90 (P)

>IGLV8-90*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggttaaccaggagccatcactctcagtggtctccaggagggaacagtcacactc
acttgtggcctcagctctgtgggtcagtcctctacagtaacaaacctggctgggtaccagcac
acccaggccagggtcctcgaggattatctatgacacaagcagccgccccctctgggggtc
cctgatcgcttctctggatccatctctgagaacaaaactgcctcaccatcacagaagcc
caacctgaggatgaggtgactacatcatatatgagtgggtggtgctta

SEQ ID NO. 366 IGLV8-90-1 (P)

>IGLV8-90-1*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtggtgacccaggaggcatcggtgttagtggtctcctggagggatagtcacactc
acttgtggcctcagctctggatcaatcactacaagtaactaccccaactgggtccagcag
acccaggggcgggtcctcgcatgatgatctatggcacaaaaagccgccccctctgggggtcc
ctgatcgcttctctagatccatctctgggaacaaaagccgccccctaccatcacaggagccc
agtctgaggatgaggtgactattactgttttacacgacatggcagtgaggagcagctaca
attac

SEQ ID NO. 367 IGLV8-90-3 (P)

>IGLV8-90-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgtggtgacccaggagtcacagtcctcagtggtctccaggaggaaacagtcacactc
ccttgtggcctcagctctgtgggtcagtcactacaagtaactacaccagctggtaccagc
agaccaaggccagtcctcctcgcatgcttgtctatgacacaagcagctgtccctctgagg
ttcctgatcacttctctggatccatctctgggaacaaaagccaccctcaccatcacaggag
cccagcctgaggacgaggtgactactactgtggcatgcatgatgtcagtgaggagcagct
aaaattacc

SEQ ID NO. 368 IGLV8-90-4 (P)

>IGLV8-90-4*01|Canis lupus familiaris_boxer|P|V-REGION|
 catatTTTGGTgactcaggagccatcactgtcagtggtctccatgaggagacagtcacactc
 acttTGTGGCctcagctctgggtcagtcactacaagtaactacccaggtataccagcaga
 acccaggcaaggctcctagcacagttatctacaacaaaaacagctgcccctctgggggtcc
 atggtcgattctctggatccatctctggaagcaagccgcttcacaatcacaggagccc
 agcctgaggttgaggctgactactactgtgttacagaacatggctcctcacatgggaaca
 gcctcactcac

SEQ ID NO. 369 IGLV8-92-1 (P)

> IGLV8-92-1*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagactgtgggtcaccaggatccgtcactctcagtggtctccaggaggacagtcacattc
 acatgtggcctcagctctgggtaagtctctacaagaaactacccagctggtaccagcag
 acccaaggccaggctccttgcatgcttatctacagcacaagcagacacccctctggggtc
 cctgatcgcttctctggatccatctctgggaacaaagtcgcccctaccatcacaggagcc
 cagcctgaggataagactattattgttctactgcatatgggtagttacattta

SEQ ID NO. 370 IGLV8-93 (F)

>IGLV8-93*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtggtaaccaggagccatcactctcagtggtctccaggaggacagtcacactc
 acatgtggcctcagctctgggtcagtcctctacaagtaattacccctggctggtaccagcag
 acccaaggccgggtcctcgcacgattatctacaacacaagcagccgcccctctggggtc
 cctaatecgttctctggatccatctctgggaacaaagccgcccctaccatcacaggagcc
 cagcccaggatgaggctgactattactgttccttgtatagggtagttactga

SEQ ID NO. 371 IGLV8-99 (F)

>IGLV8-99*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtgggtcaccagaaagccatcactctcagtggtctccaggaggacagtcacactc
 atatgtggcttcagctctgggtcagtcctctacaagtaattacccctggctggtaccagcag
 acccaaggccgggtcctcgcacaattatctacagcacaagcagccgcccctctggggtc
 cctaatecgttctcctggatccatctctgggaacaaagccgcccctaccatcacaggagcc
 cagcctgaggacagaggtgactattactgttccttgtatatgggtagttactga

SEQ ID NO. 372 IGLV8-102 (ORF)

>IGLV8-102*01|Canis lupus familiaris_boxer|ORF|V-REGION|
 cagattgttagtgaccaggaaccatcactgtctccaggaggacagtcctactcacttgt
 ggctcagctctgggtcagtcactacaagtaactactccagctggtaccagcagacccca
 gggcggtcctcgcacgattatctacaacactaacagccacccctctggagtccttgat
 cgcttctctggatccatctctgggaacaaagccgctcaccatcacaggagccagcct
 gaggacgaggctgactactactgtgttacagaacatggtagtgggagcagcttcacttac

SEQ ID NO. 373 IGLV8-108 (F)

>IGLV8-108*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtgggtgactcaggagtcacagtcctcagtggtctccaggaggacagtcacactc
 acgtgtgacctcagctctgggtcagtgactacaagtaacaacccagctggtaccagcag
 acccaaggccgatctcctcgcagcttatctatgacacaagcagctgtccctcggaggtc
 cctgatcgcttctctggatccatttctgggaacacagctgcccctaccatcacaggagcc
 cagcctgaggacaaggtgactactactgtagtatgcatgatgtcagtgaggagcagctac
 aattacc

SEQ ID NO. 374 IGLV8-113 (P)

>IGLV8-113*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagactgtgggtcaccaggagccatcactctcagtggtctccaggaggacagtcacactc
 acatgtggcctcagttctgggtcagtcactataagtaactacccagctggtcccagcag
 acccagggcaggctcctcacacaataatctacaggacaaacagctgacctctggggtc
 cctgatcgcttctctggatccatctctgggaacaaagccgcccctcagcatcacagtcgcc
 cagcctgaggacagaggtgactattactgttcattgtatatgggtagtaacattta

SEQ ID NO. 375 IGLV8-113-3 (P)

>IGLV8-113-3*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagattgtgggtgaccaggagccatcactctcagtggtctagaggaggacagtcacactc

acttgtggcctcagctctgagtcacatacaactacccagctgatcccagcagaccc
cagggcagggtccctcacacaattatctatgacaaaaacagccgcccctctgggggtccctg
atcactttctcaggatccatctgtgggaacaaagccaccctcaccatcacaggaaccagc
ctgaggacaaggctgactactactgtggtatccaacatggcagtaggaggagcctcatta
acc

SEQ ID NO. 376 IGLV8-117 (P)

>IGLV8-117*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgttgtagctcaggagtcacagtcctcagtgctccaggaggagcagtaaacctc
acgtgtagcctcagctctgggtcagtgactacaagtaagtactccagctggaccagtaga
cccaaggccgatctcctcgcatgcttatctatgacacaagcagccgtccctctgaggtcc
ctgatcgcttctctggatccatctccgggaacaaagctgcctcaccatcacaggagccc
agcctgaggacgaggtgactactactgtggtatgcatgatgtcagtgaggaggattaca
attacc

SEQ ID NO. 377 IGLV8-118-3 (P)

>IGLV8-118-3*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgtgggtggccaggaggcattgttgtagtcagtgctcctctggaggaggagtcacactca
cttgtggcctcagctctgggtcagtcactacaagtaactacccaactgggtccagcaga
ccccaggggcgggtcctggcagcattatgtacagcacaaaagactgcccctctgggggtcc
ctgattgcttctctagatccatctctgggaacaaagccgcccctcaccatcacaggagccc
agtctgaggacgaggttattactgttttacacgacatggtagtgaggagctgctacactta
cc

SEQ ID NO. 378 IGLV8-119 (P)

>IGLV8-119*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgttggttaaccaggagccatcactctcagtgctcctggaggaggacagtcacactc
acttgtggcctcagctctgggtcagtcctctacaggtacaaaacctggctggtaccagcac
accccaggccaggctcctcgagcagattatctatgacacaagcagccgcccctctgggggtc
ctgatacgcttctctgagatccatctctgggaacaaagctgcctcaccatcacagaagcc
cagcctgaggatgaggtgcctaccactgttcgctgtatatgagtggtggtgctta

SEQ ID NO. 379 IGLV8-120 (P)

>IGLV8-120*01|Canis lupus familiaris_boxer|P|V-REGION|
cagattgttggtgacccaggagcagtcgttgtagtcagtgctcctggagggatagtcacactc
acttgtggcctcagctctggatcaatcactacaagtaactacccaactgggtccagcag
accccaggggcgggtcctcgagatgatctatggcacaaaaagccgcccctctgggggtcc
ctgatacgcttctctgagatccatctctgggaacaaagccgcccctcaccatcacaggagccc
agtctgaggatgaggtgactattactgttttacacgacatggcagtgaggagcagctaca
attacc

SEQ ID NO. 380 IGLV8-121 (P)

>IGLV8-121*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgttggtgacccaggagtcacagtcctcagtgctcctcagtcggaacagtcacactc
acttgtggcctcagctctgggtcagtcactacaagtaactacaccagctggtaccagcag
acccaaggccagtcctcctcgcatgcttgctatgacacaagcagctgtccctctgaagtt
cctgatacacttctctggatccatttctgggaacaaagccgcccctcaccatcacaggagcc
cagcctgaggacgaggtgactactactgtggtatgcatgatgtcagtgaggagcagctaa
aattacc

SEQ ID NO. 381 IGLV8-121-1 (P)

>IGLV8-121-1*01|Canis lupus familiaris_boxer|P|V-REGION|
catatgttggtgactcaggagccatcactgtcagtgctcctatgagggacagtcacactc
acttgtggcctcagctctgggtcagtcactacaagtaactacccaaggtataccagcaga
accaggcaaggctcctagcacagttatctacaacaaaaacagctgcccctctgggggtcc
atgggtcgatttctctggatccatctctggaagcaaagccgcccctcacaatcacaggagccc
agcctgaggttgaggtgactactactgtgttacagaacatggctcct

SEQ ID NO. 382 IGLV8-124 (P)

>IGLV8-124*01|Canis lupus familiaris_boxer|P|V-REGION|
cagactgttggtcaaccaggatccgtcactctcagtgctcctcaggaggagcagtcacattc

acatgtggcctcagctctgggtaagtctctgcaagaaactacccagctggtaccagcag
 acccaaggccaggctccttgcatgcttatctacagcacaagcagccgcccctctggggtc
 cctgatcgcttctctggatccatctctgggaacaaagtcgcccctcaccatcacaggagcc
 cagcctgaggatgagactattattgttcactgcatatgggtagtacattta

SEQ ID NO. 383 IGLV8-128 (F)

>IGLV8-128*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtggtaaccaggagccatcactctcagtgtctccaggaggagacagtcacactc
 acatgtggcctcagctctgggtaagtctctacaagtaattaccctggctggtaccagcag
 accctaggccgggctcctcgacgattatctacagacaagcagccgcccctctggggtc
 cctaatecgcttctctggatccatctctgggaacaaagtcgcccctcaccatcacaggagcc
 cagcctgaggagcagagctgactattactgttccttgatatatgggtagttacactga

SEQ ID NO. 384 IGLV8-137 (P)

>IGLV8-137*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagactgtgggtaccaaggatccatcactctcagtgtctccaggaggagacagtcacattc
 acatgtggcctcagctctgggtaagtctttacaagtaactacccagctggtaccagcag
 acccatggccgggctcctcgcatgcttatctacagcacaaggagctgccccccggggtc
 cctgatcgcttctctggatccatctctgggaacaaagttgcccctcaccatcacaggagcc
 cagcctgaggatgagactattattgttcactgtgtatgggtagttacattta

SEQ ID NO. 385 IGLV8-142 (F)

>IGLV8-142*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtgggtacccagaagccatcactctcagtgtctccaggaggagacagtcacactc
 atatgtggcctcagctctgggtaagtctctacaagtaattaccctggctggtaccagcag
 acccaaggccgggcttctcgcaattatctacagcacaagcagccgcccctctggggtc
 cctaatecgcttctctggatccatctctgggaacaaagtcgcccctcaccatcacaggagcc
 cagcctgaggagcagagctgactattactgttccttgatatatgggtagttacactga

SEQ ID NO. 386 IGLV8-150-1 (ORF)

>IGLV8-150-1*01|Canis lupus familiaris_boxer|ORF|V-REGION|
 cagattgtgggtgaccaggaaccatcactgtcagtgtctccaggaggagacactcacactc
 acttgtggcctcagctctgggtaagtctctacaagtaactacccagctggtaccagcag
 accccaggccaggctcctagcacagttatctacaacacaaacagccgcccctctgggtgc
 cctgatcacttctctggatccgtctctgggaacaaagtcgcccctcatcatcacaggagcc
 cagcctgaggagcagagctgactactctgttgagaacatgtcagtgggagcagcttc
 acttacc

SEQ ID NO. 387 IGLV8-153 (F)

>IGLV8-153*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtggtaaccaggagccatcactctcagtgtctccaggaggagacagtcacactc
 acatgtggcctcagctctgggtaagtctctacaagtaattaccctggctggtaccagcag
 acccaaggccgggctcctcgacgattatctacaacacaagcagccgcccctctggggtc
 cctaatecgcttctctggatccatctctgggaacaaagtcgcccctcaccatcacaggagcc
 cagcccaggagatgagagctgactattactgttccttgatatcgggtagttacactga

SEQ ID NO. 388 IGLV8-156 (P)

>IGLV8-156*01|Canis lupus familiaris_boxer|P|V-REGION|
 cagactgtgggtaccaaggatccatcactctcagtgtttccaggaggagacagtcacattc
 acatgtggcctcagctctgggtaagtctttacaagtaactacccagctggtaccagcag
 acccatggccgggctcctcgcatgcttatctacagcacaagcagctgccccccggggtc
 cctgatcgcttctctggatccatctctgggaacaaagttgcccctcaccatcacaggagcc
 cagcctgaggatgagactattattgttcactgtgtatgggtagttacattta

SEQ ID NO. 389 IGLV8-161 (F)

>IGLV8-161*01|Canis lupus familiaris_boxer|F|V-REGION|
 cagactgtgggtacccagaagccatcactctcagtgtctccaggaggagacagtcacactc
 atatgtggcctcagctctgggtaagtctctacaagtaattaccctggctggtaccagcag
 acccaaggccgggcttctcgcaattatctacagcacaagcagccgcccctctggggtc
 cctaatecgcttctctggatccatctctgggaacaaagtcgcccctcatcatcacaggagcc
 cagcctgaggagcagagctgactattactgttccttgatatatgggtagttacactga

Germline J λ sequences

SEQ ID NO. 390 IGLJ1 (F)

>IGLJ1*01|Canis lupus familiaris_boxer|F|J-REGION|
ttgggtatttcggtgaaggagaccagctgaccgtcctcg

SEQ ID NO. 391 IGLJ2 (F)

>IGLJ2*01|Canis lupus familiaris_boxer|F|J-REGION|
tatgggtatttcggtcagaggagaccagctgaccatcctcg

SEQ ID NO. 392 IGLJ3 (F)

>IGLJ3*01|Canis lupus familiaris_boxer|F|J-REGION|
tagtggtggttcggcgaggacccatctgaccgtcctcg

SEQ ID NO. 393 IGLJ4 (F)

>IGLJ4*01|Canis lupus familiaris_boxer|F|J-REGION||
ttacgtggttcgggtcaggaacccaactgaccgtccttg

SEQ ID NO. 394 IGLJ5 (F)

>IGLJ5*01|Canis lupus familiaris_boxer|F|J-REGION|
tattgtggttcggcgaggacccatctgaccgtcctcg

SEQ ID NO. 395 IGLJ6 (F)

>IGLJ6*01|Canis lupus familiaris_boxer|F|J-REGION|
tggtgtggttcggcgaggacccacctgaccgtcctcg

SEQ ID NO. 396 IGLJ7 (F)

>IGLJ7*01|Canis lupus familiaris_boxer|F|J-REGION|
tgctgtggttcggcgaggacccacctgaccgtcctcg

SEQ ID NO. 397 IGLJ8 (F)

>IGLJ8*01|Canis lupus familiaris_boxer|F|J-REGION|
tgctgtggttcggcgaggacccacctgaccgtcctcg

SEQ ID NO. 398 IGLJ9 (F)

>IGLJ9*01|Canis lupus familiaris_boxer|F|J-REGION|
ttacgtggttcgggtcaggaacccaactgaccgtccttg

Table 4. Canine constant region genes

IGHC sequences

Functionality is shown between brackets, [F] and [P], when the accession number (underlined) refers to rearranged genomic DNA or cDNA and the corresponding germline gene has not yet been isolated.

SEQ ID NO. 399 IGH α (F)

>IGHA*01|Canis lupus familiaris_boxer|F|**CH1**|
nagtccaaaaccagccccagtggtgttcccgctgagcctctgccaccaggagtcagaaggg
tacgtgggtcatcggtgctggtgcagggattcttccacccggagcctgtgaacgtgacc
tggaatgccggcaaggacagcacatctgtcaagaacttccccccatgaaggctgctacc
ggaagcctatacaccatgagcagccagttgacctgccagccgcccagtgccctgatgac
tcgtctgtgaaatgccaaagtgcagcatgcttccagccccagcaaggcagtgctgtgtgcc
tgcaaa
>IGHA*01|Canis lupus familiaris_boxer|F|**H-CH2**|
gataactgtcatccgtgtctctcatccaagtcctctgtgcaatgagccccgctgtcacta

cagaagccagccctcgaggatctgcttttaggctccaatgccagcctcacatgcacactg
 agtggcctgaaagaccccaagggtgccaccttcacctggaacccctccaaaggggaaggaa
 cccatccagaagaatcctgagcgtgactcctgtggtgctacagtgtgtccagtgtccta
 ccaggctgtgctgatccatggaacccatggggacaccttctcctgcacagccaccaccct
 gaatccaagagcccgatcactgtcagcatcaccaaaaccaca
 >IGHA*01|Canis lupus familiaris_boxer|F|CH3-CHS|
 gagcacatccccgcccagggtccacctgctgccgccgctcggaagagctggccctcaat
 gagctggtgacactgacgtgcttgggtgaggggcttcaaaccaaaagatgtgctcgtaga
 tggctgcaagggaacccaggagctacccaagagaagtacttgacctgggagccctgaag
 gagcctgaccagaccaacatgtttgccgtgaccagcatgctgaggggtgacagccgaagac
 tggaaagcagggggagaagtctcctgcatggtgggccaagaggetctgcccattgctctc
 accagaagaccatcgaccgcctggcggttaaaccacccacgtcaacgtgtctgtggtc
 atggcagaggtggacggcatctgtctac
 >IGHA*01|Canis lupus familiaris_boxer|F|M|
 gactcacagtgtcttgacggttacccggagccacttccctggctggtgctggacctgtcg
 caggaggacctggaggaggtgcccaggagccagcctgtggccactaccgtcacccctt
 ctaccctcttctactgagtctctctacagcagcactgactgtgacaagcgtgctgg
 ggcccaactgacagcagagaggggccccagtag

SEQ ID NO. 400 IGHD (ORF)

>|IGHD*01|Canis lupus familiaris_boxer|ORF|CH1|
 gaatcgctcacttctgctcccccttgggtctcaggatgtaagggtcccaaaaatggtaggac
 ataaccctggcctgcttggcaaaaggacccttctctagattctgtgcgggtcacgacaggc
 ccagagtcacaggcccagatggaaaagaccacactgaagatgctaaagataccggaccac
 actcagggtgtctcctgctccacccctggaaaccaggcctgcactactgcgaagccatc
 aggaaagataacaaagagaagctgaagaaagccatccactggcca
 >IGHD*01|Canis lupus familiaris_boxer|ORF|H1|
 gcatcctgggaaactgctatctcctgttgactcatgcgccatcccgacccagggaccac
 acccaagccccagcatggccagggtctca
 >IGHD*01|Canis lupus familiaris_boxer|ORF|H2|
 gtgcctcccaccagccacacccagacgcaagcccaggagccaggatgccagtgagacacc
 atcctcaga
 >IGHD*01|Canis lupus familiaris_boxer|ORF|CH2|
 gagtgttggaaaccacacccctcccagcctctacatgctgcgccctcccctgcgggga
 ccatggctccaggagaagctgctttcacctgcctggtgggtgggagatgaccttcagaag
 gccacactgtcctgggaggtagccggggcgccccccagcgaggctgtggaggagaggcca
 ctgcaggagcatgagaatggctcccagagctggagcagccgctggtcttggccatatcc
 ctgtgggcctcaggagccaacatcacctgcacgctgagcctcccagcatgccttcccag
 gtggtgtccgcagcagccagagagcat
 >IGHD*01|Canis lupus familiaris_boxer|ORF|CH3|
 gctgccagagcaccagcagcctcaatgtccatgacctgacctgcccagcagcctcc
 tggctcctgtgctgaggtgtccggcttctcaccctgacatcctcctcacctggatcaag
 gaccagattgaggtggacccttcttgggttcgccaactgcaacccccatggcccagccgggc
 agtggcacgttccagacctggagtctcctgctgtcctcgctcccagggccctcaccgg
 ccacctacacgtgtgtagtcaggcacgaggcctcccgaagctgtcaacaccagctgg
 agcctggacagt
 >IGHD*01|Canis lupus familiaris_boxer|ORF|M1|
 ggtctgacatgacccccccagccctcagagccacgacgagagcagcggggactccatg
 gatctggaagatgccagcgactgtggccacgttcgctgcctcttctcgctcctcactctg
 ctctacagcggcttcgtcaccttctctcaa
 >IGHD*01|Canis lupus familiaris_boxer|ORF|M2|
 gtgaag

SEQ ID NO. 401 IGHE (F)

>IGHE*01|Canis lupus familiaris_boxer|F|CH1|
 nccaccagccaggacctgtctgtgttcccccttggcctcctgctgtaagacaacatcgcc
 agtacctctgttacactgggctgtctggtcaccggctatctccccatgtcgacaactgtg
 acctgggacacggggtctctaaataagaatgtcacgaccttccccaccacctccacgag
 acctacggcctccacagcatcgtcagccaggtgaccgcctcgggcgagtgggccaacag
 aggttcacctgcagcgtggctcacgctgagtcaccgccaatcaacaagaccttcagt
 >IGHE*01|Canis lupus familiaris_boxer|F|CH2|
 gcatgtgccttaaacttcattccgcctaccgtgaagctcttccactcctcctgcaacccc

gtcgggtgataccacacaccaccatccagctcctgtgcctcatctctggctacgtcccaggt
gacatggaggtcatctggctgggtgatgggcaaaaggctacaaacatattcccatacact
gcacccggcacaaaaggagggcaacgtgacctctaccacagcgagctcaacatcacccag
ggcgagtggtatccccaaaaacctacacctgccaggtcacctatcaaggctttaccttt
aaagatgaggctcgcaagtgtca
>IGHE*01|Canis lupus familiaris_boxer|F|CH3|
gagtccgacccccgaggcgtgagcagctacctgagccacccagcccccttgacctgtat
gtccacaaggcgcccaagatcacctgcctggtagtgacctggccaccatggaaggcatg
aacctgacctggtaccgggagagcaaagaacccgtgaacccgggcccccttgaacaagaag
gatcaattcaatgggacgatcacagtcacgtctaccctgccagtgaaacccaatgactgg
atcgagggcgagacctactattgcagggtgacccacccgcacctgccccaggacatcggtg
cgctccattgccaaggccccct
>IGHE*01|Canis lupus familiaris_boxer|F|CH4-CHS|
ggcaagcgtgcccccccgatgtgtacttgttctgccacccgaggaggagcaggggacc
aaggacagagtcacccctcacgtgcctgatccagaacttcttccccgggacatttcagtg
caatggctgcgaaaacgacagccccatccagacagaccagtaaccaccacggggccccac
aaggctctcggtccaggcctgccttcttcatcttcagecgccctggagggttagccgggtg
gactgggagcagaaaaacaaattcacctgccaagtgggtgcatgaggcgctgtccggctct
aggatcctccagaatgggtgtccaaaacccccggtaaa
>IGHE*01|Canis lupus familiaris_boxer|F|M1|
gagctccaggagctgtgcgcggatgccactgagagtgaggagctggacgagctgtgggcc
agcctgctcatcttcatcacccctcttctgctcagcgtgagctacggcgccaccagcacc
ctcttcaag
>IGHE*01|Canis lupus familiaris_boxer|F|M2|
gtgaagtgggtactcgccaccgtcctgcaggagaagccacaggccgccccagactacgcc
aacatcggtgcggccggcacag

SEQ ID NO. 402 IGHG1 [F]

>AF354264|IGHG1*01|Canis lupus familiaris|(F)|CH1||
gcctccaccacggccccctcggttttccactggccccagctgcgggtccacttccggc
tccacgggtggccctggcctgcctggtgtcaggctacttccccgagcctgtaactgtgtcc
tggaaattccggctccttgaccagcggtgtgcacaccttcccgctccgtcctgcagtcctca
gggcttccactccctcagcagcatggtgacagtgccctccagcaggtggccccagcgagacc
ttcacctgcaacgtggtccaccagccagcaacactaaagtagacaagcca
>IGHG1*01|Canis lupus familiaris|(F)|H|
gtgttcaatgaatgcagatgcactgatacacccccatgccca
>IGHG1*01|Canis lupus familiaris|(F)|CH2|
gtccctgaacctctgggagggccttcggtcctcatcttccccgaaacccaaggacatc
ctcaggattaccgaaacacccgaggtcacctgtgtggtgtagatctgggcccgtgaggac
cctgaggtgcagatcagctggttcgtggatggtaaggaggtgcacacagccaagaccag
tctcgtgagcagcagttcaacggcacctaccgtgtggtcagcgtcctccccattgagcac
caggactggctcacagggaaggagttcaagtgcagagtcacacacatagacctcccgctct
cccatcgagaggaccatctctaaggccaga
>IGHG1*01|Canis lupus familiaris|(F)|CH3-CHS|
gggaggggcccataagcccagtggtgtatgtcctgcgccatccccaaaggagttgtcatcc
agtgcacagtcagcatcacctgcctgataaaagacttctaccacctgacattgatgtg
gagtggcagagcaatggacagcaggagccccgagaggaagcaccgcatgacccccgccccag
ctggacggagacgggtcctacttctgtacagcaagctctctgtggacaagagccgctgg
cagcagggaagacccttcacatgtgcgggtgatgcatgaaactctacagaaccactacaca
gatctatccctctccattctccgggtaaa

SEQ ID NO. 403 IGHG2 (F)

>IGHG2*01|Canis lupus familiaris_boxer|F|CH1|
ncctccaccacggccccctcggttttccactggccccagctgcgggtccacttccggc
tccacgggtggccctggcctgcctggtgtcaggctacttccccgagcctgtaactgtgtcc
tggaaattccggctccttgaccagcggtgtgcacaccttcccgctccgtcctgcagtcctca
gggcttactccctcagcagcatggtgacagtgccctccagcaggtggccccagcgagacc
ttcacctgcaacgtggccccacccggccagcaaaactaaagtagacaagcca
>|IGHG2*01|Canis lupus familiaris_boxer|F|H|
gtgccccaaaagagaaaatggaagagttcctcgccacctgattgtcccaaatgccca
>IGHG2*01|Canis lupus familiaris_boxer|F|CH2|
gccccgaaatgctgggagggccttcggtcttcatcttccccgaaacccaaggacacc

ctcttgattgcccgaacacctgaggtcacatgtgtggtggtggatctggaccagaagac
 cctgaggtgcagatcagctggttcgtggacggtaagcagatgcaaacagccaagactcag
 cctcgtgaggagcagttcaatggcacctaccgtgtggtcagtgctctccccattgggcac
 caggactggctcaagggaagcagttcacgtgcaaagtcaacaacaaagccctcccatcc
 ccgacgagagaccatctccaaggccaga
 >IGHG2*01|Canis lupus familiaris_boxer|F|CH3-CHS|
 gggcaggcccatcaacccagtgtgtatgtcctgcccacatcccgaggaggttgagcaag
 aacacagtcagcttgacatgcctgatcaaagacttcttcccacctgacattgatgtggag
 tggcagagcaatggacagcaggagcctgagagcaagtaccgcacgaccccgccccagctg
 gacgaggacgggtcctacttctgtacagcaagctctctgtggacaagagccgctggcag
 cggggagacaccttcatatgtgcggtgatgcataagctctacacaaccactacacacag
 aatccctctcccattctccgggtaaa
 >IGHG2*01|Canis lupus familiaris_boxer|F|M1|
 gagctgatcctggatgacagctgtgctgaggacaggaggggagctggacgggctgtgg
 accaccatctccatcttcatcaccctcttctgtcagcgtgtgctacagcggcactgtc
 accctcttcaag
 >|IGHG2*01|Canis lupus familiaris_boxer|F|M2|
 gtgaagtggatcttctcatcagtggtggagctgaagcgcacgattgtccccgactacagg
 aatatgatcgggcagggggcc

SEQ ID NO. 404 IGHG3 [F]

>AF354266|IGHG3*01|Canis lupus familiaris|(F)|CH1|
 gccctccaccacggccccctcggttttcccactggccccagctgtgggtcccaatccggc
 tccacgggtggccctggcctgctggtgtcaggctacatccccgagcctgtaactgtgtcc
 tggaaattccgtctccttgaccagcgggtgtgcacaccttcccgtccgtcctgcagtcctca
 gggctctactccctcagcagcatggtgacagtgcctccagcaggtggcccagcgagacc
 ttcacctgcaatgtggcccacccggccaccaactaaagtagacaagcca
 >IGHG3*01|Canis lupus familiaris|(F)|H|
 gtggccaaagaatgagtgcaagtgttaactgttaactgtcccatgccc
 >IGHG3*01|Canis lupus familiaris|(F)|CH2|
 ggttgtggcctgctgggagggtcctcggtcttcatctttccccaaaaacccaaggacatc
 ctgctgactgcccggacacccacagtcacttgtgtggtggtggatctggaccagaaaac
 cctgaggtgcagatcagctggttcgtggatagtaagcaggtgcaaacagccaacacgcag
 cctcgtgaggagcagtcacatggcacctaccgtgtggtcagtgctctccccattgggcac
 caggactggccttccaggaagcagttcaagtgcacaaagtcaacaacaaagccctcccatcc
 cccattgaggagatcatctccaagacccca
 >IGHG3*01|Canis lupus familiaris|(F)|CH3-CHS|
 gggcaggcccatcagcctaattgtgtatgtcctgcccacatcgcggtgatgagatgagcaag
 aatacgggtcacctgacctgtctggtcaaagacttcttcccacctgagattgatgtggag
 tggcagagcaatggacagcaggagcctgagagcaagtaccgcacgaccccgccccagctg
 gatgaagtgggtcctacttctatacagcaagctctccgtggacaagagccgctggcag
 cggggagacaccttcatatgtgcggtgatgcataagctctacacaaccactacacacag
 atatccctctcccattctccgggtaaa

SEQ ID NO. 405 IGHG4 [F]

>AF354267|IGHG4*01|Canis lupus familiaris|(F)|CH1|
 gccctccaccacggccccctcggttttcccactggccccagctgcgggtccacttccggc
 tccacgggtggccctggcctgctggtgtcaggctacttcccagcctgtaactgtgtcc
 tggaaattccggctccttgaccagcgggtgtgcacaccttcccgtccgtcctgcagtcctca
 gggctctactccctcagcagcagcaggtgacagtgccctccagcaggtggcccagcgagacc
 ttcacctgcaacgtgggtccacccggccagcaactaaagtagacaagcca
 >IGHG4*01|Canis lupus familiaris|(F)|H|
 gtgcccagaagagtcacactgcaagtgtatatccccatgccc
 >IGHG4*01|Canis lupus familiaris|(F)|CH2|
 gtccctgaatcactgggagggtcctcggtcttcatctttccccgaaacccaaggacatc
 ctgaggtattaccgaacacccgagatcacctgtgtggtggttagatctgggcgtgaggac
 cctgaggtgcagatcagctggttcgtggatggttaaggaggtgcacacagccaagacgcag
 cctcgtgagcagcagttcaacagcacctaccgtgtggtcagcgtcctccccattgagcac
 caggactggctcaccggaaggagttcaagtgcagagtcacacacataggcctcccgctcc
 cccatcgagaggactatctccaaagccaga
 >IGHG4*01|Canis lupus familiaris|(F)|CH3-CHS|
 gggcaggcccatcagcccagtgtgtatgtcctgcccacatccccaaaggagttgtcatcc

agtgacacgggtcacccctgacctgcctgatcaaagacttcttcccacctgagattgatgtg
 gaggaggagcaatggacagccggagcccgagagcaagtaccacacgactgcgccccag
 ctggacgaggacgggtcctacttctgtacagcaagctctctgtggacaagagccgctgg
 cagcaggggagacaccttcacatgtgcgggtgatgcatgaagctctacagaaccactacaca
 gatctatccctctcccattctccgggtaaa

SEQ ID NO. 406 IGHM (F)

>IGHM*01|Canis lupus familiaris boxer|F|CH1|
 nagagtccatccccccaaacctcttccccctcatcacctgtgagaactccctgtccgat
 gagacctcgtggccatgggctgcctggccgggacttctgcctggctccatcaccttc
 tcttggaagtacgagaacctcagtgcaatcaacaaccaggacattaagaccttccctca
 gttctgagagagggcaagtatgtggcgacctctcaggtgttctgcctccgtggacatc
 atccaggggttcagacgagatcacatgcaacgtcaagcactccaatggtgacaaatct
 gtgaacgtgccccatcaca
 >IGHM*01|Canis lupus familiaris boxer|F|CH2|
 gggcctgtaccaacgtctcccaacgtgactgtcttcatcccccgcgacgccttctct
 ggcaatggccagcgcaagtcccagctcatctgccaggtgcaggtttcagccccaagcag
 atttccgtgtcttgggtccgtgatggaaagcagattgagctctggcttcaacacaggaag
 gcagagggcggaggagaagagcatgggcctgtgacctacagcatectcagcatgctgacc
 atcaccgagagtgctgtggctcagccagagcgtgttcacctgccacgtggagcacaatggg
 atcatcttccagaagaacgtgtctcccatgtgcacctcc
 >IGHM*01|Canis lupus familiaris boxer|F|CH3|
 aatacacccgttggcatcagcatcttcacatccccccctcctttgccagcatcttcaac
 accaagtccagccaagctgtcctgcctggctcactgacctggccacttatgacagcctgacc
 atctcctggacctgcagaatggcgaggtctgaaaacccacaccaacatctctgagagc
 catcccaacaacaccttcagtgccatgggggaagccactgtctgcgtggaggaatgggag
 tcaggcgagcagttcacctgcacagtgacccacacagatctgcctcaccgctgaagaag
 accatctccaggcccaag
 >IGHM*01|Canis lupus familiaris boxer|F|CH4-CHS|
 gatgtcaacaagcacatgccttctgtctacgtcctgccccgagccgggagcagctgagc
 ctgcgggaatcggcctcactcacctgcctgggtgaaaggettctcacccccagatgtgttc
 gtgcagtggtgcagaagggccagcccggtgccccctgacagctacgtgaccagcgccccg
 atgcccagcccccaagccccggcctctactttgtccacagcatectgacctgagtgag
 gaggactggaatgcgggggagacctacacctgtgttgtaggcatgagggcctgccccat
 gtggtgaccgagaggagcgtggacaagtcaccggtaaaacccaccttgtacaacgtgtcc
 ctggtcttatctgacacagccagcacctgctac
 >IGHM*01|Canis lupus familiaris boxer|F|M1|
 gggggggagggtgagtgccgaggaggaaggcttcgagaacctgaataccatggcatccacc
 ttcacgtcctcttctcctcctcagtgcttctacagcaccacagtcactctgttcaag
 >IGHM*01|Canis lupus familiaris boxer|F|M2|
 gtgaaa

IGKC sequences

SEQ ID NO. 407 IGKC (F)

>IGKC*01|Canis lupus familiaris boxer|F|C-REGION|
 cggaatgatgccagccagccgtctatttgttccaacctctccagaccagttacacaca
 ggaagtgcctctgttgtgtgcttgcctgaatagcttctaccccaagacatcaatgtcaag
 tggaaagtggatggtgtcatccaagacacaggcatccaggaaagtgtcacagagcaggac
 aaggacagtacctacagcctcagcagcaccctgacgatgtccagtactgagtacctaagt
 catgagttgtactcctgtgagatcactcacaagagcctgcctccacctcatcaagagc
 ttccaaaggagcgagtgctcagagagtgagac

IGLC sequences

[F], Functionality defined for the available sequence of the gene (partial gene in 3' because of gaps in the sequence).

SEQ ID NO. 408 IGLC1 (F)

>IGLC1*01|Canis lupus familiaris_boxer|F|C-REGION|
ggtcagcccaagtcctcccccttggtcacactcttcccgccctcctctgaggagctcggc
gccacaaggctaccctgggtgtgcctcatcagcgacttctaccccagtgacctgaaagtg
gcttggaaggcagatggcagcaccatcatccaggcggtggaaccaccaagccctccaag
cagagcaacaacaagtacggccagcagctacctgagcctgacgctgacaagtggaaa
tctcacagcagcttcagctgcttggtcacgcaccaggggagcaccgtggagaagaaggtg
gccccgcagagtgtctct

SEQ ID NO. 409 IGLC2 (F)

>IGLC2*01|Canis lupus familiaris_boxer|F|C-REGION|
ggtcagcccaaggcctccccctcagtcacactcttcccaccctcctctgaggagctcggc
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SEQ ID NO. 410 IGLC3 (F)

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SEQ ID NO. 411 IGLC4 (F)

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SEQ ID NO. 412 IGLC5 (F)

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SEQ ID NO. 415 IGLC8 (F)

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gccccgcagagtgtctt
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// End of canine Ig sequences

Table 5. PCR Primers

SEQ ID NO. 417 1F: ACATAATACACTGAAATGGAGCCC

SEQ ID NO. 418 1R: GTCCTTGGTCAACGTGAGGG

SEQ ID NO. 419 2F: CATAATACACTGAAATGGAGCCCT

SEQ ID NO. 420 2R: GCAACAGTGGTAGGTCGCTT

Table 6. Miscellaneous sequence data**Pre-DJ**

This is a 21609 bp fragment upstream of the Ighd-5 DH gene. The pre-DJ sequence can be found in Mus musculus strain C57BL/6J chromosome 12, Assembly: GRCm38.p4, Annotation release 106, Sequence ID: NC_000078.6

The entire sequence lies between the two 100 bp sequences shown below:

Upstream of the Ighd-5 DH gene segment, corresponding to positions 113526905-113527004 in NC_000078.6:

ATTTCTGTACCTGATCTATGTCAATATCTGTACCATGGCTCTAGCAGAGATGAAATATG
AGACAGTCTGATGTCATGTGGCCATGCCTGGTCCAGACTTG (SEQ ID NO. 421)

2 kb upstream of the ADAM6A gene corresponding to positions 113548415 – 113548514 in NC_000078.6:

GTCAATCAGCAGAAATCCATCATAATGAGACAAAGTTATAATCAAGAAATGTTGCCCA
TAGGAAACAGAGGATATCTCTAGCACTCAGAGACTGAGCAC (SEQ ID NO. 422)

ATACAGACTCTATCAAAACTTCTCTTGCCTGGGGCAGCCGAGCTGACAATGTGCAATCTGAAGAGGAGCAG
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[illegible]

ATGATGAGTCCTGCCAGTTCCTGTTTCTGTTAGTGCTCTGGATTCAGG

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 TTATTTGTGGTGGGGCAGGTCATATCTTCCAGAATGTGAGGTTTTGTTACATCCTAATGAGATATTCACA
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AAACCAACGGT

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CACAGTG

ATACAGACTCTATCAAAACCTTCCTTGCCTGGGGCAGCCGAGCTGACAATGTGCAATCTGAAGAGGAGCAG
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CLAIMS:

1. A transgenic rodent or rodent cell comprising a genome comprising an engineered partly canine immunoglobulin light chain locus comprising canine immunoglobulin λ light chain variable region gene segments, wherein the engineered immunoglobulin locus is capable of expressing immunoglobulin comprising canine variable domains and wherein the transgenic rodent produces more, or is more likely to produce, immunoglobulin comprising λ light chain than immunoglobulin comprising κ light chain.
2. The transgenic rodent according to claim 1, wherein more λ light chain producing cells than κ light chain producing cells are likely to be isolated from said rodent.
3. The transgenic rodent according to claim 1, wherein the transgenic rodent produces at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% and up to about 100% immunoglobulin comprising λ light chain.
4. The transgenic rodent cell according to claim 1, wherein the transgenic rodent cell, or its progeny, has at least a 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% and up to about 100% probability of producing immunoglobulin comprising λ light chain.
5. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the engineered immunoglobulin locus comprises canine V_λ gene segment coding sequences and J_λ gene segment coding sequences and rodent non-coding regulatory or scaffold sequences from a rodent immunoglobulin light chain variable region gene locus.
6. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding

sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin λ light chain variable region gene locus.

7. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the partly canine immunoglobulin locus comprises one or more canine V_λ and J_λ gene segment coding sequences and one or more rodent immunoglobulin λ constant region coding sequences.
8. The transgenic rodent or rodent cell according to any of claims 1 to 4, wherein the engineered immunoglobulin locus comprises canine V_λ and J_λ gene segment coding sequences embedded in rodent non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain variable region gene locus.
9. The transgenic rodent or rodent cell according to claim 8, wherein the engineered immunoglobulin variable region locus comprises one or more canine V_λ gene segment coding sequences and one or more J-C units wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent λ constant region coding sequence.
10. The transgenic rodent or rodent cell according to claim 9, wherein the rodent λ constant region coding sequence comprises a rodent $C_{\lambda 1}$, $C_{\lambda 2}$, $C_{\lambda 3}$ coding sequence, or a combination thereof.
11. The transgenic rodent or rodent cell according to claim 9 to 10, comprising one or more canine V_λ gene segment coding sequences located upstream of one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ coding sequence.
12. The transgenic rodent or rodent cell according to claim 9 or 10, comprising one or more canine V_λ gene segment coding sequences located upstream of one or more J-C units, wherein each J-C unit comprises a canine J_λ gene segment coding sequence and a rodent C_λ coding sequence and rodent C_λ non-coding sequences.

13. The transgenic rodent or rodent cell according to any of claims 9 to 12, wherein the J-C units comprise canine J_λ gene segment coding sequences and rodent λ constant region coding sequences embedded in non-coding regulatory or scaffold sequences of a rodent immunoglobulin κ light chain locus.
14. The transgenic rodent or rodent cell according to claim 8, wherein the engineered immunoglobulin locus comprises a rodent immunoglobulin κ locus in which one or more rodent V_κ gene segment coding sequences and one or more rodent J_κ gene segment coding sequences have been deleted and replaced by one or more canine V_λ gene segment coding sequences and one or more J_λ gene segment coding sequences, respectively, and in which rodent C_κ coding sequence in the locus have been replaced by rodent $C_{\lambda 1}$, $C_{\lambda 2}$, $C_{\lambda 3}$ coding sequence, or a combination thereof.
15. The transgenic rodent or rodent cell according to claim 14, wherein the engineered immunoglobulin locus comprises one or more canine V_λ gene segment coding sequences upstream of one or more canine J_λ gene segment coding sequences which are upstream of one or more rodent C_λ coding sequences.
16. The transgenic rodent or rodent cell according any of the preceding claims wherein an endogenous rodent immunoglobulin κ light chain locus is deleted, inactivated, or made nonfunctional one or more of:
 - a. deleting or mutating all endogenous rodent V_κ gene segment coding sequences;
 - b. deleting or mutating all endogenous rodent J_κ gene segment coding sequences;
 - c. deleting or mutating all endogenous rodent C_κ coding sequence;
 - d. deleting or mutating a 5' splice site and adjacent polypyrimidine tract of a rodent C_κ coding sequence;
 - e. deleting, mutating, or disrupting an endogenous intronic κ enhancer (iE_κ) and 3' enhancer sequence.

17. The transgenic rodent or rodent cell according to any of the preceding claims wherein expression of an endogenous rodent immunoglobulin λ light chain variable domain is suppressed or inactivated by one or more of:
 - a. deleting or mutating all endogenous rodent V_λ gene segments
 - b. deleting or mutating all endogenous rodent J_λ gene segments; and
 - c. deleting or mutating all endogenous rodent C_λ coding sequences.
18. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the engineered immunoglobulin locus expresses immunoglobulin light chains comprising a canine λ variable domain and rodent λ constant domain.
19. The transgenic rodent or rodent cell according to any of claims 1 to 4, wherein the genome of the transgenic rodent or rodent cell comprises an engineered immunoglobulin locus comprising canine V_κ and J_κ gene segment coding sequences.
20. The transgenic rodent or rodent cell according to claim 19, wherein the canine V_κ and J_κ gene segment coding sequences are inserted into a rodent immunoglobulin κ light chain locus.
21. The transgenic rodent or rodent cell according to claim 19 or 20, wherein the canine V_κ and J_κ gene segment coding sequences are embedded in rodent non-coding regulatory or scaffold sequences of the rodent immunoglobulin κ light chain variable region gene locus.
22. The transgenic rodent or rodent cell according to any of claims 19 to 21, wherein the canine V_κ and J_κ coding sequences are inserted upstream of a rodent immunoglobulin κ light chain constant region coding sequence.
23. The transgenic rodent or rodent cell according to any of claims 1 to 4, wherein the genome of the transgenic rodent or rodent cell comprises an engineered

immunoglobulin locus comprising canine V_κ and J_κ gene segment coding sequences inserted into a rodent immunoglobulin λ light chain locus.

24. The transgenic rodent or rodent cell according to claim 23, wherein the canine V_κ and J_κ gene segment coding sequences are embedded in rodent non-coding regulatory or scaffold sequences of the rodent immunoglobulin λ light chain variable region gene locus.
25. The transgenic rodent or rodent cell according to claims 23 or 24, comprising a rodent immunoglobulin κ light chain constant region coding sequence inserted downstream of the canine V_κ and J_κ gene segment coding sequences.
26. The transgenic rodent or rodent cell according to claim 25, wherein the rodent immunoglobulin κ light chain constant region is inserted upstream of an endogenous rodent C_{λ2} coding sequence.
27. The transgenic rodent or rodent cell according to any of claims 23 to 26, wherein expression of an endogenous rodent immunoglobulin λ light chain variable domain is suppressed or inactivated by one or more of:
 - a. deleting or mutating all endogenous rodent V_λ gene segment coding sequences.
 - b. deleting or mutating all endogenous rodent J_λ gene segment coding sequences;
and
 - c. deleting or mutating all endogenous C_λ coding sequences or splice sites.
28. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the engineered canine immunoglobulin light chain locus comprises a rodent intronic κ enhancer (iE_κ) and 3'E_κ regulatory sequences.
29. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the transgenic rodent or rodent cell comprises an engineered partly canine

immunoglobulin heavy chain locus comprising canine immunoglobulin heavy chain variable region gene coding sequences and non-coding regulatory or scaffold sequences of the rodent immunoglobulin heavy chain locus.

30. The transgenic rodent or rodent cell according to claim 29, wherein the engineered canine immunoglobulin heavy chain locus comprises canine V_H, D and J_H gene segments.
31. The transgenic rodent or rodent cell according to claim 30, wherein each canine V_H, D or J_H coding gene segment comprises V_H, D or J_H coding sequence embedded in non-coding regulatory or scaffold sequences of the rodent immunoglobulin heavy chain locus.
32. The transgenic rodent or rodent cell according to claim 31, wherein the heavy chain scaffold sequences are interspersed by functional ADAM6A genes, ADAM6B genes, or a combination thereof.
33. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the rodent regulatory or scaffold sequences comprise enhancer, promoters, splice sites, introns, recombination signal sequences, or combinations thereof.
34. The transgenic rodent or rodent cell according to any of the preceding claims, wherein an endogenous rodent immunoglobulin locus has been deleted and replaced with the engineered partly canine immunoglobulin locus.
35. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the rodent is a mouse or a rat.
36. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the rodent cell is an embryonic stem (ES) cell or a cell of an early stage embryo.

37. The transgenic rodent or rodent cell according to any of the preceding claims, wherein the rodent cell is a mouse or rat embryonic stem (ES) cell, or mouse or rat cell of an early stage embryo.
38. A cell of B lymphocyte lineage obtained from the transgenic rodent of any of the preceding claims, wherein the engineered immunoglobulin locus expresses a chimeric immunoglobulin heavy chain or light chain comprising a canine variable region and a rodent immunoglobulin constant region.
39. A hybridoma cell or immortalized cell line derived from a cell of B lymphocyte lineage according to claim 38.
40. Antibodies or antigen binding portions thereof produced by the cell of claims 38 or 39.
41. A nucleic acid sequence of a V_H , D , or J_H , or a V_L or J_L gene segment coding sequence derived from an immunoglobulin produced by the cell of claims 38 or 39.

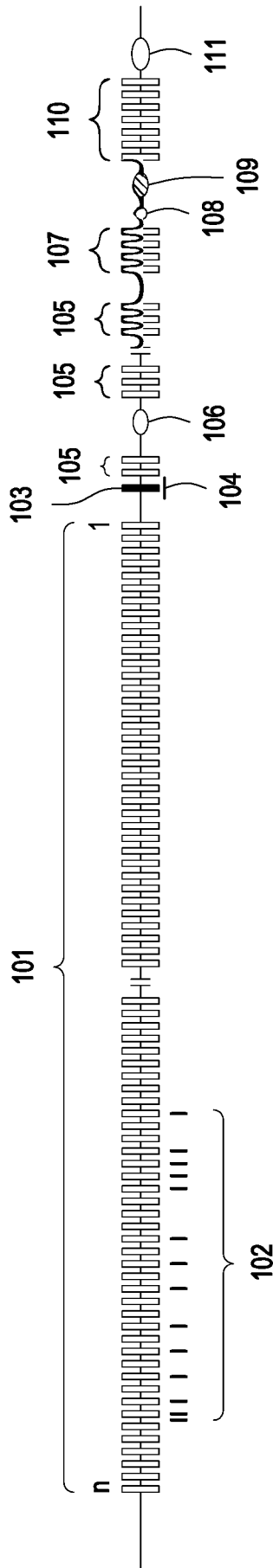


FIG. 1A

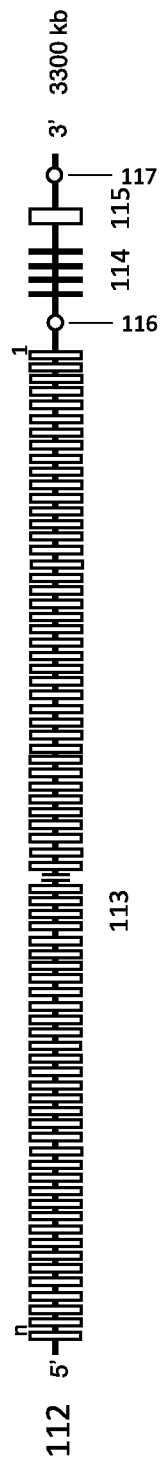


FIG. 1B

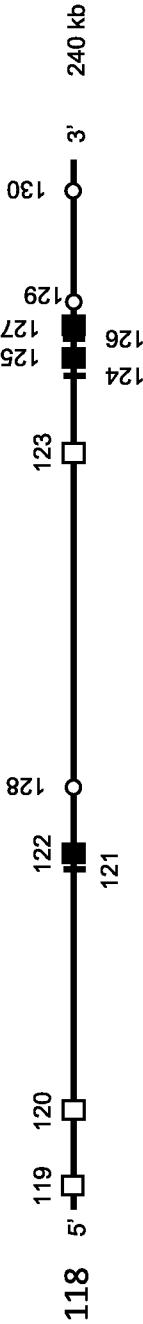


FIG. 1C

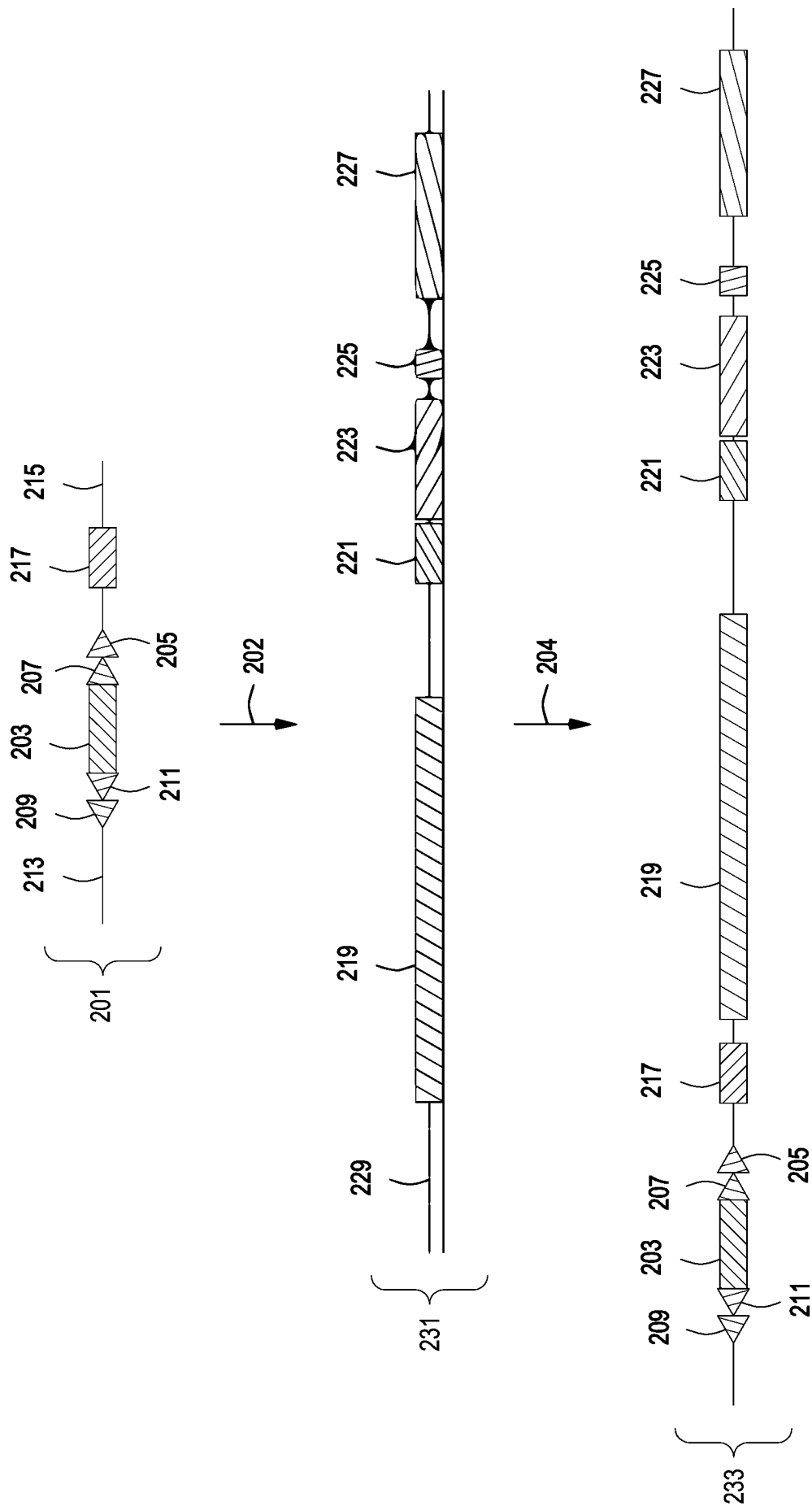


FIG. 2

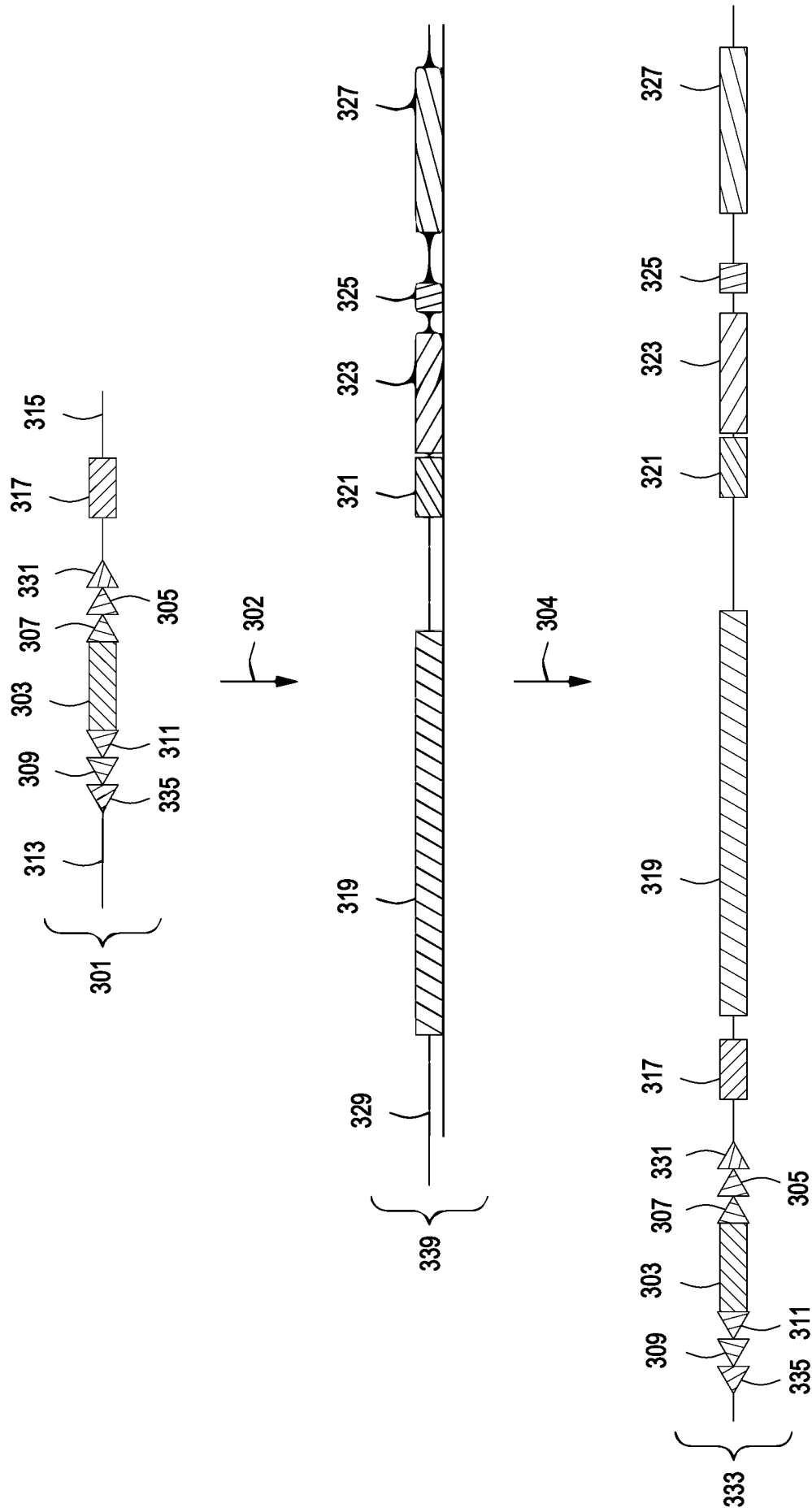


FIG. 3

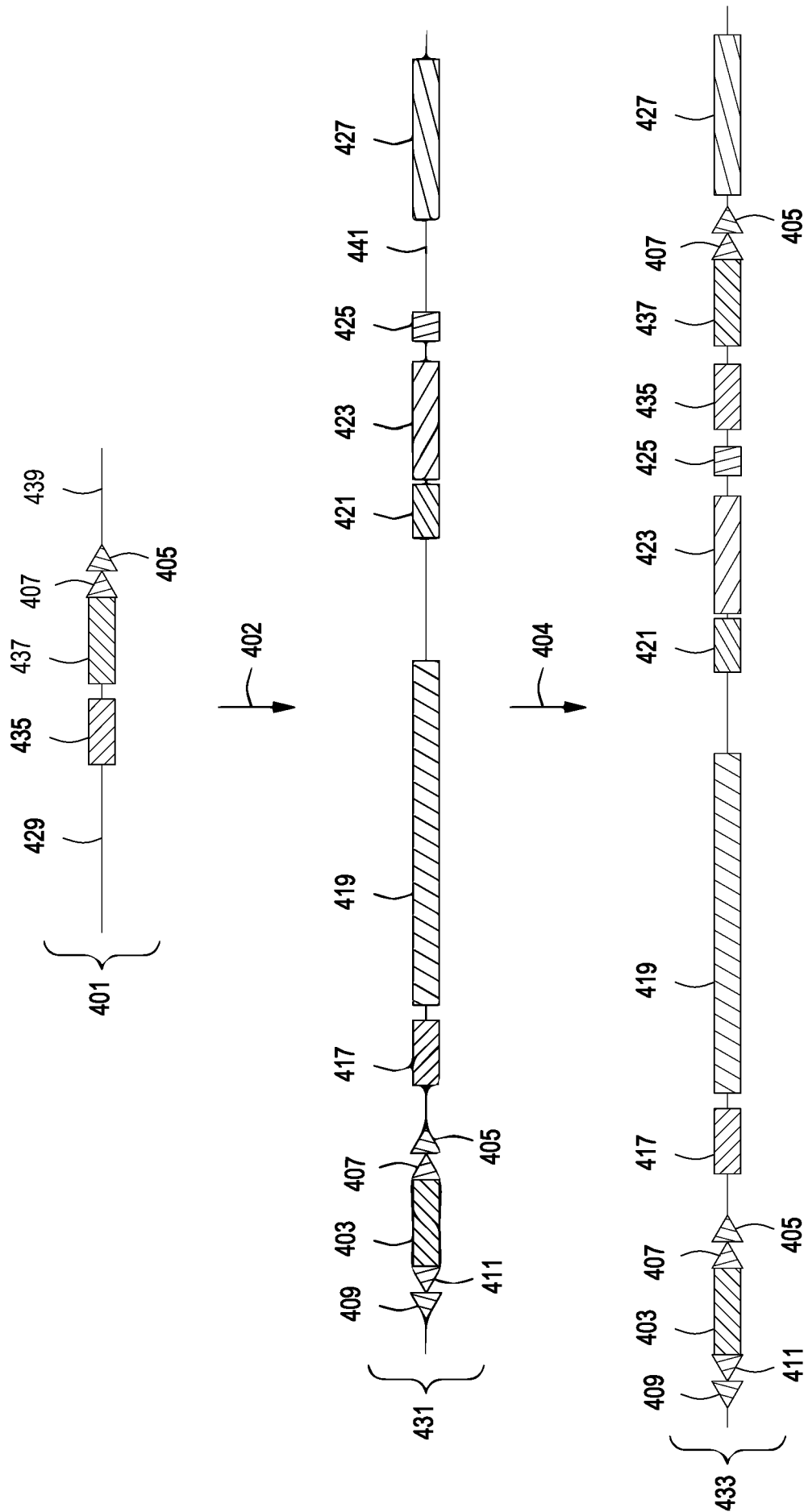


FIG. 4

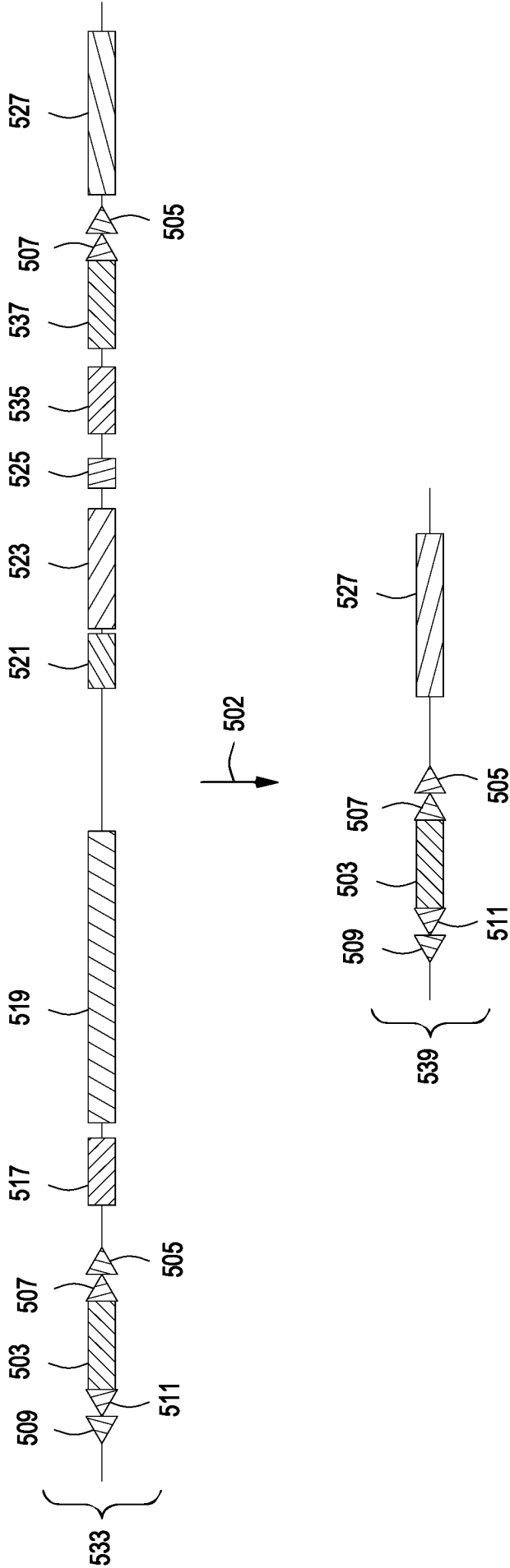


FIG. 5

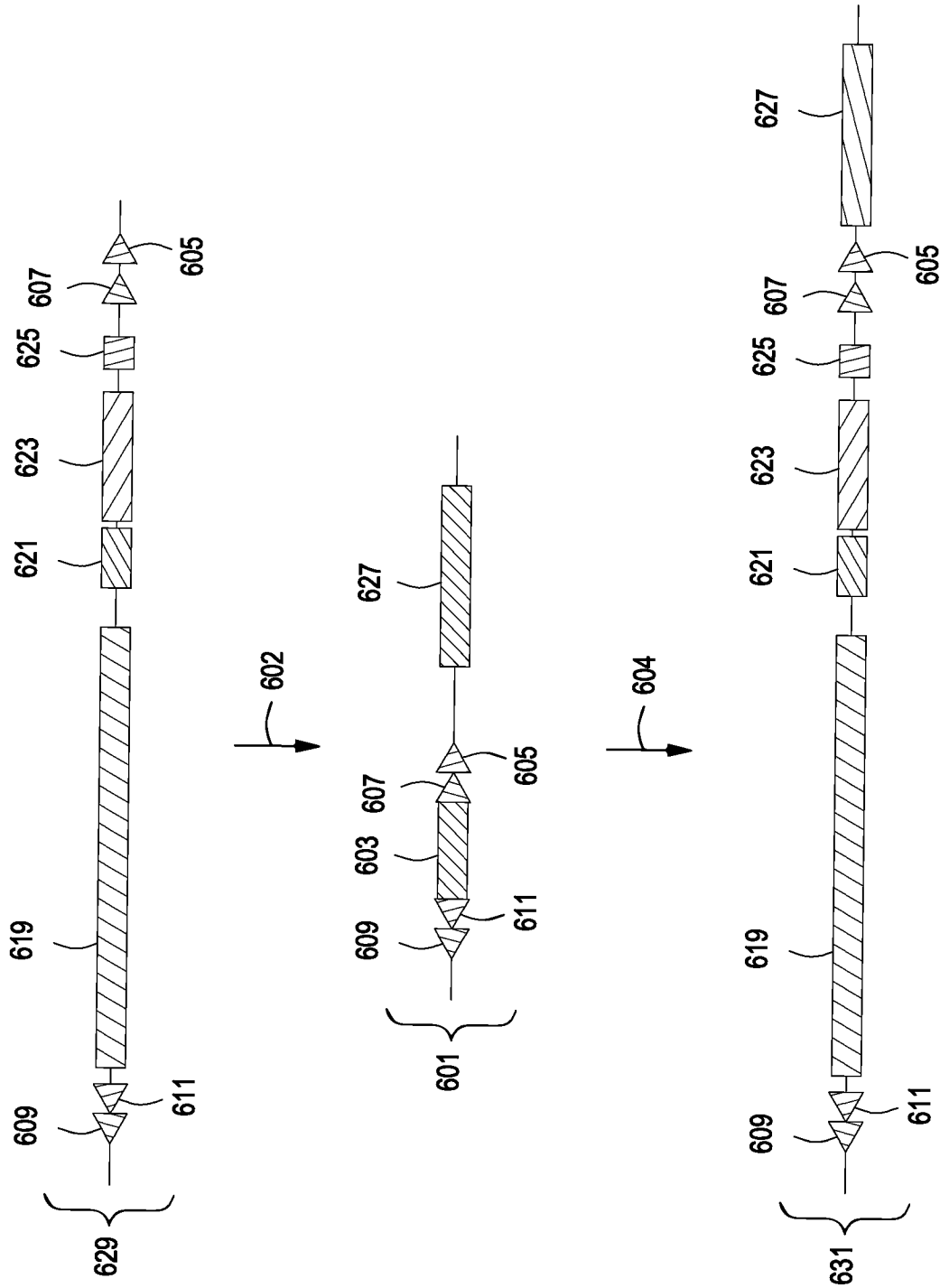


FIG. 6

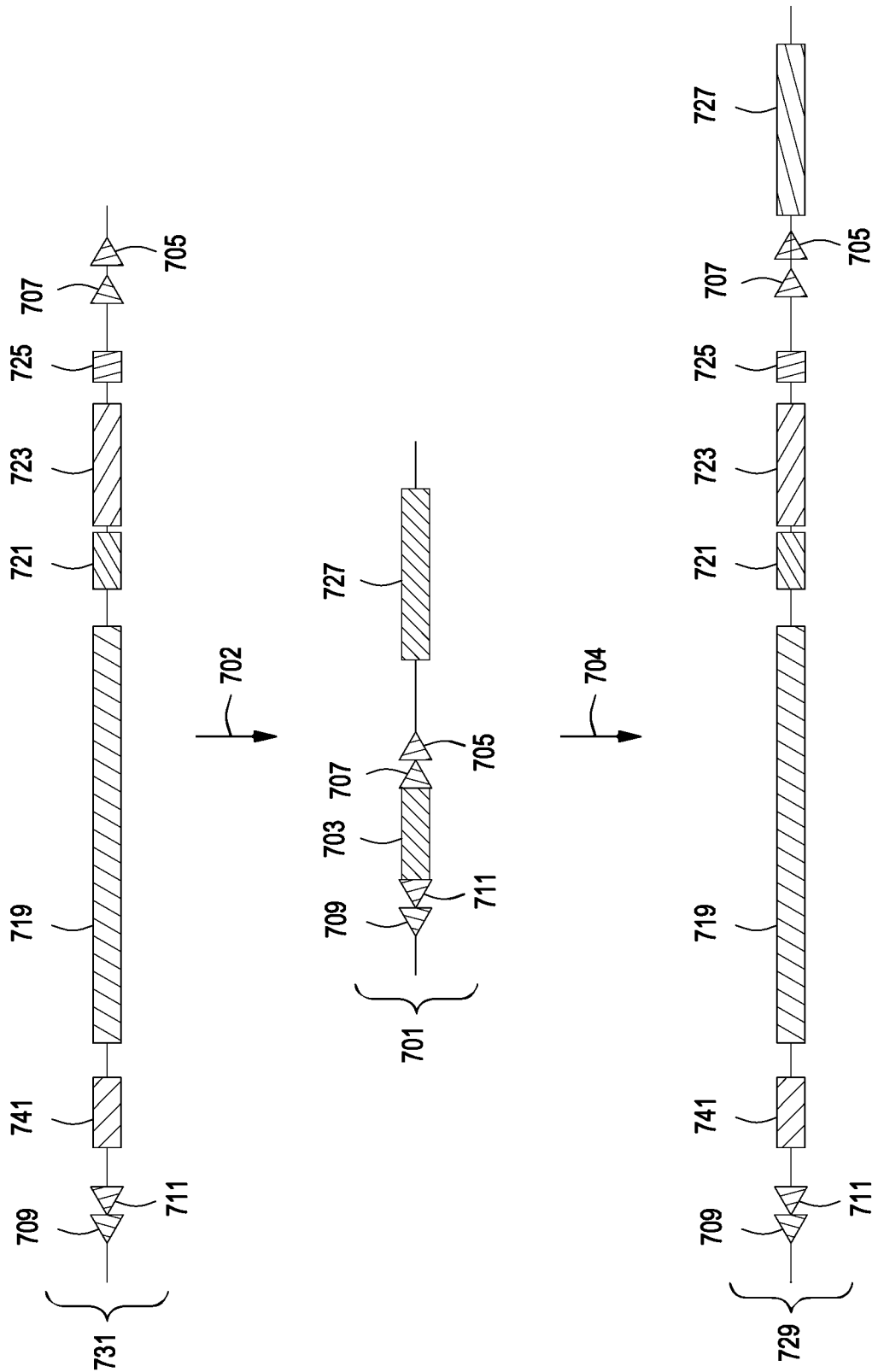


FIG. 7

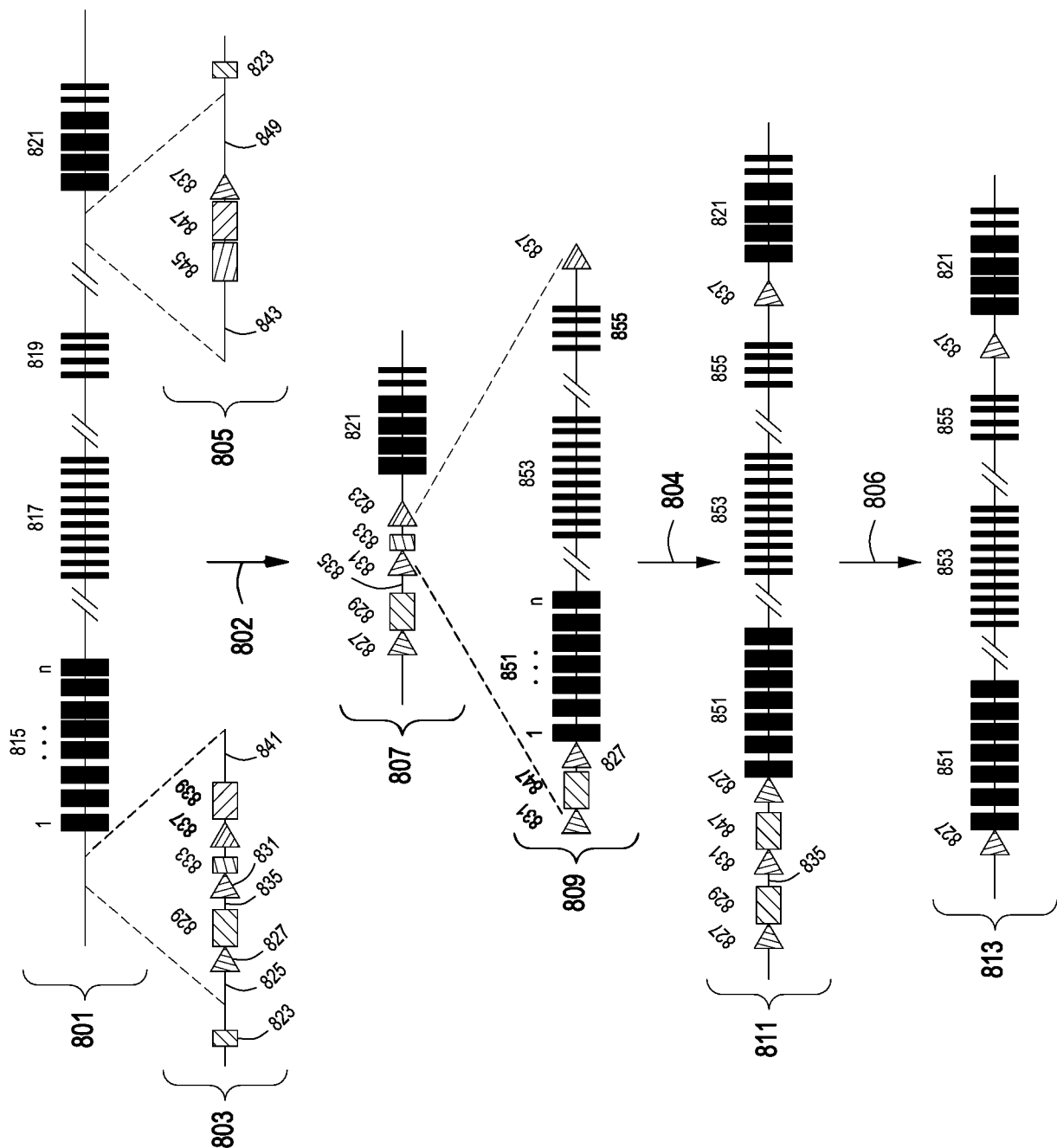


FIG. 8

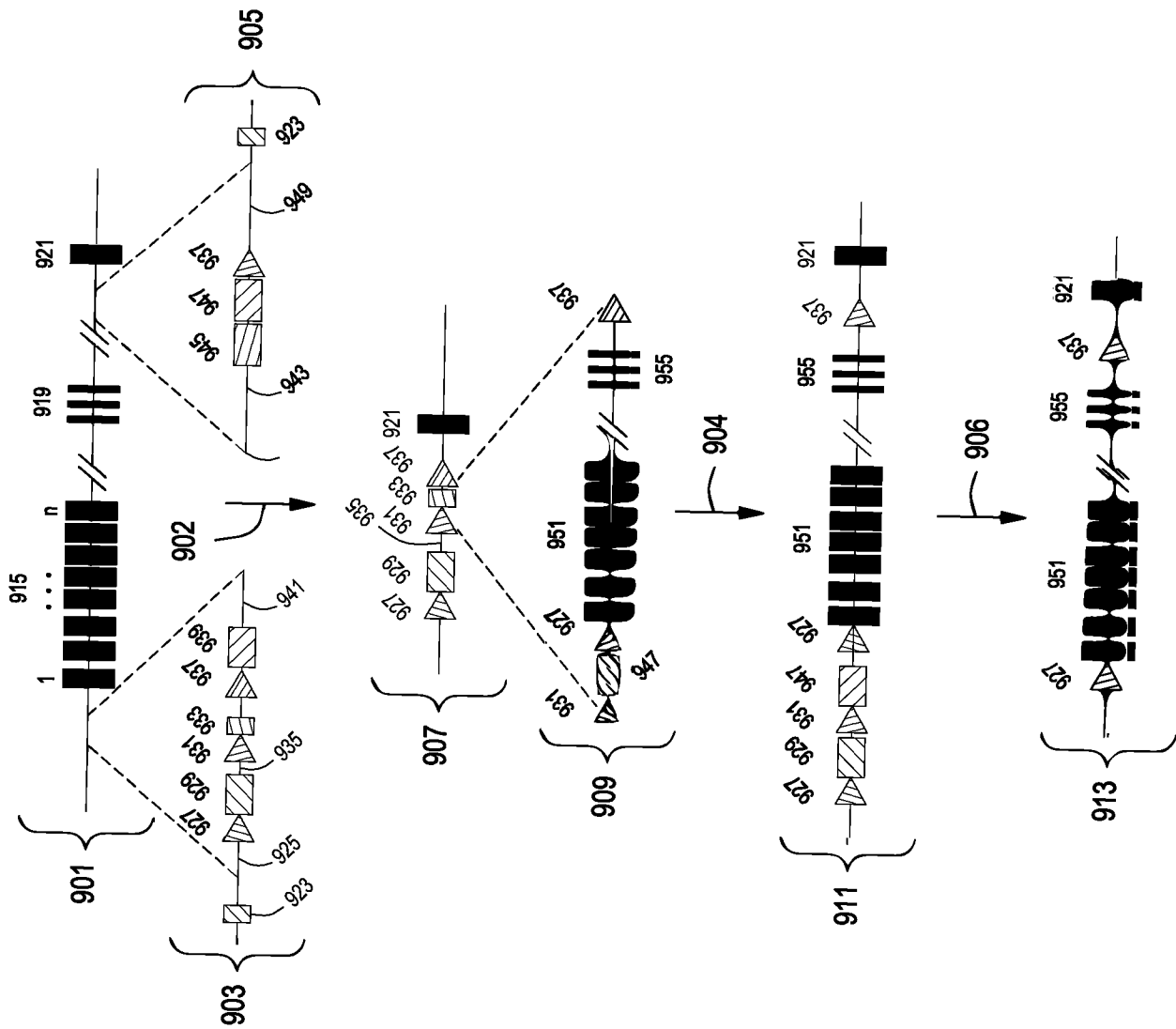


FIG. 9

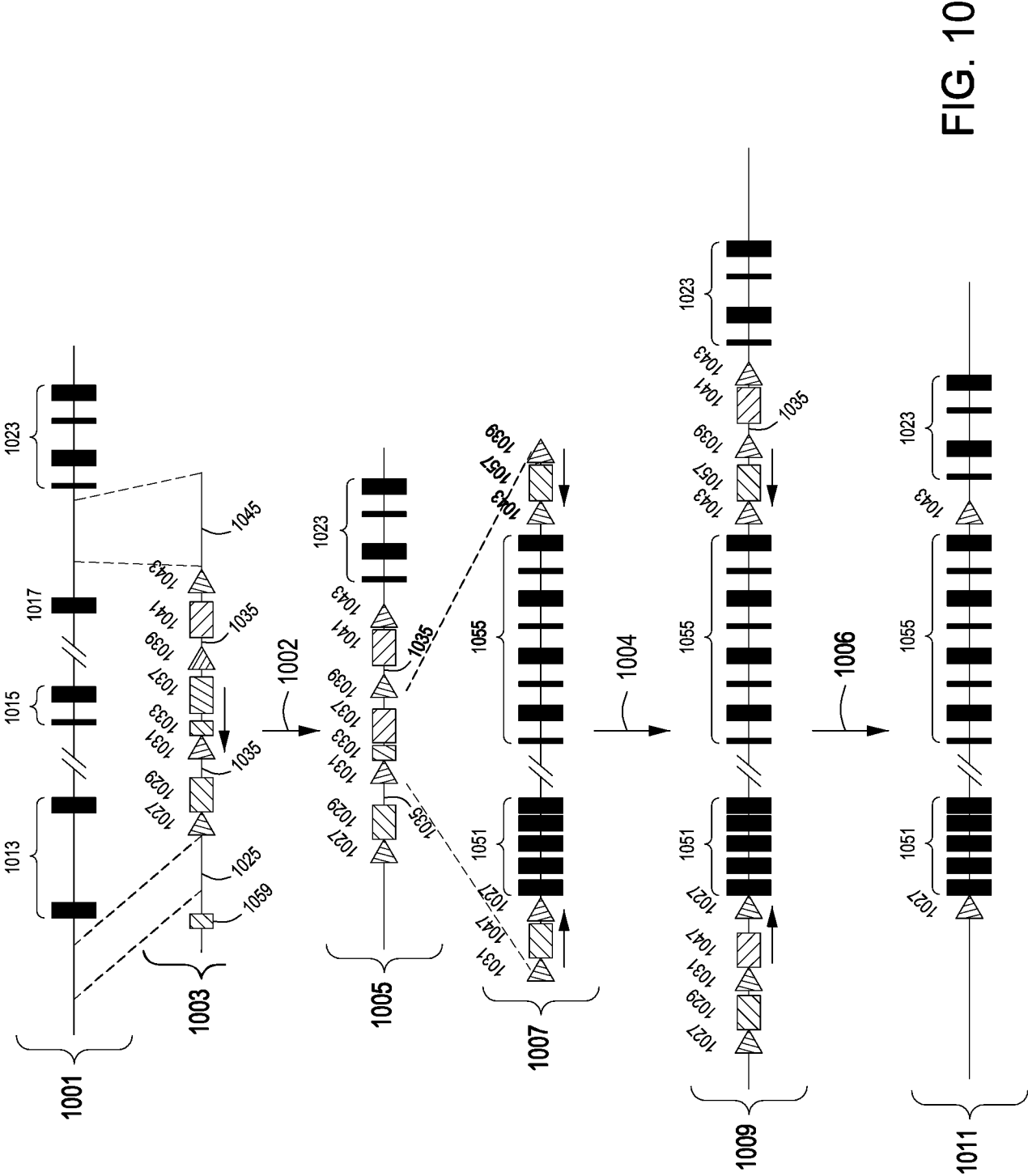


FIG. 10

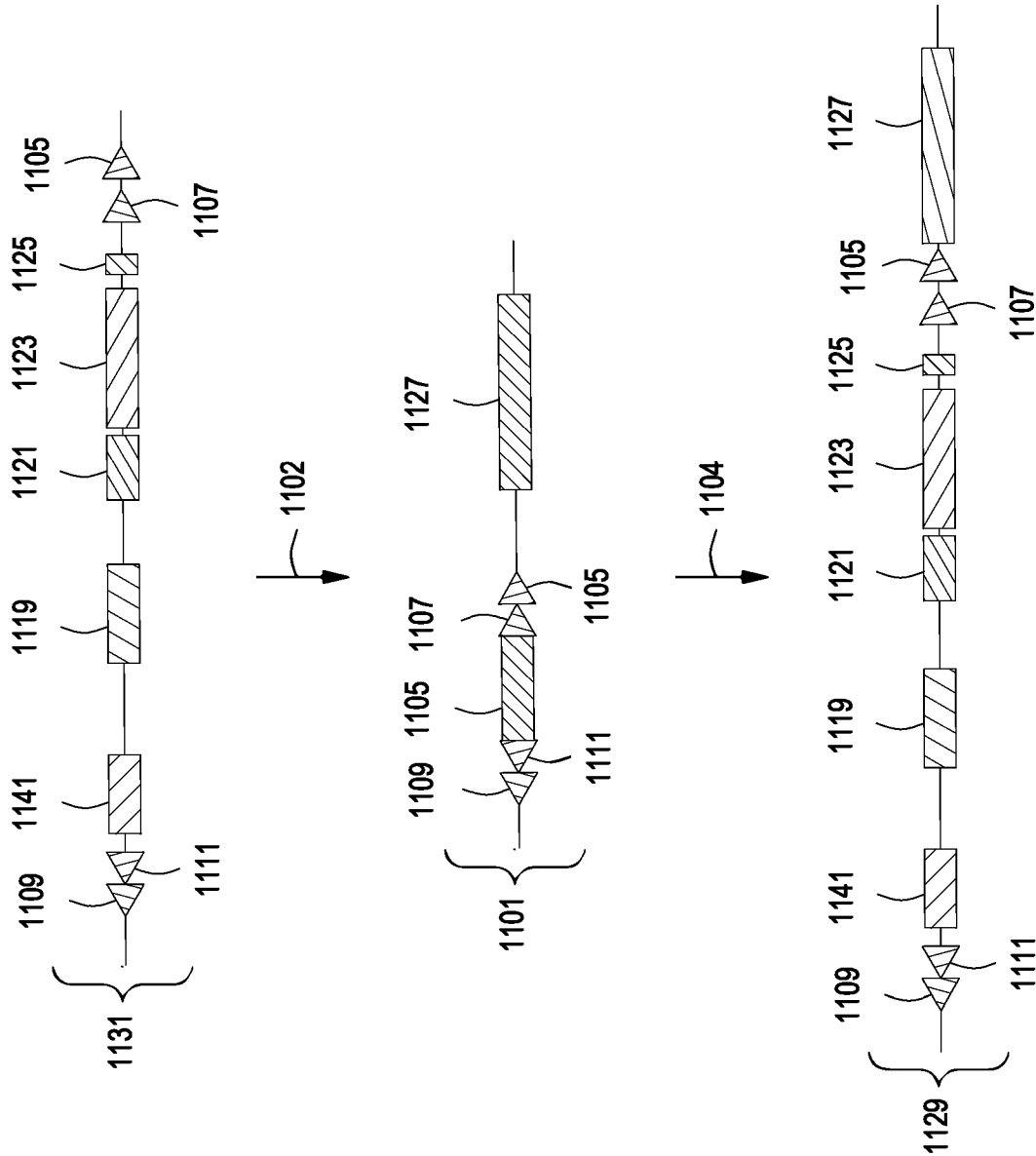


FIG. 11

14/29

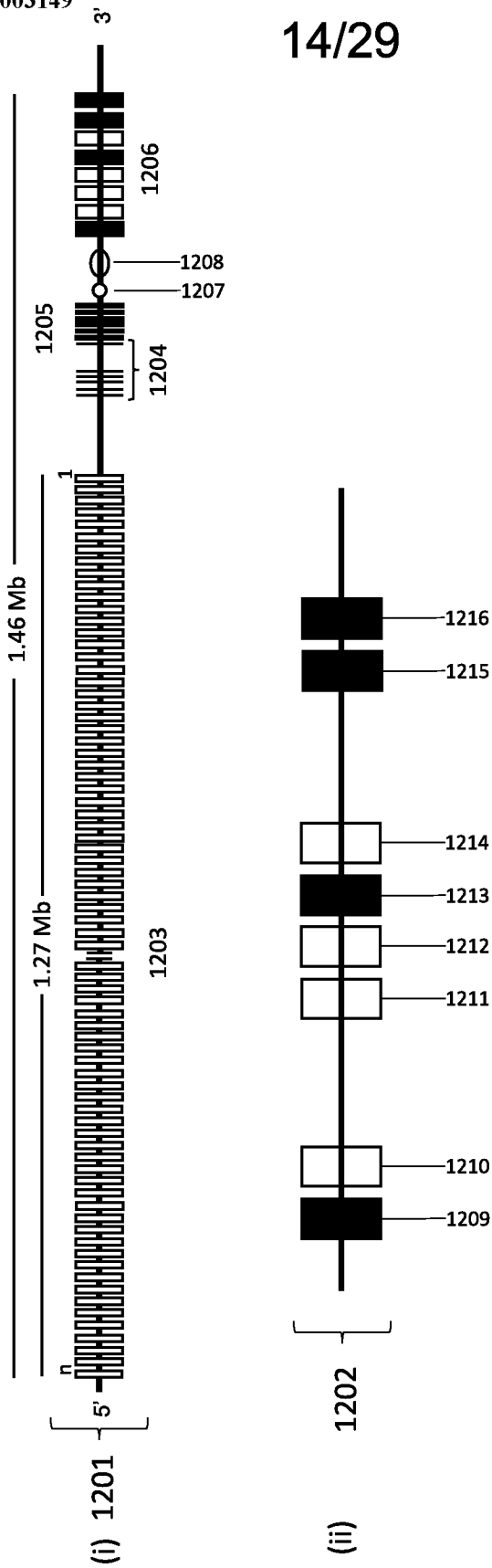


FIG. 12A

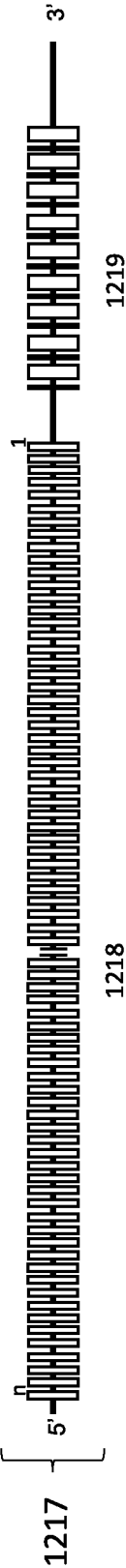


FIG. 12B

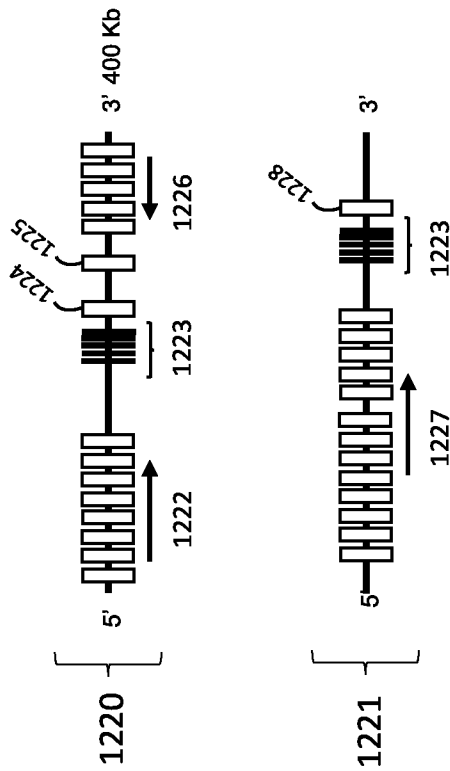


FIG. 12C

17/29

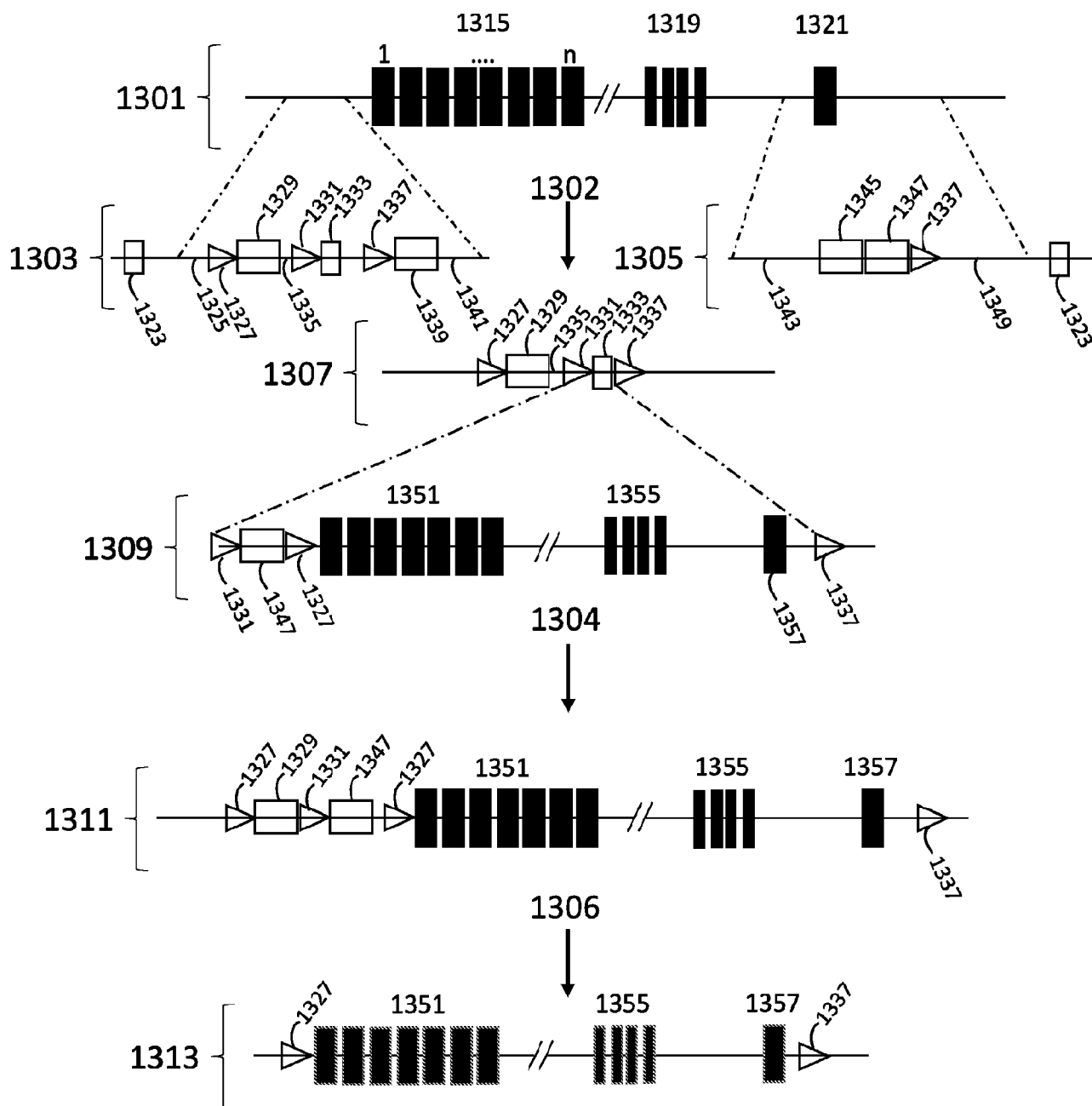


FIG. 13

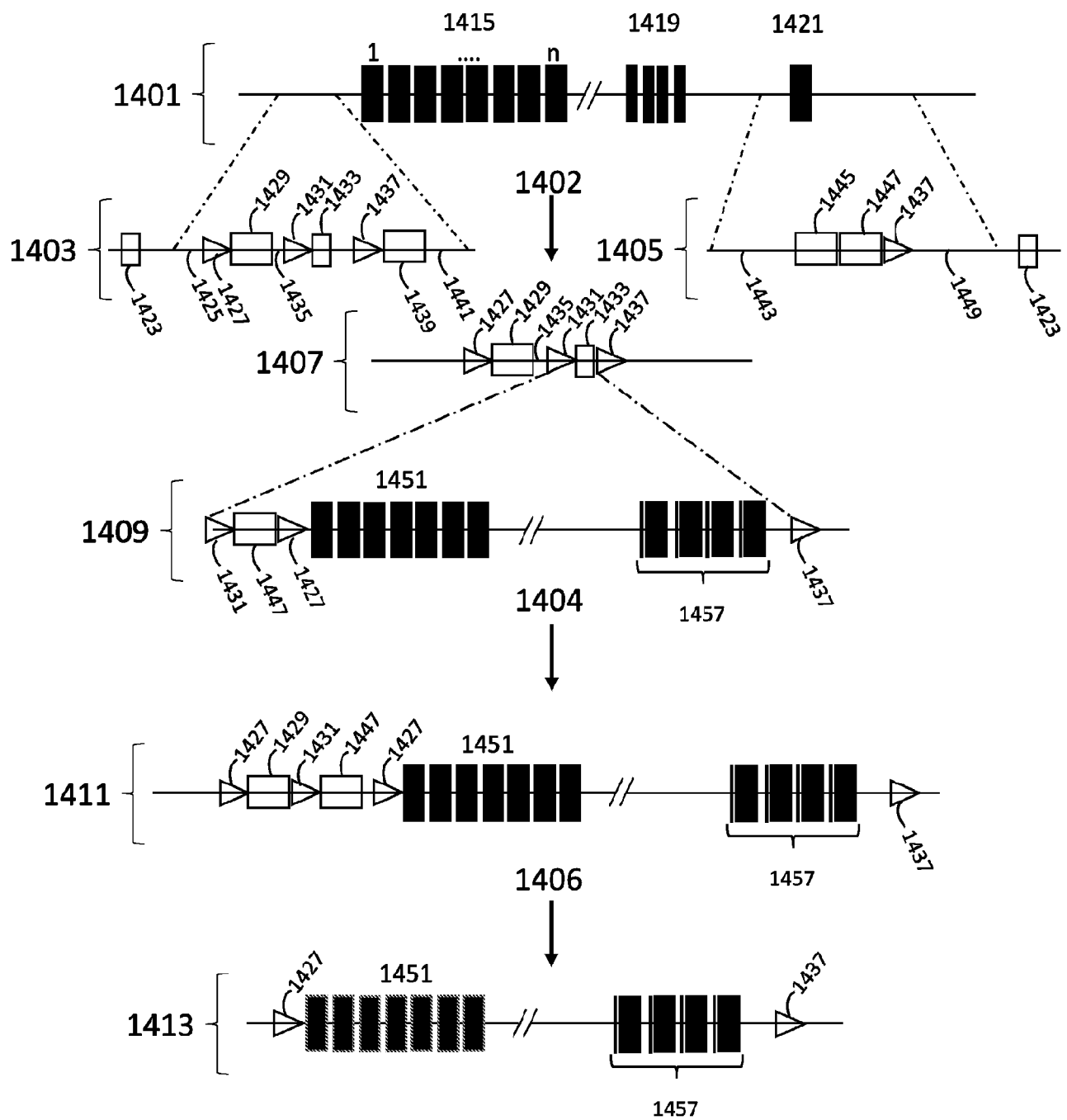


FIG. 14

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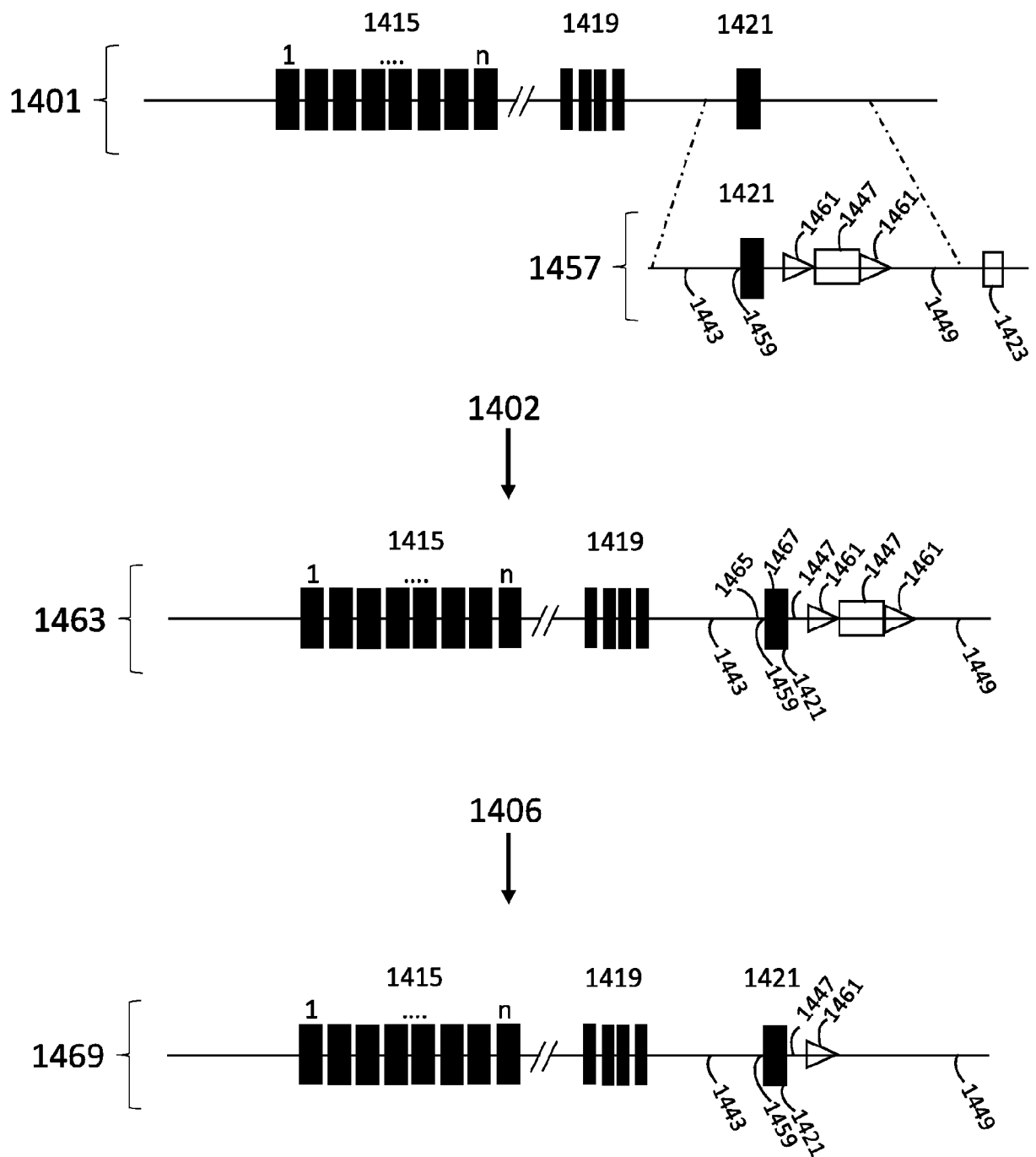


FIG. 14, cont'd.

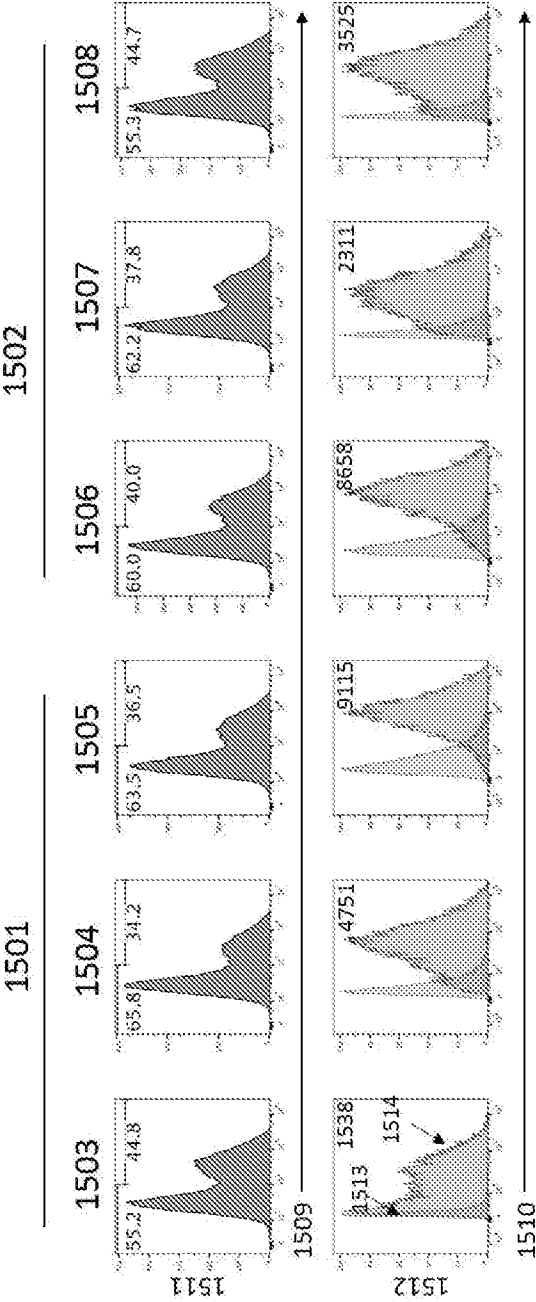


FIG. 15

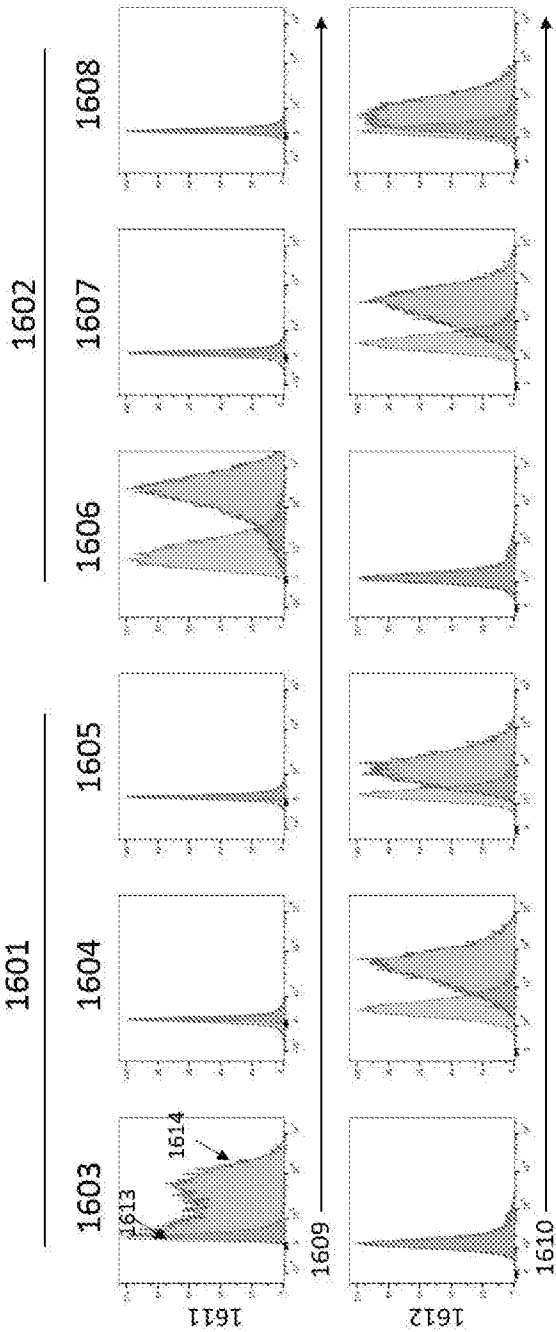


FIG. 16

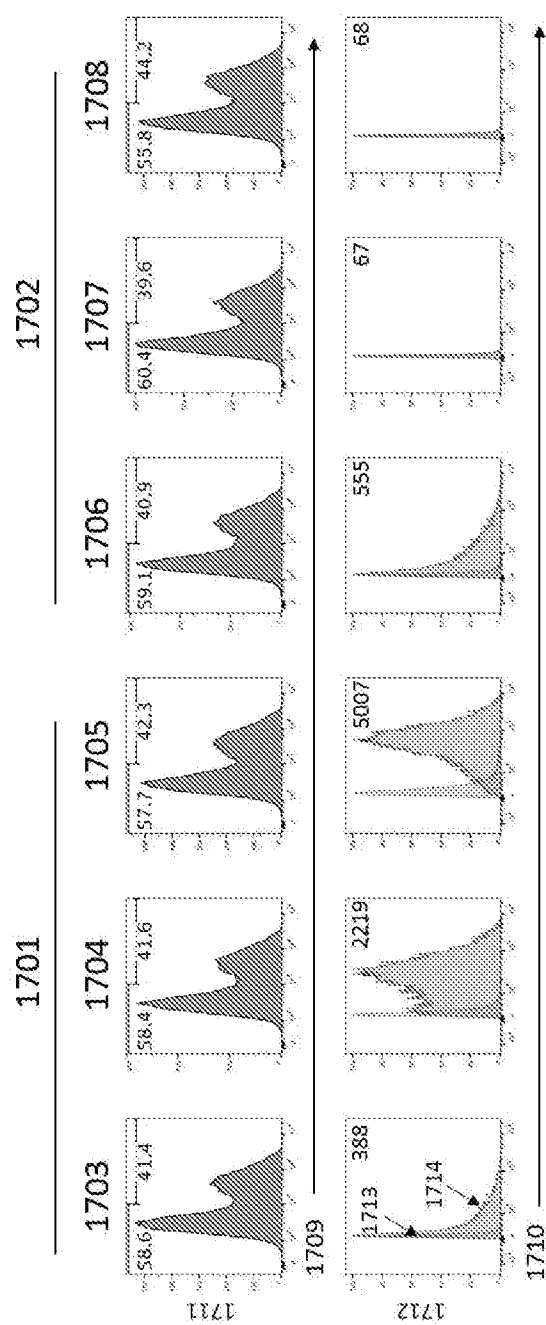


FIG. 17

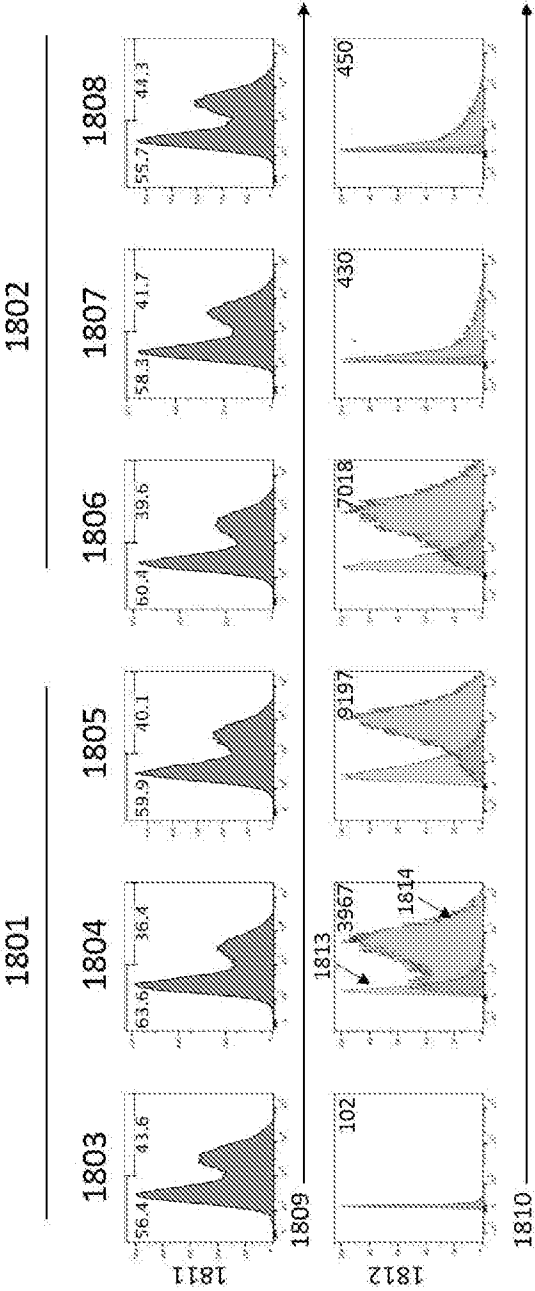


FIG. 18

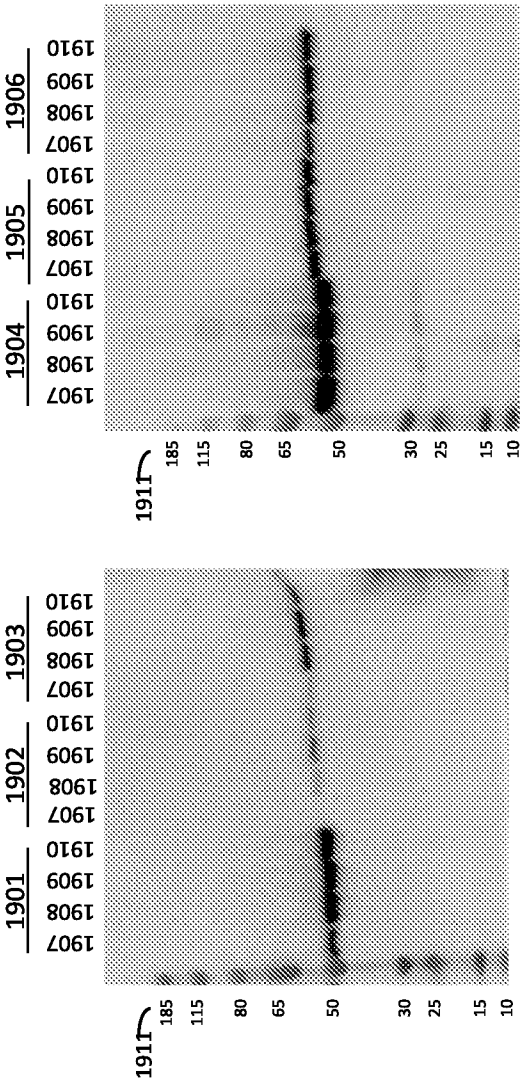


FIG. 19B

FIG. 19A

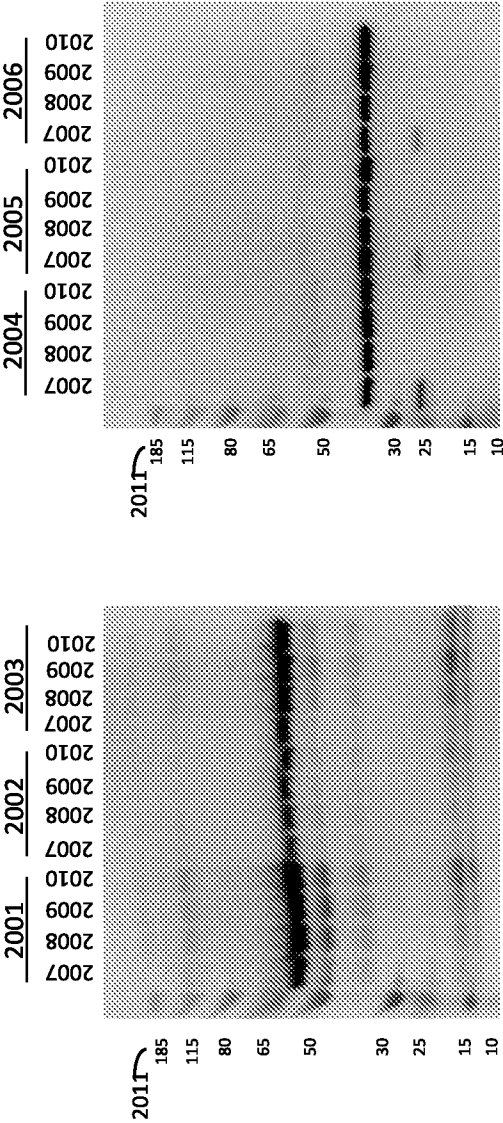


FIG. 20B

FIG. 20A

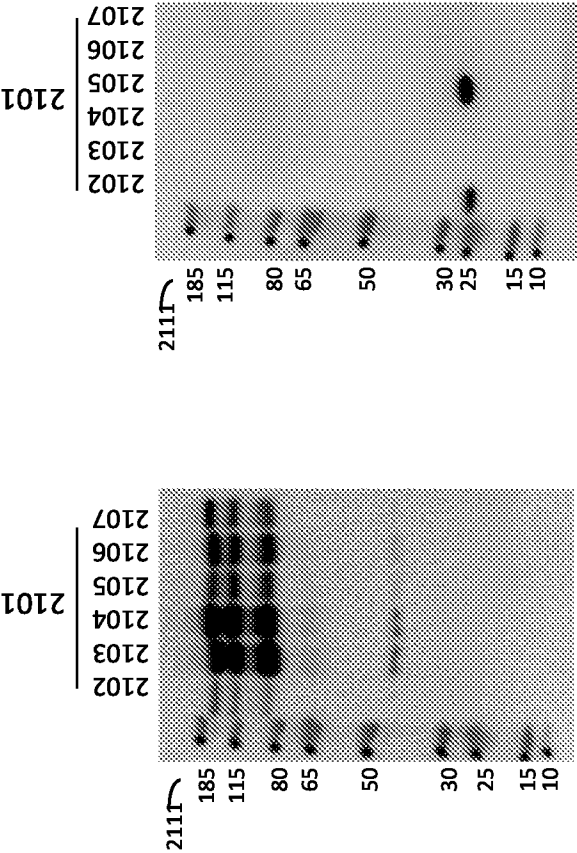


FIG. 21B

FIG. 21A

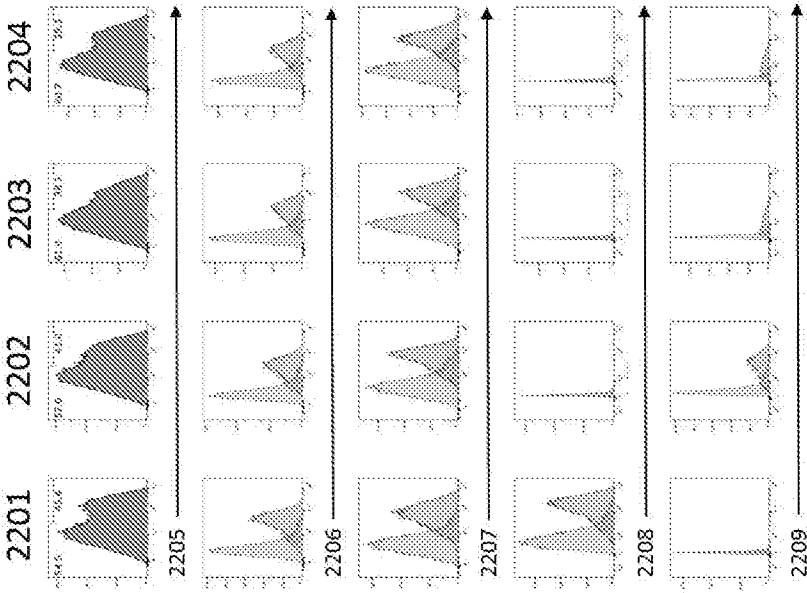


FIG. 22

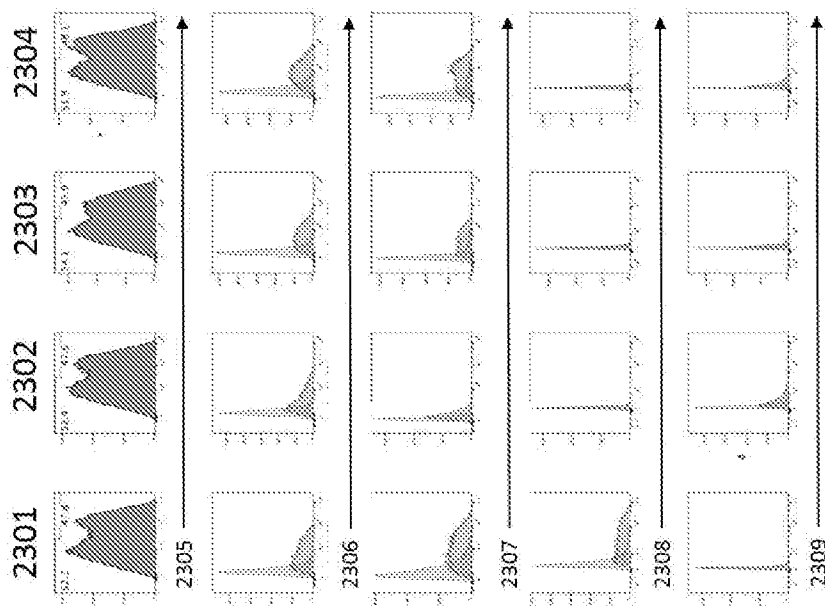


FIG. 23

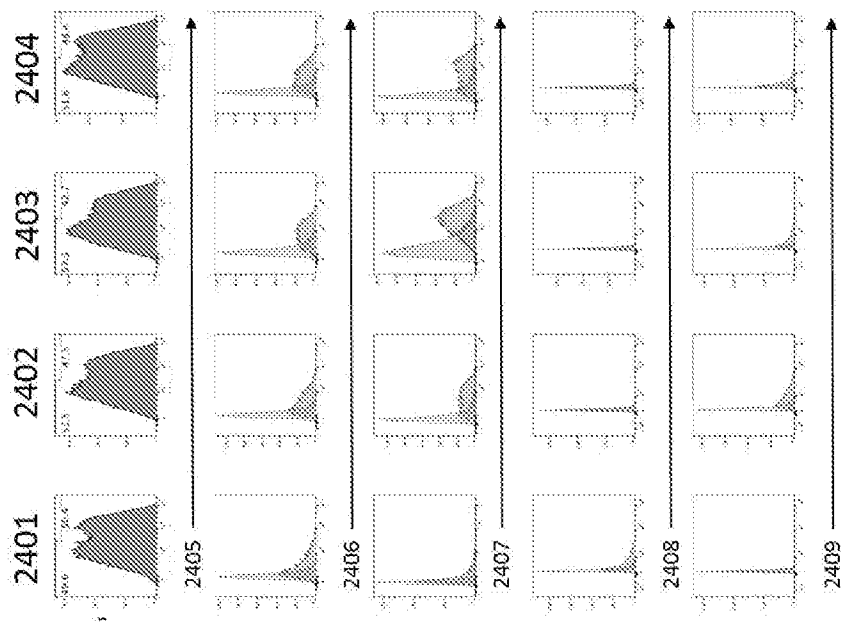


FIG. 24

SEQUENCE LISTING

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<140>

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<151> 2019-07-01

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gtgcagaagt tccaggcaga gtcaccctga tggcagacac aaccacaagc acagccaaca	240
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<210> 4
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<212> DNA
<213> Canis lupus familiaris

<400> 4
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<210> 5
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 5
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gcagacgctg tgaagggccg attcaccatc tccagagaca atgccaagaa cacgctgtat 240
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<210> 6
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 6
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<210> 7
<211> 297
<212> DNA
<213> Canis lupus familiaris

<400> 7
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<210> 8
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 8
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<210> 9
<211> 297
<212> DNA
<213> Canis lupus familiaris

<400> 9
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<210> 10
<211> 293
<212> DNA
<213> Canis lupus familiaris

<400> 10
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ccaggaaagg ggcttcagtg ggtcgcatac attagcaatg atggaagtag cacaagctac 180
gcagacgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacgctctat 240
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<210> 11
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 11
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caaaagaagg ggctgcagtg ggtcggacat attagctatg atggaagtag tacatactac 180
gcagacactt tgagggacag attcaccatc tccagagaca acaccaagaa catgctgtat 240
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<210> 12

<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 12
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gcagaagctg taaagggccg attcaccatc tccagagaca acgccaagaa catggcgtat 240
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<210> 13
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 13
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<210> 14
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 14
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gcagacgctg tgaagggcca attcaccatc tccagagaca acgccaggaa cacgctctat 240
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<210> 15
<211> 293
<212> DNA
<213> Canis lupus familiaris

<400> 15
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gaaggggctg cagtgggtcg cagggtattac caatgataga agtagcacia gctatgcaga 180
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<210> 16
<211> 296

<212> DNA
<213> Canis lupus familiaris

<400> 16
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cagacgctgt gaagggccga ttcacatct ccagagaca tgccaagaac acgctgtatc 240
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<210> 17
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 17
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acagacactg tgagggacag attcaccatc tccagagaca acaccaagaa catgctgtat 240
ctgcagatga acagcctgag agccgaggac acagccgtgt attactgcat gaggaa 296

<210> 18
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 18
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tcctgtgtgg cctctggatt caccttcagt aactacaaaa tgtactgggt ccaccaggct 120
ccagggaag ggctggagtg ggtcgcaagg atttatgaga gtggaagtag cacatactac 180
gcagaagctg taaagggccg attcaccatc tccagagaca acgccaagaa catggtgtat 240
ctgcagatga acagcctgag agcctaggac acggccgtgt attactgtgt gagtga 296

<210> 19
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 19
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tcctgtgtgg cctctggatt cacctttagt agttactaca tgttttggat ccgccaggca 120
ccagggaagg gcaatcagtg ggtcgatat attacaaag atggaagtag cacatactac 180
ccagacgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacactgtat 240
ctgcagatga acagcctgac agtggaggac acagcccttt attactgtgc gagaga 296

<210> 20
<211> 296
<212> DNA

<213> Canis lupus familiaris

<400> 20

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ccaggggaagg	ggctgcagtg	ggtcgcatac	attagcagtg	atggaaggag	cacaagttac	180
acagacgctg	tgaagggccg	attcaccatc	tccagagaca	atgccaagaa	cacgctgtat	240
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<210> 21

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 21

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cctgagaagg	ggctgcagtt	ggtcgcaggt	attaacagcg	gtggaagtag	cacatactac	180
acagacgctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	cacagtgtat	240
ctgcagatga	acagcctgag	agccgaggac	acggccatgt	attactgtgc	aaagga	296

<210> 22

<211> 294

<212> DNA

<213> Canis lupus familiaris

<400> 22

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cctctgtgtc	ctctggattc	accttcagta	tctactgcat	gtgatgggtc	tgccaggctc	120
caggaaaggg	gctgcagtga	gtcgcataca	gtaacagtgg	tggaagtagc	actaggtaca	180
cagacgctgt	gaagggtcga	ttcaccacct	ccagagacaa	tgccaagaac	acactgtatc	240
tgcatgatga	cagcctgaga	gtgaggacac	agcgggtgtat	tactgtgcag	gtga	294

<210> 23

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 23

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acagacactg	tgaagggccg	attcaccatc	tccagagaca	atgccaagaa	cacgctgtac	240
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<210> 24

<211> 284

<212> DNA

<213> Canis lupus familiaris

<400> 24
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tcctatgtga cctctggatt caccttcagg agctactgga tgagctgggt cagccaggct 120
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gcagatgctg tgaaggggtg attcaccatc tccagagaca atgccaagaa cagctgtat 240
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<210> 25
<211> 292
<212> DNA
<213> Canis lupus familiaris

<400> 25
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tgcagatgaa cagcctgaga gccgaggaca tggccatgta ttactgtgca ga 292

<210> 26
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 26
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ctgcagatga acagcctgag agccgaggac acagccgtgt attcctgtgc gaagga 296

<210> 27
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 27
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gcagacattg tgaagggccg attcaccatc tccagagaca atgccaagaa catgctgtat 240
ctgcagatga acagcctgag agccgaggac atggccgtat attattgtgc aaggta 296

<210> 28
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 28
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ctgcagatga acagcctgag atccgaggac acggccgtgt attactgtgt gaagga 296

<210> 29
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 29
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gcagacgctg tgaagggccg attcatcatc tccagagaca atgccaagaa cacgctgtat 240
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<210> 30
<211> 300
<212> DNA
<213> Canis lupus familiaris

<400> 30
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gcagacgctc tgaagggccg attcaccatc tccagagaca atgcaaaaaa cacactgtat 240
ctgtagaaga acagcctgag agccgaggga ggacacggcc gtgtattact gtgcgaggga 300

<210> 31
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 31
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ctgcagatga acagcctgag agccgaggac acggccgtgt attactgtgt gaggga 296

<210> 32
<211> 303
<212> DNA
<213> Canis lupus familiaris

<400> 32

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aaatcacgca gacacagtaa agggccgatt taccatctcc agagacaaca ccaagaacac	240
gctgtatcta cagatgagca gcctgggagc cgatgacacg gccctgtatt actgtgtgag	300
gga	303

<210> 33
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 <212> DNA
 <213> Canis lupus familiaris

<400> 33	
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actgacgctg tgaagggccg attcaccatc tccagagaca acgtcaagaa ctcgctgtat	240
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<210> 34
 <211> 296
 <212> DNA
 <213> Canis lupus familiaris

<400> 34	
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ccagggaagg ggggtgcagtg ggctgcatac attaacagtg gtggaagtag cacaagctcc	180
gcagatgctg tgaagggctg attcatcatc tccagagaca acgtcaagaa cagctatat	240
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<210> 35
 <211> 294
 <212> DNA
 <213> Canis lupus familiaris

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<210> 36
 <211> 115
 <212> DNA
 <213> Canis lupus familiaris

<400> 36
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<210> 37
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 <212> DNA
 <213> Canis lupus familiaris

<400> 37
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<210> 38
 <211> 296
 <212> DNA
 <213> Canis lupus familiaris

<400> 38
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<210> 39
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 <213> Canis lupus familiaris

<400> 39
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<210> 40
 <211> 296
 <212> DNA
 <213> Canis lupus familiaris

<400> 40
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gcagacgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacgctgtat 240

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<210> 41

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 41

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<210> 42

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 42

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ggtggaagta gcacaagctt cgcagatgct gtgaaggga tgagctggtt tcgccaggct 120

ccagggaagg ggctgcaatg ggttacatgg attgggtatg atggaagtag cacatactac 180

acagacactg taaagggccg attcactatc tccatagaca acgccaagaa catgctgtat 240

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<210> 43

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 43

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tcctgtgtag cctctggatt caccttcagt aactacgaca tgagctgggt ccgccaggct 120

cctgggaagg ggctgcagtg ggtcgcagct attagctatg atggaagtag cacatactac 180

actgacgctg tgaagggccg attcaccatc tccagagaca acgccaggaa cacagtgtat 240

ctgcagatga acagcctgag agccgaggac acggctgtgt attactgtgc gaagga 296

<210> 44

<211> 297

<212> DNA

<213> Canis lupus familiaris

<400> 44

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tccagggaag ggctgcagt gggttgcagc tattagcagt agtggaagta gcacatacta 180

cgtagatgct gtgaagggcc gattcaccat ctccatagac aacgccaaga acatggtgta 240

tctgcagatg aacagcctga gagctgagga tattgctgtg tattactgtg ggaagga 297

<210> 45

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 45

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acagacactg tgaagggccg attcaccatc tccagagaca atggcaagaa cacgctgtac 240

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<210> 46

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 46

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acagacgctg tgaagggtcg attcaccatc tccagagaca acgccaagaa cacgctgtat 240

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<210> 47

<211> 295

<212> DNA

<213> Canis lupus familiaris

<400> 47

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tcctgtgtgg cctcaagggtt caccttcagt agctacagca tgcattgtct ccgtcagtct 120

cctgggatgg ggctacagtg ggtcacatac attagcagta atggaagcag cacatactat 180

gcagacgctg tgaagggtcg attcaccatc tccagagaca aagccaagaa catgctttat 240

ctacagatga acagcctgag agctcaggac atagccctgt attactgtgc agatg 295

<210> 48

<211> 293

<212> DNA

<213> Canis lupus familiaris

<400> 48

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<210> 49

<211> 293

<212> DNA

<213> Canis lupus familiaris

<400> 49

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tcctgtgtgg cctctggatt aaccttcagt agctacagca tgagctgggt ccgccaggct 120

cctgggaagg ggctgcagtg ggtcacagct attagctatg atggaagtag cacatactac 180

actgacgctg tgaagggccg attcaccatc tccagagaca acgccaggaa cacagtgtat 240

ctgcagatga acagcctgag agccgaggac acagctgtgt attactgtgt gga 293

<210> 50

<211> 293

<212> DNA

<213> Canis lupus familiaris

<400> 50

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<210> 51

<211> 295

<212> DNA

<213> Canis lupus familiaris

<400> 51

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cagacgctgt aaagggtga ttccaccatct ccagagacag caccaggaac atgctgtatc 240

tgcatatgaa cagcctgaga gctgaggaca cagccgtgca ttgctgtgcg agggga 295

<210> 52

<211> 294

<212> DNA

<213> Canis lupus familiaris

<400> 52

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acagatgctg tgaagggccg attcaccatc tccagagaac gccagaaca cagtgtttct 240

gcagatgaac agcctgagag ctgaggacaa ggccatgtat tactgtgcga ggga 294

<210> 53
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 53
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gcagatgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cagctgtat 240
ctgcagatga acagcctgag agctgaggac acagccgtgt attactgtgc gaagga 296

<210> 54
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 54
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caggaaggg gctgcagtgg gtcgcagtta ttagcagga tggaagtagc acaaactacg 180
cagacgctgt gaagggccga ttcaccatct ccagagacaa cgccaagaac atgctgtatc 240
tacagatgaa cagcctgaga gctgaggaca cggccatgta ttactgtgcg aagga 295

<210> 55
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 55
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ctgcagatga ccagcctgag agccgaggac acggccctat attactgtgc gatgga 296

<210> 56
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 56
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tgcaggatgaa cagcctgaga gccgaagaca cggccgtgta ttactgtgtg agtga 295

<210> 57
<211> 297
<212> DNA
<213> Canis lupus familiaris

<400> 57
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gcagacgctg tgaagggccg attcaccatc tccagagaca atgccaagaa cacgctgtat 240
ctgcagatga acagcctgag agccgaggac acggccgtgt attactgtgt gaaggga 297

<210> 58
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 58
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cagggaaagg gttgggggtg gttgcaatta ttaacagtgg tggaggtagc acatactatg 180
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tgcagatgaa cagcctgaga gcccaggaca tgaccgcgta ttactgtgtg agtga 295

<210> 59
<211> 253
<212> DNA
<213> Canis lupus familiaris

<400> 59
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<210> 60
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 60
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tcctgtgtgg cctctggatt caccttcagt agctactaca tgcactgggt ctgcaggctc 120
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cagacgctgt gaagggcaga ttcaccatct ccagagacaa ttccaagaac actctgtatc 240
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<210> 61
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 61
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ctgcagatga acagcctgag agctgaggac acagccgtgt attactgtgc gaagga 296

<210> 62
<211> 294
<212> DNA
<213> Canis lupus familiaris

<400> 62
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gcagatgaac agcctgagag ccgaggtcac agccgtatat tactgtgcaa ggta 294

<210> 63
<211> 284
<212> DNA
<213> Canis lupus familiaris

<400> 63
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tcctatgtga cctctggatt caccttcagg agctactgga tgagctgggt cagccaggct 120
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<210> 64
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 64
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<210> 65

<211> 292
<212> DNA
<213> Canis lupus familiaris

<400> 65
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ttcagatgaa cagcctgaga gctgaggaca cggctctgta ttactgtgca ga 292

<210> 66
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 66
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<210> 67
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 67
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ctgcagatgc ctgagagctg aggacacggc catgtattcc tgtgcagggg a 291

<210> 68
<211> 295
<212> DNA
<213> Canis lupus familiaris

<400> 68
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tcctgtgtgg cctctggatt cacctgcagt agctactaca tgtactagac ccaccaaatt 120
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ctgcaatgaa cagcctgaga gccgaggaca cagccgtgta ttactgtgtg aagga 295

<210> 69
<211> 291

<212> DNA

<213> *Canis lupus familiaris*

<400> 69

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ctgggaagg	ctgcagtggg	tcgcaaaaat	tagcaatagt	ggaagtagca	catactacac	180
agatgctgtg	aagggccgat	tcaccatctc	cagagacaat	gccaagaaca	cgctctatct	240
gcagatgaac	agcctgagag	ccgaggacac	ggccttgtat	tactgtgcag	a	291

<210> 70

<211> 296

<212> DNA

<213> *Canis lupus familiaris*

<400> 70

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ctgcagatga	acagcctgag	agccgaggac	acggctatgt	attactgtgc	aaagga	296

<210> 71

<211> 295

<212> DNA

<213> *Canis lupus familiaris*

<400> 71

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tgcatatgaa	cagcctgaga	gccaaggaca	cggccctata	tccctgtgca	atgga	295

<210> 72

<211> 296

<212> DNA

<213> *Canis lupus familiaris*

<400> 72

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gcagatgctg	tgaagggccg	gttcaccatc	tccagagaca	atgccaggaa	cacactgtat	240
ctgcagatga	acagcctgag	atccgaggac	acagccgtgt	attactgtcc	gaagga	296

<210> 73

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 73

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gcagacgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacgctgtat	240
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<210> 74

<211> 282

<212> DNA

<213> Canis lupus familiaris

<400> 74

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ccagggaagg ggctgcagtg ggtcacatgg gtttaactg gtggaagcag caaaagctat	180
gcagatgcta tgaaggggagc atttaccatc tccaggcaca aagccaagaa cacactatct	240
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<210> 75

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 75

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<210> 76

<211> 292

<212> DNA

<213> Canis lupus familiaris

<400> 76

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ccaggaaagg gctgcagtg attgcatata ttagctatga tggaagtagc acaggttaca	180
aagacgctgt gcagggccga ttcaccatct ccagagacaa cgccaagaac acgctgtatc	240
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<210> 77

<211> 295

<212> DNA

<213> Canis lupus familiaris

<400> 77
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tgcagttgaa cagcctgaga gccgaggaca ccgctgtgta ttactgtgcg aggga 295

<210> 78
<211> 293
<212> DNA
<213> Canis lupus familiaris

<400> 78
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<210> 79
<211> 293
<212> DNA
<213> Canis lupus familiaris

<400> 79
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<210> 80
<211> 282
<212> DNA
<213> Canis lupus familiaris

<400> 80
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cctgagagcc gacgacacgg ccgtgtgttg ctgtgcgagg ga 282

<210> 81
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 81
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cccgggaagg gggtagcagt ggtcacatag atttatgcta gtggaagtag cacaagctac 180
acagatgctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacagtgttt 240
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<210> 82
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 82
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tcctgtgtgg cctctagatt caccttcagt agctactaca tatactgtat ccaccaagct 120
ccaggggaagg ggctgcaggt ggtcgcatgg attagctatg atggaagtag aacaagctac 180
gccgacgcta ttagaggcca attcatcatc tccagagaaa acaccaagaa cacgctgtat 240
ctgtagatga acagcctgag tgccaaggac acggcactat atccctgtgc gaggaa 296

<210> 83
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 83
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ccaggggaagg ggctgcagtg ggtcgcacag attagcagtg atggaagtag cacatactac 180
ccagacgctg tgaaggggtca attcaccatc tccagagaca atgccaagaa cacgctgtat 240
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<210> 84
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 84
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ccacaggctg tgaagggccg attcaccatc tccagagaca acgccaagaa cacgctctat 240
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<210> 85
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<212> DNA
<213> Canis lupus familiaris

<400> 85

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gcagacgccca tgaagggcca atttaccatc tccagagaca attccaagaa tacgctgtat	240
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<210> 86
 <211> 297
 <212> DNA
 <213> Canis lupus familiaris

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ccagggaaag ggctggagtg ggtcgcaatt attaacagt gtggaggtag catatactac	180
gcagacacag tgaagggccg attcaccatc tccagagaaa acgccaagaa cacgctctat	240
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<210> 87
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 <212> DNA
 <213> Canis lupus familiaris

<400> 87 gaactcacac tgcaggagtc agggccagga ctggtgaagc cctcacagac cctctctctc	60
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 <213> Canis lupus familiaris

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accaccagg ggaaggcact ggagtcaatg ccacatctgg tgggagaacg ctaagtacca	180
cagcctgtct ctgaacagca gcaagatgta tagaaagtcc aacacttga aagataaagg	240
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<210> 89
 <211> 299
 <212> DNA
 <213> Canis lupus familiaris

<400> 89 ctggcacccc tgcaggagtc tgtttctggg ctggggaaac ccaggcagac ccttacactc	60
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acccaccagg ggaaggcact ggagtcaatg ccacgtctgg tgggagaaca ctaagtacca	180
cagcctgtct ctgaacagca gcaagatgta tagaaagtcc aacacttgga aagataaagg	240
attatgtttc acaccagaag cacatctatt caacctgatg aacaatcagc ctgatgaga	299

<210> 90
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 <212> DNA
 <213> Canis lupus familiaris

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<210> 91
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<400> 91 ctactacggt agctactac	19
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<210> 93
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<400> 93 gtatagtagc agctggtac	19
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<210> 94
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<400> 94 agttctagta gttggggct	19
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<210> 95
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<400> 95 ctaactgggg c	11
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<210> 97
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 <212> DNA
 <213> Canis lupus familiaris

<400> 97
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<210> 98
 <211> 50
 <212> DNA
 <213> Canis lupus familiaris

<400> 98
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<210> 99
 <211> 48
 <212> DNA
 <213> Canis lupus familiaris

<400> 99
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<210> 100
 <211> 51
 <212> DNA
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<400> 100
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<210> 101
 <211> 54
 <212> DNA
 <213> Canis lupus familiaris

<400> 101
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<210> 102
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

<400> 102
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tacctgcaaa agccaggcca gtctccacag cttctgatct acttggtttc caaccgcttc 180

actggcgtgt cagacagggt cagtggcagc gggtcaggga cagatttcac cctgagaatc 240

agcagagtgg aggctaacga tactggagtt tattactgcg ggcaaggtag acagcttcct 300

cc 302

<210> 103

<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 103
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ttccgacaga agccaggcca gtctccacag cgtttgatct ataaggctct caacagagac 180
cctgggggtcc cagacagggtt cagtggcagc gggtcaggga cagatttcac cctgagaatc 240
agcagagtgg aggctgatga tgctggagtt tattactgcg ggcaaggat acaagatcct 300
cc 302

<210> 104
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 104
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cc 302

<210> 105
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 105
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ttccgacaga agccaggcca gtctccacag ggcctgatct ataaggctct caacagagac 180
cctgggggtcc cagacagggtt cagtggcagc gggtcaggga cagatttcac cctgagaatc 240
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cc 302

<210> 106
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 106
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ttccgacaga agccaggcca gtctccacag ggcctgatct atagggtgtc caaccgtcc 180
actggcgtgt cagacagggtt cagtggcagc gggtcaggga cagatttcac cctgagaatc 240

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 cc 302

 <210> 107
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

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 ttccgacaga agccaggcca gtctccacag cgtttgatct ataaggtctc caacagagac 180
 cctgggggtcc cagacagggtt cagtggcagc gggtcagga cagatttcac cctgagaatc 240
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 cc 302

 <210> 108
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 <212> DNA
 <213> Canis lupus familiaris

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 cctgggggtcc cagacagggtt cagtggcagc gggtcagga cagatttcac cctgagaatc 240
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 cg 302

 <210> 109
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

 <400> 109
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 cc 302

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 <211> 303
 <212> DNA
 <213> Canis lupus familiaris

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ttctggagtc ccaggctggt tcattggcag tggatcaggg acagatttca ccctgaggat	240
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tcc	303

<210> 111
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

<400> 111	
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ttccgacaga agccaggcca gtctccacag ggcctgatct acttggtttc caaccgtttc	180
tcttgggtcc cagacaggtt cagtggcagc gggtcaggga cagatttcac cctgagaatc	240
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tc	302

<210> 112
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

<400> 112	
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tacctgaaa agccaggcca gtctccacag cttctgatcg acttggtttc caaccatttc	180
actggggtgt cagacaggtt cagtggcagc gggctctggca cagattttac cctgaggatc	240
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cc	302

<210> 113
 <211> 298
 <212> DNA
 <213> Canis lupus familiaris

<400> 113	
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tgacagacatc aggccaggtt ccaaggcatc tgaaccattt ggcttccagc tgttactctg	180
gggtctcaga caggttcagt ggcaacgggt caggacaga ttccacactg aaaatcagca	240
gagtgagggc tgaggatggt agtggtttatt agtgcctgca agtacacaac cttccatc	298

<210> 114

<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 114
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tacctgcaga agccaggcca gactcctcgg ccgctgattt atgaggcttc caagcgtttc 180
tctgggtct cagacaggtt cagtggcagc gggtcaggga cagatttcac ccttaaaatc 240
agcagggtgg aggctgagga tgttgagtt tattactgcc agcaaagtct acattttcct 300
cc 302

<210> 115
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 115
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tacctgcaga agccaggcca gattccaaag gacctgatct atagggtgtc caactgcttc 180
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cc 302

<210> 116
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 116
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cc 302

<210> 117
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 117
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<210> 118

<211> 286

<212> DNA

<213> Canis lupus familiaris

<400> 118

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gggcaggctc ccaagctcct catctatggt acatccaaca gggccactgg tgtcccatcc 180

cggttcagtg gcagtgggtc tgggacagac ttcagcttca ccatcagcag cctggagcct 240

gaagatgttg cagtttatta ctgtcagcag tataatagcg gatata 286

<210> 119

<211> 285

<212> DNA

<213> Canis lupus familiaris

<400> 119

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gctcccaggc tcttcatcta tgggtcatcc aacagggcca ctggtgtccc agtccgcttc 180

agcggcagtg ggtgtgggac agatttcacc ctcatcagca gcagtctgga gtcagtctga 240

agatgttgca acatattact gccagcagta taatagctac ccacc 285

<210> 120

<211> 305

<212> DNA

<213> Canis lupus familiaris

<400> 120

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atcaactgca agtccagcca gaggcttctg tacagcttca accagaagaa ctacttagcc 120

tggtagcagc agaaaccagg agagcgtcct aagctgtcga tctacttagc ctccagctgg 180

gcattctgggg tccctgcccg attcagcagc agtggatctg ggacagattt caccctcacc 240

atcaacaacc tccaggctga agatgtgggg gattattact gtcagcagca ttatagttct 300

cctcc 305

<210> 121

<211> 287

<212> DNA

<213> Canis lupus familiaris

<400> 121

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acgaactgca gggccagtca aagcgtagt ggctacttag cctggtagct gcagaaacca 120

ggacagcgtc ctaagctgct catctactta gcctccagct gggcatctgg ggtccctgcc 180

cgattcagca gcagtggatc tgggacagat ttcaccctca ccgtcaacaa cctcgaggct 240

gaagatgtga gggattatta ctgtcagcag cattatagtt ctcctct 287

<210> 122

<211> 305

<212> DNA

<213> Canis lupus familiaris

<400> 122

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ccttgtagca acagaaatca gaacagcatc ctaaagtcct gattaatgaa gcctccagtt 180

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attgatcctg tggaggctgg cgatgctgtc aactattact gccagcagag taaggagtct 300

cctcc 305

<210> 123

<211> 289

<212> DNA

<213> Canis lupus familiaris

<400> 123

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tatcaataga aaccagggtga gattcctcga gtcctggat acgacacttc catccttaca 180

ggtcccaaac tggttcagtg gcagtgtctc caagtcagat cttactctca tcatcagcaa 240

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<210> 124

<211> 38

<212> DNA

<213> Canis lupus familiaris

<400> 124

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<210> 125

<211> 39

<212> DNA

<213> Canis lupus familiaris

<400> 125

tttatacttt cagccaggga accaagctgg agataaaac 39

<210> 126

<211> 38

<212> DNA

<213> Canis lupus familiaris

<400> 126

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<210> 127

<211> 38
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 <210> 128
 <211> 38
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 <400> 128
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 <210> 129
 <211> 306
 <212> DNA
 <213> Canis lupus familiaris

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 gggttccaga tccatttctt agaggctcca agtctggcac ctcaggctcc ctgaccaact 240
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 gtgctc 306

 <210> 130
 <211> 294
 <212> DNA
 <213> Canis lupus familiaris

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 ccagggaagg cccctaaact cctcatatac gataatgaga agcgaccctc aggtatcccc 180
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 <210> 131
 <211> 299
 <212> DNA
 <213> Canis lupus familiaris

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 cccgatcgat tctctggctc caagtctggc agcacagcca ccctgaccat ctctgggctc 240
 caggctgagg atgaggctga ttattactgc tcatcttggg acaacagtct caaagctcc 299

<210> 132
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 132
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<213> Canis lupus familiaris

<400> 133
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<400> 134
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<213> Canis lupus familiaris

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<212> DNA
<213> Canis lupus familiaris

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<212> DNA
<213> Canis lupus familiaris

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ccaggacag cccctaaaac cattatctat ttggatgata ccagaccccc tgggggtcccg 180
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<212> DNA
<213> Canis lupus familiaris

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gatcgattct ctggctccaa gtctggcagc acagccaccc tgaccatctc tgggctccag 240
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<213> Canis lupus familiaris

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<210> 142
<211> 299
<212> DNA
<213> Canis lupus familiaris

<400> 142
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<210> 143
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 143
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gatcgattct ctggctccaa gtcaggcagc acagccaccc tgaccatctc tgggctccag 240
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<212> DNA
<213> Canis lupus familiaris

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<210> 145
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<212> DNA
<213> Canis lupus familiaris

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gattaattct gtggctccac atccagcagt tcaggctccc tgaccatcac tgggctctgg 240
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<211> 298
<212> DNA
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<211> 296
<212> DNA
<213> Canis lupus familiaris

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gaccgatttt ctggctccaa atctggcaac tcaggcactc tgaccatcac tgggcttcag 240
cctgaggacg aggctgatta ttattgtcag tccattgaac ccatgcttgg tgctcc 296

<210> 148
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<212> DNA

<213> Canis lupus familiaris

<400> 148

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ccagaaacag gccccagaaa catcatctat gctgataact accgagcctc ggggggtccct	180
gatcgattct ctggctccaa gtcaggcagc acagccaccc tgaccatctc tgtgctccag	240
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<210> 149

<211> 311

<212> DNA

<213> Canis lupus familiaris

<400> 149

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ggctgggtacc aacagtcccc aggaaagtca cccagtctcc tcatttatga tgaaaccaga	180
aactctggggg tccctgatcg attctctggc tccagaactg gtagctcagc ctccctgccc	240
atctctggac tccaggctga ggacaagact gagtattact gctcagcatg ggatgatcgt	300
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<210> 150

<211> 292

<212> DNA

<213> Canis lupus familiaris

<400> 150

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ccaggaaagg cccctaaact cctcgtggac agtgatgggg atcgaccgtc aggggtccct	180
gaccgatttt ctggctctaa gtctggcaaa tcagccaccc tgaccatcac tgggcttcag	240
gctgaggacg aggctgatta ttactgtata ttgggtccac gctttgtgct ca	292

<210> 151

<211> 285

<212> DNA

<213> Canis lupus familiaris

<400> 151

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cctgacctgg aagagtccca gtattggtga ttatggtatg aaatggtaca agcagcttgc	120
aaggacagac cccagactcg tcatttatgg caatagcaat tgatcctcgg gtccccaatc	180
aattttctgg ctctggtttt ggcatcactg gctccttgac cacctctggg ctccagactg	240
aaaaataggc tgattactag tgcttctcca gtgatccagg cctgt	285

<210> 152

<211> 299

<212> DNA
<213> Canis lupus familiaris

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ctcccaggaa caggccccag aaccatcatc tataatacca atactcgacc ctctgggggtt 180
cctgatcgat tctctggctc caaatcaggc agcacagcca ccctgaccat ctctggactc 240
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<211> 293
<212> DNA
<213> Canis lupus familiaris

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cgattctctg gctccaggctc aggcagcaca gccaccctga ccatctctgg gctccaggct 240
gaggacgaag ctgattatta ctgcttcaca tacgacagta gtctcaaagc tcc 293

<210> 154
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 154
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ccaggaaatg cccctaaact cctttagat ggtactggga atcgaccctc aggggtccct 180
gaccaatctt ctggctcaa atctggcaat tcaggcactc tgaccatcac tgggctccag 240
gctgaggacg aggctgatta ttattgtcag tcctatgatc tcacgcttgg tgctcc 296

<210> 155
<211> 280
<212> DNA
<213> Canis lupus familiaris

<400> 155
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tactgcactg gaatccctag caacactgat tatagtggat tggaaattta tacttatgtg 120
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ccatctctgg actccaggct gaggatagtc ttaatgctca 280

<210> 156
<211> 296
<212> DNA

<213> Canis lupus familiaris

<400> 156

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tcctgcactg gaagcagctc caacatcggg ggatataatg ttggctgggt ccagcagctc	120
ccgggaacag gccccagaac cgatcatctat agtagtagta accgaccctc ggggggtcccg	180
gatcgattct ctggctccag gtcaggcagc acagccaccc tgaccatctc tgggctccag	240
gctgaggacg aggctgagta ttactgctca acatgggaca gcagtctcaa agctcc	296

<210> 157

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 157

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ccgagaacag gccccagaac cgatcatctat ggtaatagta actgaccctc ggggggtcctc	180
gatcaattct ctggctccaa gtcaggcagc atagccaccc tgaccatctc tgtgctccag	240
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<210> 158

<211> 298

<212> DNA

<213> Canis lupus familiaris

<400> 158

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tcccaggaac aggccccaaa accatcatct ataataccaa tactcgaccc tctgggggttc	180
ctgatcgatt ctctggctcc aaatcaggca gcacagccac cttaccatt gctggactcc	240
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<210> 159

<211> 272

<212> DNA

<213> Canis lupus familiaris

<400> 159

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gtattggtga ttatggtgtg aaatggtaca ggcagctagc aagaacagac cccagactcc	120
tcatttatag caatagcaat cgatccttga gtccccaatc aattttccgc ctctggtttt	180
gacattactg gctccttgac cacctccagg ctccagactg aaaaataggc tgattactag	240
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<210> 160

<211> 296

<212> DNA

<213> Canis lupus familiaris

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<212> DNA
<213> Canis lupus familiaris

<400> 161
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<210> 162
<211> 293
<212> DNA
<213> Canis lupus familiaris

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<212> DNA
<213> Canis lupus familiaris

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<211> 298
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<211> 296
<212> DNA
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<212> DNA
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<210> 168
<211> 299
<212> DNA
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<400> 168
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cctgaacgat tctctggctc caagtcaggc agctcagcca ctctgaccat cactgggctc 240
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<210> 169
<211> 289
<212> DNA
<213> Canis lupus familiaris

<400> 169
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<210> 170
<211> 292
<212> DNA
<213> Canis lupus familiaris

<400> 170
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tgaagatgga gctgctcttc acaggccctc ttgggacaaa attcttgggg ct 292

<210> 171
<211> 309
<212> DNA
<213> Canis lupus familiaris

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gatcgattct ctggctccag gtcaggcagc acagccaccc tgaccatctc tgggctccag	240
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<211> 296

<212> DNA

<213> Canis lupus familiaris

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gagagattct ctgtctcaa ttctggcagc tcagccaacc tgaccatctc tgggctccag	240
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<211> 295

<212> DNA

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caggaaagtc ccctaaaact atcatctatg gtaatagcaa tcgacccttg aggggtcccg	180
atcgattctc tggctccaag tatggcaatt cagccacgct gaccatcact gggctccagg	240
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<211> 299

<212> DNA

<213> Canis lupus familiaris

<400> 175

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<211> 296

<212> DNA

<213> Canis lupus familiaris

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<210> 177
<211> 285
<212> DNA
<213> Canis lupus familiaris

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<212> DNA
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<211> 294
<212> DNA
<213> Canis lupus familiaris

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<212> DNA
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gaccggtttt ccggctccaa gtctggcaac tcagccaccc tgaccatcac tgggcttcag 240
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<213> Canis lupus familiaris

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aaggacagac cccagacttc tcatctatgg caatagcaat tgatcctcgg gtccccaatc 180
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<212> DNA
<213> Canis lupus familiaris

<400> 184

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 <212> DNA
 <213> Canis lupus familiaris

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caattttctg gctctaaatc aggcagcaca gccaccctga ccatctctag gctccaggct	240
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 <212> DNA
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<400> 187	
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aaggacagac cccagacttc tcatttatgg caatagcaat tgatcctcgg gtccccaatc	180
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<210> 212
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 <212> DNA
 <213> Canis lupus familiaris

<400> 212	
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<210> 217

<211> 299

<212> DNA

<213> Canis lupus familiaris

<400> 217

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<210> 218

<211> 299

<212> DNA

<213> Canis lupus familiaris

<400> 218

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<210> 219

<211> 299

<212> DNA

<213> Canis lupus familiaris

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cctgatcgat tctctggctc catatcaggc agcacagcca ccctgactat tgctggactc 240

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<210> 220

<211> 266

<212> DNA

<213> Canis lupus familiaris

<400> 220

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atggacagac cccagactcc tcatactatg caatagcaat tgattctcgg gtccccagtc 180

tattttctgg ctctggtttt ggcatcactg gtccttgac cacctccggg ctccagactg 240

aaaaataggc tgatttctag tgcttc 266

<210> 221
<211> 296
<212> DNA
<213> Canis lupus familiaris

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<210> 222
<211> 309
<212> DNA
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<400> 222
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<210> 223
<211> 296
<212> DNA
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<210> 224
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<212> DNA
<213> Canis lupus familiaris

<400> 224
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gatcgattct ctggctccaa gtcaggcagc acagccaccc tgaccatctc tgggctccag 240

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<211> 296

<212> DNA

<213> *Canis lupus familiaris*

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<210> 226

<211> 296

<212> DNA

<213> *Canis lupus familiaris*

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<210> 227

<211> 299

<212> DNA

<213> *Canis lupus familiaris*

<400> 227

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<210> 228

<211> 292

<212> DNA

<213> *Canis lupus familiaris*

<400> 228

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aatccagctc tgagtcagga cacatcagga gtgtccaata tgtgtcctgc taccaacagc 120

tccatgagtg ggcagtcaaa tcctcatgta ttatgatggc ttgaccttct gtggaccctg 180

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<211> 296

<212> DNA

<213> Canis lupus familiaris

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<211> 297

<212> DNA

<213> Canis lupus familiaris

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<211> 297

<212> DNA

<213> Canis lupus familiaris

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<210> 232

<211> 296

<212> DNA

<213> Canis lupus familiaris

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<211> 286

<212> DNA

<213> Canis lupus familiaris

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<211> 284

<212> DNA

<213> Canis lupus familiaris

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<211> 284

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<213> Canis lupus familiaris

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<211> 288

<212> DNA

<213> Canis lupus familiaris

<400> 236

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<211> 287
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<211> 288
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<213> Canis lupus familiaris

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 <213> Canis lupus familiaris

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<210> 246
 <211> 288
 <212> DNA
 <213> Canis lupus familiaris

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<210> 247
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 <212> DNA
 <213> Canis lupus familiaris

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<210> 248
 <211> 286
 <212> DNA
 <213> Canis lupus familiaris

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 acctgtgggg gagacagcat tggaagtaaa agtgtttact ggtaccagca gaagctgggc 120
 caggcccctg ttgattatct atagagacag caacaggccg acagggatcc ctgagcgatt 180
 ctctggcgcc aacacgggga acatggccac cctgactatc agcggggccc tggccgtgga 240
 cgaggctgac tattactgcc aggtgtggga cagcagtgt aaggct 286

<210> 249

<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 249
tcccttgggc tgaatcagcc tccctccgtg ttggtggccc tgggacagat ggcaacaaac 60
acctgctccg gagatgtctt agggaaaaga tatgcatatt ggtaccagca taagccaagc 120
caagcccctg tgctcctaata caataaaaat aatgagctgg gttctgggat ccctgaccga 180
ttctctggct ccaactcggg caacacggcc accctgacca tcagtggggc ccgggccgag 240
gacgaggctg actattactg ccagtcctat gacagcagt gaaatgct 288

<210> 250
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 250
tcctatgagc tgactcagcc accatccgtg aatgtgaccc tgaggagac ggcccacatc 60
acctgtgggg gagacagcat tggaaagtaa tatgttcaat ggatccagca gaatccaggc 120
caggcccccg tggtgattat ctataaagat agcaacaggc cgacagggat ccctgagcga 180
ttctctggcg ccaactcagg gaacacggct accctgacca tcagtggggc cctggccgaa 240
gacgaggctg actattactg ccaggtgggg gacagtggta ctaaggct 288

<210> 251
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 251
tcctatgtac tgactcagct gccatcagt actgtgaacc tgggacagac caccagcatc 60
acctgtggtg gagacagcat tggagggaga actgtttact ggtaccagca gaagcctggc 120
cagcgcccc tgctgattat ctataatgat agcaattggc cctcagagat ccctgcctga 180
ttctctggct ccaactcagg gaacagggcc tccctaacca tcattggggc ctgggcctaa 240
gacgagtctg agtattacgg agagggtgtg gacagcagt ctaaggct 288

<210> 252
<211> 283
<212> DNA
<213> Canis lupus familiaris

<400> 252
tcctatatgc tgactcagca gccattggca agtgtaaacc tcagccagt ggccagcacc 60
acctgtggtg gagataacat tggagaaaaa actgtccaat ggaaccagca gaagcctggc 120
taagctccca ttacggctat ctataaaggt agtgatctgc cctcagggat tcctgagcaa 180
ttccctggcc ccaactcggg aaacggggcc tccctgaaca tcagcggggc taagccgacg 240
actaggctat tactgccagt cagcagacat tagtggtgaag gct 283

<210> 253
<211> 288

<212> DNA
<213> Canis lupus familiaris

<400> 253
tcctatgtgc tgacacagct gccatccgtg agtgtgaccc tgaggcagac ggcccgcac 60
acctgtgggg gagacagcat tggaagtaaa aatgtttact ggtaccagca gaagctgggc 120
caggcccctg tactgattat ctatgatgat agcagcaggc cgtcagggat ccctgagcga 180
ttctccggcg ccaactcggg gaacacggcc accctgacca tcagcggggc cctggccgag 240
gatgaggctg actattactg ccaggtgtgg gacagcagta ctaagcct 288

<210> 254
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 254
tccactgggt tgaatcaggc ttccctccgtg ttggtggccc tgggacagat ggaaacaatc 60
acctgctcga gagatgtctt agggaaaaga tatgcatata ggtaccagca taagccaagc 120
caagcccctg tgctcctaata caataaaaat aatgagcagg attctgggat ccctgaccgg 180
ttctctggct ccaactcggg caacacggcc accctgacca tcagtggggc ccgggctgag 240
gacgaggctg agtattactg ccagtcctat gacagcagtg gaaatgtt 288

<210> 255
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 255
tcctatgtgc tgacacagct gccatccgtg aatgtgaccc tgaggcagcc ggcccacatc 60
acctgtgggg gagacagcat tggaagtaaa agtgttcact ggtaccaaca gaagctgggc 120
caggcccctg tactgattat ctatggtgat agcaacaggc cgtcagggat ccctgagcga 180
ttctctggtg acaactcggg gaacacggcc accctgacca tcagtggggc cctggccgag 240
gacgaggctt actattactg ccaggtgtgg gacagcagtg ctcaggct 288

<210> 256
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 256
tccagtgtgc tgactcagcc tccttcagta tcagtgtctc tgggacagac agcaaccatc 60
tcctgctctg gagagagtct gagtaaatat tatgcacaat ggttcagca gaaggcaggc 120
caagtccctg tgttggtcat atataaggac actgagcggc cctctgggat ccctgaccga 180
ttctccggct ccagttcagg gaacacacac accctgacca tcagcggggc tcgggccgag 240
gacgaggctg actattactg cgagtcagaa gtcagtactg gtactgct 288

<210> 257
<211> 288
<212> DNA

<213> Canis lupus familiaris

<400> 257

tcctatgtgt tgactcagct gccttcagtg tcagtgaacc tgggaaagac agccagcatc	60
acctgtgagg gaaataacat aggagataaa tatgcttatt ggtaccagca gaagcctggc	120
caggcccccg tgctgattat ttatgaggat agcaagcggc cctcagggat ccctgagcga	180
ttctctggct ccaactcggg gaacacggcc accctgacca tcagcggggc cagggccgag	240
gatgaggctg actattactg tcaggtgtgg gacaacagt ctaaggct	288

<210> 258

<211> 288

<212> DNA

<213> Canis lupus familiaris

<400> 258

tccagtgtgc tgactcagcc tccctcgggt tcagtgtccc tgggacagac ggccagcatc	60
acctgctctg gagagagtct gagcagatac tatgcacaat ggtatcagca gaagccaggc	120
caagccccca tgacagtcac atatggggac agagagcgac cctcagggat ccctgaccga	180
ttctccagct ccagttcaga gaacacacac accttgacaa tcagtggagc ccaggctgag	240
gatgaggctg aatattactg tgagatatgg gacgccagt ctgatgat	288

<210> 259

<211> 288

<212> DNA

<213> Canis lupus familiaris

<400> 259

tcctactgtg tgaccagcc accctcagtg tcagtgaacc tgggacagac ggccagcatc	60
acctgtgggg gagacaacat tgcaagcaca tatgtttcct ggcagcagca gaagtcgggt	120
caagcccctg tgacgattat ctatcgtgat agcaaccggc cctcagggat ccctgagcga	180
ttctctggct ccaactcggg gaacacggcc accctgacca tcagcagggc ccaggccgag	240
gatgaggctg actattactg ccaggtgtgg aagagtggta ataaggct	288

<210> 260

<211> 317

<212> DNA

<213> Canis lupus familiaris

<400> 260

ttgccgtgc tgaccagcc tacaatgca tctgcctccc tggaagagtc ggtcaagctg	60
acctgcactt tgagcagtga gcacagcaat tacattgttc agtggtatca acaacaacca	120
gggaaggccc ctcggtatct gatgtatgtc aggagtgatg gaagctacaa aaggggggac	180
gggatcccca gtcgcttctc aggtccagc tctggggctg accgctatct aaccatctcc	240
aacatcaagt ctgaagatga ggatgactat tattactgtg gtgcagacta tacaatcagt	300
ggccaatacg gttaagc	317

<210> 261

<211> 303

<212> DNA

<213> *Canis lupus familiaris*

<400> 261

ttgcccgtagc tgaccagcc tccaagtga tctgcctccc tggaagcctc ggtcaagctc	60
acatgcactc tgagcagtga gcacagcagt tactatatatt actggtatga acaacaacaa	120
ccagggaagg cccctcggtg tctgatgagg gttacagtg atggaagcca cagcaggggg	180
gacgggatcc ccagtcgctt ctcaggctcc agctctgggg ctgaccgcta ttttaaccatc	240
tccaacatcc agtctgagga tgaggcagat tattactgtg gtgcacccgc tggtagcagt	300
agc	303

<210> 262

<211> 317

<212> DNA

<213> *Canis lupus familiaris*

<400> 262

ttgcccgtagc tgaccagcc tacaagtga tctgcctccc tggaagagtc ggtcaagctg	60
acctgcactt tgagcagtga gcacagcaat tacattgttc attggtatca acaacaacca	120
gggaaggccc ctcggtatct gatgtatgtc aggagtgatg gaagctacaa aaggggggac	180
gggatcccca gtcgcttctc aggctccagc tctggggctg accgctattt aaccatctcc	240
aacatcaagt ctgaagatga ggatgactat tattactgtg gtgcagacta tacaatcagt	300
ggccaatacg gtttaagc	317

<210> 263

<211> 299

<212> DNA

<213> *Canis lupus familiaris*

<400> 263

ttgcccgtagc tgaccagcc tccaagtga tctgcctccc tggaagcctc ggtcaagctc	60
acatgcactc tgagcagtga gcacagcagt tactatatatt actggtatca acaacaacca	120
gggaaggccc ctcggtatct gatgaagggtt aacagtgatg gaagccacag caggggggac	180
gggatcccca gtcgcttctc aggctccagc tctggggctg accgctattt aaccatctcc	240
aacatccagt ctgaggatga ggcagggttat tactatgggtg taccctgggt agcagtagc	299

<210> 264

<211> 317

<212> DNA

<213> *Canis lupus familiaris*

<400> 264

ttgcccatgc tgaccagcc tacaagtga tctgcctccc tggaagagtc ggtcaagctc	60
acatgcactt tgagcagtga gcacagcaat tacattgttc aatggtatca acaacaacca	120
gggaaggccc ctcggtatct gatgcatgtc aggagtgatg gaagctacaa caggggggac	180
gggatcccca gtcgcttctc aggctccagc tctggggctg accgctattt aaccatctcc	240
aacatcaagt ctgaagatga ggatgactat tattacagt gtgcatacta tacaatcagt	300

ggccaatacg gttaagc 317

<210> 265
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 265
ttgcccatgc tgaccagcc tccaagtga tctgcctccc tggaagcctc ggtcaagctc 60
acatgcactc tgagcagtga gcaaagcagt tactatatatt actggtatca acaacaacaa 120
ccagggaagg cccctcggtg tctgatgaag gttaacagt atggaagcca cagcagggcg 180
tcgggatccc cagtcgcttc tcaggctcca gctctggggc tgaccgctat ttaaccatct 240
ccaacatcca gtctgaggat gaggcagatt attactgtgg tgtaccact ggtagcagta 300
gc 302

<210> 266
<211> 317
<212> DNA
<213> Canis lupus familiaris

<400> 266
ttgcccatgc tgaccagcc tacaagtga tctgcctccc tggaagagtc agtcaagctc 60
acctgcactt tgagcagtga gcacagcaat tacattgttc gatggtatca acaacaacca 120
gggaaggccc ctcggtatct gatgtatgtc aggagtgatg gaagctacaa cagggggggac 180
gggatcccca gtcgcttttc aggctccagc tctggggctg accgctatct aaccatctcc 240
aacatcaagt ctgaagatga ggctgagtat tattacgggtg gtgcagacta taaaatcagt 300
gaccaatatg gttaaga 317

<210> 267
<211> 303
<212> DNA
<213> Canis lupus familiaris

<400> 267
ttgcccgtagc tgaccagcc tccaagtga tctgcctgcc tggaacctc ggtcaagctc 60
acatgcactc tgagcagtga gcacagcagt tactatatatt actggtatca acaacaacaa 120
ccagggaagg cccctcggtg tctgatgaag gttaacagt atggaagcca cagcaggggg 180
gacgggatcc ccagtcgctt ctcaggctcc agctctgggg ctgaccgcta tttaaccatc 240
tccaacatcc agtctgaaga tgaggcagat tattactgtg gtgtaccgc tggtagcagt 300
agc 303

<210> 268
<211> 323
<212> DNA
<213> Canis lupus familiaris

<400> 268
caggctgtgc tgaccagcc gccctccctc tctgcatccc tgggatcaac agccagactc 60
acctgcaccc tgagcagtgg cttcagtgtt ggagctact acatatactg gtaccagtag 120

aagccaggga gccctccccg gtatctcctg tactaactac tactcaagta cacagctggg	180
ccccgggggtc cccagccatt tctctggatc caaagacaac tcggccaatg cagggtcct	240
gctcacctct gggctgcagc ctgaggacga ggctgactac tactgtgcta caggttattg	300
ggatggggagc aactatgctt acc	323

<210> 269
 <211> 304
 <212> DNA
 <213> Canis lupus familiaris

<400> 269	
cagcctgtgc tgaccagcc gccctccctc tctgcatccc tgggaacagc ggccagaaat	60
acctgcactc tgagcagtga cctcagtgtt ggagctgtg ctataagctg atcccagcag	120
aagccaggga gccctccctg gtatctcctg aactactaaa cacacccatg caagcaccag	180
gactcacatc tgtagccgct tctctggatt tgaggatgcc tctgccagt cagggtcctg	240
ctcatctctg gaggctgacc atcactgtgc taagatcatg gcagtggggg cagctagtgt	300
taca	304

<210> 270
 <211> 277
 <212> DNA
 <213> Canis lupus familiaris

<400> 270	
cagcctgtgc tgaccagcc gccgtcctct ctgcatccct gggaacaaca gccagactca	60
cctgcaccct gagcagtggc ttcaatatgt ggggctacca tatattctgg taccagcaga	120
agccaggag ccctccccgg tatctgtga acttctactc agataagcac cagggtcca	180
aggacacctc ggccaatgca gggatcctgc tcatctctgg gctccagcct gaggacgagg	240
ctgactacta ctgtaaaatc tggtagctg gtctggg	277

<210> 271
 <211> 218
 <212> DNA
 <213> Canis lupus familiaris

<400> 271	
cagcctctgc taccagcca ccccttctc tgcgtctcca ggtactacag ccagaccac	60
ctgcaccctg agcagtggca acagtgttg cagctgttcc ttataacggc tcccacaaag	120
acagagggcc ctccctggta tctgctgagg ttcccctcta atagacacca tgtctctgga	180
tccacacata ccttgccaa tgcagggtc ctgctcat	218

<210> 272
 <211> 319
 <212> DNA
 <213> Canis lupus familiaris

<400> 272	
cagcctgtgc tgaccaagt ccctctctt ctgcatctcc tggaacaaca gtcagactca	60

cttgcacctg gagcagtggc tccagcactg gcagctacta tatacactgg ttccagagcc	120
acagagccag agccacagag ctctccctgg tatctcctgt actactactc agactcagat	180
aagcaccagg gctctggggg tctcagctct gtctcctgat ccaaggatgc ctcagttatt	240
ggagggtctt ctcatctctg ggctgcagcc tgaggattag actgaccttc actgtctaata	300
cagaaacaat aatgcttct	319

<210> 273
 <211> 314
 <212> DNA
 <213> Canis lupus familiaris

<400> 273 cagcctgtgc tgaccagct gccctccctc tctgcatacc ggggaacaaa ctccagatgt	60
acctacacc tgagcagtgt cgccaactac taaacatact tctcaaagag aatacagggc	120
accttcaca gtacatcctg tactactact cagactcaag tgcatgattg ggatttgggg	180
tcccaggcac ttctctggat ccaagatgc ctcagccaat gcagggatcc tgctgatctc	240
tgggctgcag ccagaggaca agtctgactg tcaactgtgt acagatcatg gcagtgggag	300
cagcttccga tact	314

<210> 274
 <211> 314
 <212> DNA
 <213> Canis lupus familiaris

<400> 274 cagccagggc tgaccagcc acactccctc tctgcatact agggagaaac agccacacat	60
acctgcaccc tgagcgggtg cttcagtgtt ggcagctgcc atatatactg gatccagaag	120
aagccagaga gccctccctg atgtctcctg aactactact aagactcaga taaggcctcg	180
acgtccccag ccctactctg aatccaaaga caccttgccc aaggtgggaa tcctgctcat	240
ctctgggctg cagccggagg acaaggctgt ctcttactgt ataatatggc acagtgggtc	300
tggtcacagg gaca	314

<210> 275
 <211> 307
 <212> DNA
 <213> Canis lupus familiaris

<400> 275 caccctgtgc tgaccagct gccctccctc tctgcatccc tgggaacaac agccagactc	60
atgtgcaccc tgagcagtgg ctgcagtggg ggccatacgc tggttccagc agccaggagg	120
cctcctgagt acctgctgat ggtctactga gactcaccag ggccccgggtg gccccagccg	180
cttctctggc tccaaggaca cctcggccaa tgcagggtc ctgctcatct ctaggctgca	240
gcctgaggac gaggctgact gtcactgtgt tacagaccat ggcagtggga gcagctcccg	300
aaactca	307

<210> 276

<211> 326
<212> DNA
<213> Canis lupus familiaris

<400> 276
cagccagggc tggcccagct tccccccacc tccctctgca tctccaggaa caacagccag 60
actcacatga accatgagca gtggcttcat cgttggcgct gctacatata ctggttccaa 120
cagaagccag ggagcaccgc cccagtatct cctgaggttc tactcagact cagataagca 180
ctagggctca acgaccccag ccctgttctg gatctgaaga cacctccgcc gaagcagggc 240
ctctgctcat ctctgggctg cagcgtgagg acaaggctga ctcttatggg acaatctggc 300
acagtgggtcc tggtcacagg gacaca 326

<210> 277
<211> 305
<212> DNA
<213> Canis lupus familiaris

<400> 277
cagcctgtgc tgaccagct gccctccctt tctgcatccc tgggaacaac agccagactc 60
acatgcaccc tgagcagcgg ctgcagcggg ggccacacat tggttccagc agccaggagg 120
cctcctgagt acctgctgat ggtctactga gactcaccag ggccccgggtg ttgccagcct 180
cttctctggc tccaaggaca cctcggccaa tgcaggactc ctgctcatct ctgggctgca 240
gcctgaggat gaggctgact gtcactgtgc tacagacat ggagtgagg gcagctccgg 300
atact 305

<210> 278
<211> 305
<212> DNA
<213> Canis lupus familiaris

<400> 278
cagcctgtgc tgaccagct gccctccctt tctgcatccc tgagaacaac agccagactc 60
acctgcaccc tgagcagtggt ctgcagtggt ggccatattg tggttccagc agccaggaag 120
cctcctgagt atctgctgac ggtcttctga gactcaccag ggccccgagg tccccagcct 180
cttctctggc tccaaggaca cctcagccaa tgcaggactc ctgctcatct ctgggctgca 240
gcctgaggat gaggctgact gtcactgtgc tacagacat ggagtgagg gcagctcccg 300
atact 305

<210> 279
<211> 300
<212> DNA
<213> Canis lupus familiaris

<400> 279
caccctgggc tgaccagtc gtcctccctc tctgcatccc tgggaacaac agccagactc 60
acctgcaccc tgagcagtggt cttcagaaat gacaggtagt taataagttg gttccagcag 120
aaatcaggga gcccttctg gtgtctcctg tattattact cgaactcaag tacacatttg 180
ggctctgagg ttcccagctg cttctctgga tccaagacaa ggccacaccc acactgagta 240

gacccctctc tgggtgggtc tagagctcca gctccacctg aggctgatgc acaattgcag 300

<210> 280

<211> 321

<212> DNA

<213> Canis lupus familiaris

<400> 280

cagccagggc tggcccagct gccctccctc tctgcatctc caggaacaac agccagactc 60

acatgaacca tgagcagtgg cttcattgtt ggtggctgct acatatactg gttccaacag 120

aagccaggga gcatgcccc cagtatctcc tgaggttcta ctcagactca gataagcacc 180

aggctctaac atccccagcc cggctctgga tctgaagaca ctcagccgaa gcagggcctc 240

tgctcatctc tgggctgcag catgaggaca aggctgactc ttactgtaca atctggcaca 300

gtggtcctgg tcacaggga a 321

<210> 281

<211> 220

<212> DNA

<213> Canis lupus familiaris

<400> 281

cagcctgtgc tgaccattg ccctccctct ctgcatcctg ggaaataaca accagactca 60

cctgcactct gagcagcggc tgcagcgggt gccatacagt ggttccagca gcaaggaagc 120

ctcctgagta cctgctgacg ttctactgag actcaccagg gctctagggt cccagccac 180

ttctctgggt tcaaggacac cacggccaat gcagggcact 220

<210> 282

<211> 309

<212> DNA

<213> Canis lupus familiaris

<400> 282

cagcctgtgc tgaccagtc gccctccctc tcggcatctt tggaacaaca gtcagactca 60

cctgtaccct gatcagtggc tccagtgttg gcagctatta catcaactgg ttccagaaga 120

agccacggag ccctccccag tatctcctgt actactactt agactcagat aagcaccagg 180

gctctgggggt cccagctgc ttctcctgat ccaaggatgc ctcagtcatt ggaggacacc 240

ctcatctctg aactgcagcc tgaggactag actgaccttc gctgtctaata cagaaacaat 300

aatgcttct 309

<210> 283

<211> 315

<212> DNA

<213> Canis lupus familiaris

<400> 283

cagcctgtgc tgaccagcc tccctctctc tctgcatctc tgggaacaat agccagacaa 60

acatgcagcc tgagcagggg ctacagtatg gggacttatg tcatacgctg gttccagcag 120

tagcaagaaa ctctcctgag tatctgctga gggtatactg agcctcagca ggtctctggg 180

gacccagct gagtcttttag atccaagatg cctcagccaa ttcagggtc ctgcttatct	240
ctgtgctgca gcctgaggac aagggttact attactgttc tgtacatcat ggaattgtga	300
gcagctatac ttacc	315

<210> 284
 <211> 325
 <212> DNA
 <213> Canis lupus familiaris

<400> 284	
cagcttgtgg tgaccagcc gccctccctc tctgcatccc tgggatcatc cgccagactc	60
acctgcaccc tgagcagtgg cttcagtgtt ggcagttatt ctgtaacttg gttccagcag	120
aagccaggga gccctctctg gtacctcctg tactaccact cagactcaga taagcaccag	180
ggctccaggg tccccagccg cttctctgga tccaaggaca cctcggccaa tgcagggtc	240
ctgctcatct ctgggtctga gcctgaggat gaggctgact actactgtgc ctccgctcat	300
ggcagtggga gcaactacca ttact	325

<210> 285
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 285	
cagccagtgc tgaccagct gccctccttc tctgtatctc tgggaacaac agtcagactc	60
acctgcaccc tgagcagtgt tggcagctac taaacatcct tttcaaggag aaaccaagga	120
gccccccacc ccggtatctc ctatactact attcagactc agataaacc caggtctctg	180
gggtccccag ccacttctct gcatccaaag actcctaggc caatgcaggg ctctgtctcg	240
cctctgggct gcagcctgag gacgaggctg actatcactg tgctataaat catgacagtg	300
ggagtagttc ctgatact	318

<210> 286
 <211> 309
 <212> DNA
 <213> Canis lupus familiaris

<400> 286	
cagccttgg tgaccagcg ccctccctct ctgcatctcc tgaaacaaca gtcagactca	60
catgcaccct gagcagtggc cccagtgtct gcagctacta catacactgg ttccagtgga	120
agccacggtg cccgccccgg tatctcctgt actactactc agactcagat gagcaccagg	180
gctctgggggt cccagccgc ttctcctgat ccaaggatgc ctgagccagg gcagggtcc	240
ctcatctctg ggctacagtc tgagggtctac actgaccttc actgtctaata cggaacaata	300
aatgtttct	309

<210> 287
 <211> 303
 <212> DNA
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cctatgggga acccagatcc ttcccctgat ccaaggatgc ctcaagtcaat gcagggtcaa 240

agagagggga ttatttagag tggacaattg gggcctttgg ccaggag 287

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<211> 298

<212> DNA

<213> Canis lupus familiaris

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<212> DNA

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<400> 297

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<212> DNA

<213> Canis lupus familiaris

<400> 298

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cttctctggc tccaaggaag cctcgcccaa tgcagggtc ctgctcatct ctgggctgca	240
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gtcccaagcc acatctctgg atccaaagaa acctc 215

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<212> DNA
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cctcctgagt acctgctgat ggtctactga gactcaccag ggccctgggg tccccagcct	180
cttctctggc tccaaggaca ccttggccaa tgcagggctc ctgctcatct ctgggctgca	240
gcctgagaat gaggctgact gtcactgtgc tacagacatc ggcagtggga acagctcca	300
atact	305

<210> 326
 <211> 323
 <212> DNA
 <213> Canis lupus familiaris

<400> 326 taaaacaaaa ccaaacaaaa ccaaacaaaa acaaaacaaa acaaaataac agccagattc	60
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gccaggggagc cctccctgtt acctcctgta ctactactca gaatcagata aacaccatgg	180
ctccgggatc accagctgct tccctggccc tatggacacc tcggccaatg cagggtcct	240
gctcatcctt gggctgcagc ctgaggacga ggctgactac tactgcgcta tactccacag	300
cagtgggagc agctactctt acc	323

<210> 327
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

<400> 327 aagcctgtgc tgaccagcgc ccctccctct ctgcatccct gggaacaaca gccagactca	60
cctgcaccct gagcagcggc tggagtgggt gctataggct gggtccagca gccaggaagc	120
ctcctgagta cctgctgatg gtctactgag actcaccagg ctatggggctc cccagcatct	180
tctctggctc caaggaagcc tcggccaatg cagggtcctt gctcatctct ggctgcagc	240
ctgaggctga ggctgactgt cactgtgcta cagacatgg cagtgggagc agctcccgat	300
ac	302

<210> 328

<211> 308
<212> DNA
<213> Canis lupus familiaris

<400> 328
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cctgtaccgt gaacagtggc tccagtgttg gcagctatta catcaactgg ttccagtata 120
agccatggag ctctccctag tatcacctgt actactactt agactcagat aagcaccagg 180
gctctgggggt cccagctgc ttctcctgat ccaaggatgc ctcagtcatt ggagggcacc 240
ctcatctctg ggctgcagcc tgaggactag actgaccttc acgtctaata agaaacaata 300
atgcttct 308

<210> 329
<211> 304
<212> DNA
<213> Canis lupus familiaris

<400> 329
ctgcctgtgc tgaccagcc gccctccctc tctgcatccc tgggatcaac agccagactc 60
acctgcacac tgagcagtgg ctgcagcggg gcccatatgc tggttccagc agccaggagg 120
cctcctgtgt acctgctgat ggtctactga gactcaccag ggccccagtg tccccagcca 180
ctactctggg ttcaaagaca cctcggccaa tgcaggtcac tcagatagct gcgaaattca 240
tacaacaagg gtcctcatgg ggactcatgg gcaccccttc agattttcct gcctgcatga 300
acag 304

<210> 330
<211> 300
<212> DNA
<213> Canis lupus familiaris

<400> 330
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cacatgaacc atgagcagtg gcttcattgt tggcggctgc tacatatact ggttccaaca 120
gaagccaggg agtccccctc ccccatatc tcctgagttt ctactcagac tcagataagc 180
accagggtc aaaatcccca gccctgttct ggatctgaag acacctcagc caaagcagcg 240
cctctgtcga tctctgggct gcagggtgag gataagaatg actcttactc tacaatctgg 300

<210> 331
<211> 314
<212> DNA
<213> Canis lupus familiaris

<400> 331
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tctgcaccca gagcagtggc cccagtgttg gcagctacta caaacactgg ttccagcaga 120
agccacggag ccctccccag tacctcctgt actacttctc agactcagat gagcaccagg 180
gctctgggga ctgcagccac ttcccctgat ccaaggatgc ctgaggaaag cagggtctcc 240
tcctctctgg gctacagcct gaggactaga ctgaccttca ctgtctaata agaaacaata 300

atgcttctta cagt 314

<210> 332

<211> 305

<212> DNA

<213> Canis lupus familiaris

<400> 332

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acctgcaccc tgagcagcag ctgcagcggg gccatatgc tggttccagc atgcaagagg 120

cctcctgagt acctactgat ggtctactga gactcaccag gccctgggg tccccagcct 180

cttctccggc tccaaggaca ctttgccaa tgcagggctc ctgctcatct ctgggctgca 240

gcctgagaat gaggctgact gtcactgtgc tacagacat gccagtggga acagctcca 300

atact 305

<210> 333

<211> 307

<212> DNA

<213> Canis lupus familiaris

<400> 333

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acctgcatcc ttcccagggc ctgaatgttg gcaggctactg aacatactgg acaaggagaa 120

tcaaggaggc atcaggagtt cctcagatc cagataagt ccagggcacg gggttctcag 180

ccacttctat ggatctaag atgcctcagg caatgcagg ctctgctca tgtctgggct 240

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cgatact 307

<210> 334

<211> 303

<212> DNA

<213> Canis lupus familiaris

<400> 334

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cctgcaccct gagcagcggc tggagtggg gctataggct gggtccagca gccaggaagc 120

ctcctgagta cctgctgatg gtctactgag actcaccagg ctatggggtc cccagcatat 180

tctctggctc caaggaagcc tcggccaatg cagggtcct gctcatctct gggctgcagc 240

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act 303

<210> 335

<211> 291

<212> DNA

<213> Canis lupus familiaris

<400> 335

cagactgtgg tcaccaagga tccatcactc tcagtgtttc caggaggagc agtcacattc 60

acatgtggcc tcagctctgg gtcagtcttt acaagtaact accccagctg gtaccagcag	120
acccatggcc gggctcctca catgcttatac tacagcacia gcagctgccc ccccggggtc	180
cctgatcgct tctctggatc catctctggg aacaaagttg ccctcaccat cacaggagcc	240
cagcctgagg atgagactat tattgttcac tgcgtatggg tagtacattt a	291

<210> 336
 <211> 309
 <212> DNA
 <213> Canis lupus familiaris

<400> 336 cagcctgtgc taacccagtc gccctccctc ttgacatctt tggaacaaca gtcagactca	60
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agccatggag ctctccctgg tatcacctat actacttctt agactcagat aagcaccagg	180
gctctggggt ccccgagctgc ttctcctgat ccaaggatgc ctgagtcatt ggagggcacc	240
ctcatctctg ggctgcagcc tgaggactag actgaccttc actgtctaata cagaaacaat	300
aatgcttct	309

<210> 337
 <211> 217
 <212> DNA
 <213> Canis lupus familiaris

<400> 337 ctgcctgtgc tgaccagcc gccctccctc tctgcatccc tgggatcaac agccagactc	60
acctgcacac tgagcagtg ctgcagcggg agccatatgc tggttccagc agccaggagg	120
cctcctgggt acctgctgat ggtctactga gactcaccag ggccccagtg tccccagcca	180
ctactctgga tgcaaagaca cctcggccaa tgcaggt	217

<210> 338
 <211> 300
 <212> DNA
 <213> Canis lupus familiaris

<400> 338 cagggatggc ccagctgttc cccacctcc ctctgcatct ccaggaacaa cagccagact	60
cacatgaacc atgagcagtg gcttcattgt tggcggctgc tacatatact ggttccaaca	120
gaagccaggg agtccccctc ccccatatc tcctgagttt ctactcagac tcagataagc	180
accagggtc aaaatcccca gccctgttct ggatctgaag acacctcagc caaagcagcg	240
cctctgctca tctctgggct gcagggtgag gataagaatg actcttactc tacaatctgg	300

<210> 339
 <211> 307
 <212> DNA
 <213> Canis lupus familiaris

<400> 339 caacctttgc ggaccagcg cactccctct gcatctcctg gaacaacagt tagactcatc	60
tgcacccaga gcagtggccc cagtgttggc agctactaca aacactggtt ccagcagaag	120

ccacggagcc ctccccggtg cttcctgtac tactttctcag actcagatga gcaccagggc	180
tctggggacc gcagccactt ctcctgatcc aaggatgact caggaaaggc agggctccct	240
catctctggg ctacagcctg aggactagac tgaccttcac tgtctaataca gaaacaataa	300
tgcttct	307

<210> 340
 <211> 301
 <212> DNA
 <213> Canis lupus familiaris

<400> 340 cagcctgtga tgacccagct gtcctccctc tctgcatccc tggaacaac aaccagacac	60
acctgcaccc tgagcagtggt cttcagaaat aacagctgtg taataagttg attccagcag	120
aagtcaggga gccctccctg gtgtctcctg tactattact cagactcaag tatacatttg	180
ggctctgagg ttcccagctg cttctctgga tccaagacaa ggccacaccc acactgagta	240
gacccatccc tgggtgggtc tagagctcca gcccactgg aggctgatgc acaattgcag	300
c	301

<210> 341
 <211> 317
 <212> DNA
 <213> Canis lupus familiaris

<400> 341 cagcctgtgc taaccagtc gctctccctc ttgacatctt tggaacaaca gtcagactca	60
cctgtaccgt gaacagtggc tccagtgttg gcagctatta catcaactgg ttccagtata	120
agccatggag ctctccctag tatcacctgt actactactt agactcagat aagcaccagg	180
gctctgggggt cccagctgc ttctcctgat ccaaggatgc ctcagtcatt ggagggcacc	240
ctcatctcgg ggctgcagcc tgaggactag actgaccttc actgtctaata cagaaacaat	300
aatgcttcta acagtga	317

<210> 342
 <211> 288
 <212> DNA
 <213> Canis lupus familiaris

<400> 342 cccagcgccc tttctctctg catccctggg aacaacagcc agactcacct gcaccctgag	60
cagcggctag agtgggtggct ataggctgggt tccagcagcc aggaagcctc ctgagtacct	120
gctgatggtc tactgagact caccaggcta tgggggtccc agcatcttct ctggctccaa	180
ggacacctcg gccaatgcag ggctcctgct catctctggg ctgcagcctg aggtcgaggc	240
tgactgtcac tgtgtacag accatggcag tggggagcag tcccgata	288

<210> 343
 <211> 278
 <212> DNA
 <213> Canis lupus familiaris

<400> 343
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 ctggtaccag cagaagccag ggagccctcc ctgttacctc ctgtactact actcagaatc 120
 agataaacac catggctccg ggatcaccag ctgcttcctt ggccctatgg acacctcggc 180
 caatgcaggg ctctgtctca tctcagggct gcagcctgag gacgaggctg actactactg 240
 cggatatactc cacagcagtg ggagcagcta ctcttacc 278

<210> 344
 <211> 307
 <212> DNA
 <213> Canis lupus familiaris

<400> 344
 caggctgtga cgacacactc ctcccttctc tctgcacctt tgggatcatc aaccagactc 60
 acctgcatcc ttcccagggc ctgaatgttg gcaggtactg aacatactgg acaaggagaa 120
 tcaaggaggc atcaggagtt ccctcagatc cagataagt ccagggcacg gggttctcag 180
 ccacttctat ggatctaata atgcctcagg caatgcaggt ttcctgtctca tgtctgggct 240
 gcagcctgag gacgaggctg actatgacta tgctgcacat tgtgggggtg gagcagctcc 300
 cgatact 307

<210> 345
 <211> 305
 <212> DNA
 <213> Canis lupus familiaris

<400> 345
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 acctgcaccc tgagcagcag ctgcagcggg gcccatatgc tggttccagc atgcaagagg 120
 cctcctgagt acctactgat ggtctactga gactcaccag ggccctgggg tcccagcct 180
 cttctctggc tccaaggaca ctttggccaa tgcagggctc ctgctcatct ctgggctgca 240
 gcctgagaat gaggctgact gtcactgtgc tacagacat ggcagtggga acagctcca 300
 atact 305

<210> 346
 <211> 275
 <212> DNA
 <213> Canis lupus familiaris

<400> 346
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 tgtgactcca gactggaga gtcattaata gtgactatcc acgttagttc cagcagaagc 120
 ctagacaaac tcgcaccaca cacacaacaa aactcacgg actcccaccc agttctcagg 180
 ctccctccag gctcaaaact gccctcacct ttttggggct ccagcctgag aaagaagggtg 240
 agtactacca tatgctggct tatcttggtt ctggg 275

<210> 347

<211> 290
<212> DNA
<213> Canis lupus familiaris

<400> 347
caggctgtgg tgactcagga accctcactg accgtgtccc tggagggaca gtcactctca 60
cctgtgcctc cagcactggc gaggtcacca atggacacta tccatactgg ttccagcaga 120
agcctggcca agtccccagg acattgattt ataatacaca cataatactc ctggaccctt 180
acccggttct caggctgcct ctttgggggc aaagctgcct tgaccatcac aggggcccag 240
cccgaggatg aagctgagga ctactgctgg ctagtatata tggtaatagg 290

<210> 348
<211> 289
<212> DNA
<213> Canis lupus familiaris

<400> 348
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tagtcaagtc cccagggcat tgacttagga tacaagcaat aaacacttct ggatccctac 180
caagctttca gtttccctcc ttggatgtaa aactcccctg accttctctg gttccctagc 240
ctgaggccaa ggctgattac cactggtggg tactcatagt ggtgctgca 289

<210> 349
<211> 263
<212> DNA
<213> Canis lupus familiaris

<400> 349
caggctcatgg tgactcagga gccttcatgg ccatgtcccc aggagggaca gtcactctca 60
cctatgcctc cagcacagga cactatccat actggatcca agaaaatatt ggccaagtca 120
gggccattta ttataataa aaacaacaaa tactgatttc tcatgctccc ttcttgggag 180
caaacttgac atgaccatct cctagtgtccc agcctgagga cgaggatgag taccatggg 240
ggctacacta tagtggtgct ggg 263

<210> 350
<211> 246
<212> DNA
<213> Canis lupus familiaris

<400> 350
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ctatgcctcc agcacagaac actatccata ctggatccag gaaaatattg gccaaagtcta 120
gagcatttat ttataaaaga aacaataaat actgatttct aggctccctt cttgggaata 180
aatctgactt gaccatctgc tagtgcgcag cctgaggacg aggctgagta cccctagggg 240
ttacac 246

<210> 351
<211> 296

<212> DNA
<213> Canis lupus familiaris

<400> 351
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acctgtgcct ccagccactg gcatagtaac aatgctcagt atccttcctg gttttaccag 120
aagcctggcc aagttcccag ggcatgtgatt taggatacaa gcaatgaaaa ttcctggacc 180
cccaccaagt gtcaggttc cctttgtgga gcaatattct cctgaccctc tacagtgcct 240
tggtgagaac atagctgagt ggcaactggtg gctgctttta ttgtgatgct ggggtgc 296

<210> 352
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 352
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acctgcgcct ccagctactg gcatagtaac aatgctcagt atccttactg gtttttagcag 120
aatcctggcc aagtccccag ggcatgtgatt taggatacaa gcaatgaaca cacctggacc 180
cccacatgt gtcaggttc cctttgtgga gcaatattct cctgaccctc tacagtgcct 240
tggtgagaac atagctgagt ggcaactggtg gctgctttta ttgtgatg 288

<210> 353
<211> 275
<212> DNA
<213> Canis lupus familiaris

<400> 353
cagactgttg tggcatagga gccttcatgg ccatatcccc aggagggaca gtcactctca 60
cctatccctc cagcacagga cactatctat actggatcta gtagcatact ggccaagtct 120
aggtcattta ttataataa aaacaataaa tactcataga cctccactca tttctcaggc 180
tcccatcttg ggggcaaadc tgactggatt gtcccctagt gccagcctg aggatgaggc 240
tgagtaccgc tggggctaca ctatggtggt gtggg 275

<210> 354
<211> 275
<212> DNA
<213> Canis lupus familiaris

<400> 354
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cctatccctc cagcacagga cactatctat actggatcta gtagcatact ggccaagtct 120
aggtcattta ttataataa aaacaataaa tactcataga cctccactca tttctcaggc 180
tcccatcttg ggggcaaadc tgactggatt gtcccctagt gccagcctg aggatgaggc 240
tgagtaccgc tggggctaca ctatggtggt gtggg 275

<210> 355
<211> 299
<212> DNA

<213> Canis lupus familiaris

<400> 355

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acatgtggcc tcagctccgg gtcagtctct acaagtaact accccaactg gtcccagcag	120
accccagggc aggctcctcg cacgattatc tacaacacaa acagccgcc ctctggggtc	180
cctaatacgct tctctggatc catctctggg aacaaagccg ccctcacat cacaggagcc	240
cagcctgagg acgaggctga ctactactgt gctctgggat taagtagtag tagtagtta	299

<210> 356

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 356

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acatgtggcc tcagctctgg gtcagtctct acaagtaacc accctagctg gtaccagcag	120
acccaaggga aggctcctcg catgcttattc tacaacacaa acaaccgcc ctctgggatc	180
cctaattgct tctctggatc catctctggg aacaaagcct ccctcacat cacaggagcc	240
cagcctgagg acgagactga ctattactgt ttattgtata tgggtagtaa cattta	296

<210> 357

<211> 307

<212> DNA

<213> Canis lupus familiaris

<400> 357

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acatgtggcc tcagctctgg gtcagtcctt acaagtaact accccagctg gtttcagcag	120
accccaggcc gggctcctag aacagttatc tacaacacaa acagctgcc ctctggggtc	180
cctaatacgct tctctggatc catctctggc aacaaagccg ccctcacat cacaagagcc	240
cagcctgagg atgaggctga ctctgtgtgt gctgaatatc aaagcagtgg gagcagctac	300
acttacc	307

<210> 358

<211> 296

<212> DNA

<213> Canis lupus familiaris

<400> 358

cagactgtgg taacccagga accatcactc tcagtgtctc catgaggac agtcacactc	60
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acccaaggcc gggctcctca cagggttattc tacaacacaa acaaccgcc ctctggggtc	180
cctgatcgct tctctggatc catctctggg aacaaagccg ccctcacat cacagctgcc	240
cagcctgagg acgaggctga ctattactgt tcattgtata tgggtagtaa catttg	296

<210> 359

<211> 291

<212> DNA
<213> Canis lupus familiaris

<400> 359
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acatgtggcc tcagctctgg gtcagtctct acaagtaact accccagctg gtaccagcag 120
acccaaggcc gggatcctcg catgcttatac tacagcacaac acagccaccc ctctggggtc 180
cctaattgct tcactagatc catctctggg aagaaagctg ccctcaccat cacaggagcc 240
cagcctgagg atgagactat tattgttcac taaatatggg tagtacatgt a 291

<210> 360
<211> 306
<212> DNA
<213> Canis lupus familiaris

<400> 360
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acttgtggcc tcagctctgg gtcagtcact acaataaata cccagctgg tcccagcaga 120
ccccaggga ggctcctcg atgattatct atgacacaaa cagccgccc tctggggtc 180
ctgatcgctt ctctggatcc atctgtggga acaaagctgc cctcaccatc acaggagccc 240
atcctgagga tgagactgac tactactgtg gtatacaaca tggcagtggg agcagcctca 300
cttacc 306

<210> 361
<211> 307
<212> DNA
<213> Canis lupus familiaris

<400> 361
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acatgtggcc taagctctgg gtcagtcact ataagtaact accctgattg gtaccagcag 120
actccaggca ggtctcctcg catgcttatac tacaacacaa acaaccgccc ctctggggtc 180
cctaatacact tctctggatc catctctggg aacaaagccg ccctcaccat cacaggagcc 240
cagcctgagg atgaggctta ctactactgt gctgtgtatc aaggcagtgg gagcagctac 300
acttacc 307

<210> 362
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 362
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acccaagtga aagctccttg catgcttatac tacagcacaac acagctaccc ctctgggggtt 180
cctaattgct tcactggatc catctctggg aagaaagctg ccctcaccat cacaggagac 240
cagcctgagg atgagactat tattgttcac tgcatatggg tagtacactt a 291

<210> 363
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<212> DNA
<213> Canis lupus familiaris

<400> 363
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acccaaggcc ggtctcctca catgcttata tatgacacaa gcagccgtcc ttctgaggtc 180
ctgatcgctt ccctggttcc atctctggga acaaagctgc cctcactgtc agaggagccc 240
agcctgagga cgaggctgac tactactgtg gcatgcatga tgtcagtggg aggaattaca 300
attacc 306

<210> 364
<211> 302
<212> DNA
<213> Canis lupus familiaris

<400> 364
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ccccagggcg ggctcctggc acgattatct acagcacaaa agactgcccc tctgggggtcc 180
ctgactgctt ctctagatcc atctctggga acaaagccgc cctcaccatc acaggagccc 240
agtctgagga cgaggctatt actgttttac acgacatggt agtgggagct gctacactta 300
cc 302

<210> 365
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 365
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acttgtggcc tcagctctgg gtcagtctct acaggtaaca aacctggctg gtaccagcac 120
accccaggcc aggctcctcg caggattatc tatgacacaa gcagccgccc ttctggggtc 180
cctgatcgct tctctggatc catctctgag aaaaaactg ccctcaccat cacagaagcc 240
caacctgagg atgaggctga ctacatcata tatgagtggg ggtgctta 288

<210> 366
<211> 305
<212> DNA
<213> Canis lupus familiaris

<400> 366
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acttgtggcc tcagctctgg atcaatcact acaagtaact accccaactg gctccagcag 120
accccagggc gggctcctcg cagatgatct atggcacaaa aagccgcccc tctgggggtcc 180
ctgatcgctt ctgtagatcc atctctggga acaaagccgc cctcaccatc acaggagccc 240

agtctgagga tgaggctgac tattactgtt ttacacgaca tggcagtggg agcagctaca	300
attac	305
<210> 367	
<211> 309	
<212> DNA	
<213> Canis lupus familiaris	
<400> 367	
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ccttgtggcc tcagctctgg gtcactgact acaagtaaca ctacaccagc tgggtaccagc	120
agaccaagg ccagtctcct cgcattgcttg tctatgacac aagcagctgt ccctctgagg	180
ttcctgatca cttctctgga tccatttctg ggaacaaagc caccctcacc atcacaggag	240
cccagcctga ggacgaggct gactactact gtggcatgca tgatgtcagt gggagcagct	300
aaaattacc	309
<210> 368	
<211> 311	
<212> DNA	
<213> Canis lupus familiaris	
<400> 368	
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accaggcaa ggctcctagc acagttatct acaacaaaaa cagctgcccc tctgggggtcc	180
atggtcgatt ctctggatcc atctctggaa gcaaagccgc cttcacaatc acaggagccc	240
agcctgaggt tgaggctgac tactactgtg ttacagaaca tggctcctca catgggaaca	300
gcctcactca c	311
<210> 369	
<211> 291	
<212> DNA	
<213> Canis lupus familiaris	
<400> 369	
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accaaggcc aggctccttg catgcttata tacagcaca gcagacacc ttctggggtc	180
cctgatcgct tctctggatc catctctggg aacaaagtcg ccctcacat cacaggagcc	240
cagcctgagg ataagactat tattgttcac tgcatatggg tagtacattt a	291
<210> 370	
<211> 296	
<212> DNA	
<213> Canis lupus familiaris	
<400> 370	
cagactgtgg taaccagga gccatcactc tcagtgtctc caggaggagc agtcacactc	60

acatgtggcc tcagctctgg gtcagtctct acaagtaatt accctggctg gtaccagcag	120
acccaaggcc gggctcctcg cacgattatc tacaacacaa gcagccgccc ctctggggtc	180
cctaatacgct tctctggatc catctctgga aacaaagccg ccctcaccat cacaggagcc	240
cagcccgagg atgaggctga ctattactgt tccttgtata cgggtagtta cactga	296

<210> 371
 <211> 296
 <212> DNA
 <213> Canis lupus familiaris

<400> 371	
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acccaaggcc gggcttctcg cacaattatc tacagcacia gcagccgccc ctctggggtc	180
cctaatacgct tccctggatc catctctggg aacaaagccg ccctcaccat cacaggagcc	240
cagcctgagg acgaggctga ctattactgt tccttgtata tgggtagtta cactga	296

<210> 372
 <211> 300
 <212> DNA
 <213> Canis lupus familiaris

<400> 372	
cagattgtag tgacccagga accatcactg tctccaggag ggacagtcct actcacttgt	60
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gggcgggctc ctgcacgat tatctacaac actaacagcc acccctctgg agtcctgat	180
cgcttctctg gatccatctc tgggaacaaa gcggcgctca ccatcacagg agcccagcct	240
gaggacgagg ctgactacta ctgtgttaca gaacatggta gtgggagcag cttcacttac	300

<210> 373
 <211> 307
 <212> DNA
 <213> Canis lupus familiaris

<400> 373	
cagactgtgg tgactcagga gtcactcagtc tcagtgtctc caggaggac agtcacactc	60
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acccaaggcc gatctcctcg catgcttata tatgacacaa gcagctgtcc ctcggaggtc	180
cctgatcgct tctctggatc catttctggg aacacagctg ccctcaccat cacaggagcc	240
cagcctgagg acaaggctga ctactactgt agtatgcatg atgtcagtgg gagcagctac	300
aattacc	307

<210> 374
 <211> 296
 <212> DNA
 <213> Canis lupus familiaris

<400> 374	
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accccagggc aggctcctca cacaataatc tacaggacaa acagctgacc ctctggggtc	180
cctgatcgct tctctggatc catctctggg aacaacgccg ccctcagcat cacagtcgcc	240
cagcctgagg acgaggctga ctattactgt tcattgtata tgggtagtaa cattta	296

<210> 375
 <211> 303
 <212> DNA
 <213> Canis lupus familiaris

<400> 375 cagattgtgg tgacccagga gccatcactc tcagtgtcta gaggaggac agtcacactc	60
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cagggcaggc tcctcacaca attatctatg acaaaaacag ccgccctct ggggtccctg	180
atcacttctc aggatccatc tgtgggaaca aagccaccct caccatcaca ggaaccagc	240
ctgaggacaa ggctgactac tactgtggta tccaacatgg cagtaggagg agcctcatta	300
acc	303

<210> 376
 <211> 306
 <212> DNA
 <213> Canis lupus familiaris

<400> 376 cagactgttg tgactcagga gtcactcagtc tcagtgtctc caggaggac agtaacactc	60
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cccaaggccg atctcctcgc atgcttatct atgacacaag cagccgtccc tctgaggctc	180
ctgatcgctt ctctggatcc atctccggga acaaagctgc cctcaccatc acaggagccc	240
agcctgagga cgaggctgac tactactgtg gtatgcatga tgtcagtggg aggagttaca	300
attacc	306

<210> 377
 <211> 302
 <212> DNA
 <213> Canis lupus familiaris

<400> 377 cagattgtgg tggccaggag gcattgttgt cagtgtcctc tggagggaga gtcacactca	60
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ccccagggcg ggctcctggc acgattatgt acagcacaaa agactgcccc tctggggctc	180
ctgattgctt ctctagatcc atctctggga acaaagccgc cctcaccatc acaggagccc	240
agtctgagga cgaggttatt actgttttac acgacatggt agtgggagct gctacactta	300
cc	302

<210> 378
 <211> 296

<212> DNA
<213> Canis lupus familiaris

<400> 378
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acccagggc aggctcctcg caggattatc tatgacacaa gcagccgcc ttctggggtc 180
cctgatcgct tctctggatc catctctgag acaaagctg ccctcaccat cacagaagcc 240
cagcctgagg atgaggctgc ctaccactgt tcgctgtata tgagtgggtg tgctta 296

<210> 379
<211> 306
<212> DNA
<213> Canis lupus familiaris

<400> 379
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acccagggc gggctcctcg cagatgatct atggcacaaa aagccgccc tctgggggtcc 180
ctgatcgctt ctgtagatcc atctctggga acaaagccgc cctcaccatc acaggagccc 240
agtctgagga tgaggctgac tattactgtt ttacacgaca tggcagtggg agcagctaca 300
attacc 306

<210> 380
<211> 307
<212> DNA
<213> Canis lupus familiaris

<400> 380
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acttgtggcc tcagctctgg gtcactgact acaagtaact acaccagctg gtaccagcag 120
acccaaggcc agtctcctcg catgcttgct tatgacacaa gcagctgtcc ctctgaagtt 180
cctgatcact tctctggatc catttctggg acaaagccg ccctcaccat cacaggagcc 240
cagcctgagg acgaggctga ctactactgt ggtatgcatg atgtcagtgg gagcagctaa 300
aattacc 307

<210> 381
<211> 288
<212> DNA
<213> Canis lupus familiaris

<400> 381
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acttgtggcc tcagctctgg gtcagtcact acaagtaact acccaggta taccagcaga 120
accaggcaa ggctcctagc acagttatct acaacaaaaa cagctgcccc tctgggggtcc 180
atggctgatt ctctggatcc atctctggaa gcaaagccgc cttcacaatc acaggagccc 240
agcctgaggt tgaggctgac tactactgtg ttacagaaca tggctcct 288

<210> 382
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 382
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acatgtggcc tcagctctgg gtaagtctct gcaagaaact accccagctg gtaccagcag 120
acccaaggcc aggctccttg catgcttatac tacagcaciaa gcagccgccc ttctggggtc 180
cctgatcgct tctctggatc catctctggg aacaaagtcg ccctcaccat cacaggagcc 240
cagcctgagg atgagactat tattgtttcac tgcataatgg tagtacattt a 291

<210> 383
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 383
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accctaggcc gggctcctcg cacgattatc tacagaaciaa gcagccgccc ctctggggtc 180
cctaatacgct tctctggatc catctctggg aacaaagccg ccctcaccat cacaggagcc 240
cagcctgagg acgaggctga ctattactgt tccttgtata tgggtagtta cactga 296

<210> 384
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 384
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acccatggcc gggctcctcg catgcttatac tacagcaciaa ggagctgccc ccccggggtc 180
cctgatcgct tctctggatc catctctggg aacaaagttg ccctcaccat cacaggagcc 240
cagcctgagg atgagactat tattgtttcac tgtgtatggg tagtacattt a 291

<210> 385
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 385
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acccaaggcc gggcttctcg cacaattatac tacagcaciaa gcagccgccc ctctggggtc 180
cctaatacgct tcaatggatc catctctggg aacaaagccg ccctcaccat cacaggagcc 240
cagcctgagg acgaggctga ctattactgt tccttgtata tgggtagtta cactga 296

<210> 386
<211> 307
<212> DNA
<213> Canis lupus familiaris

<400> 386
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acccaggcc aggctcctag cacagttatc tacaacaaa acagccgccc ctctgggtgc 180
cctgatcact tctctggatc cgtctctggg aaaaagccg ccctcatcat cacaggagcc 240
cagcctgagg acgaggctga tgactactct gttgcagaac atgtcagtgg gagcagcttc 300
acttacc 307

<210> 387
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 387
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acccaaggcc gggctcctcg cacgattatc tacaacaaa gcagccgccc ctctggggtc 180
cctaatacgct tctctggatc catctctgga aaaaagccg ccctcaccat cacaggagcc 240
cagcccaggg atgaggctga ctattactgt tccttgtata cgggtagtta cactga 296

<210> 388
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 388
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acatgtggcc tcagctctgg gtcagtcttt acaagtaact accccagctg gtaccagcag 120
acccatggcc gggctcctcg catgcttatt tacagcacia gcagctgccc ccccggggtc 180
cctgatcgct tctctggatc catctctggg aaaaagttg ccctcaccat cacaggagcc 240
cagcctgagg atgagactat tattgtttac tgtgtatggg tagtacattt a 291

<210> 389
<211> 296
<212> DNA
<213> Canis lupus familiaris

<400> 389
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atatgtggcc tcagctctgg gtcagtctct acaagtaatt accctggctg gtaccagcag 120
acccaaggcc gggcttctcg cacaattatc tacagcacia gcagccgccc ctctggggtc 180
cctaatacgct tccctggatc catctctggg aaaaagccg ccctcatcat cacaggagcc 240
cagcctgagg acgaggctga ctattactgt tccttgtata tgggtagtta cactga 296

<210> 390
 <211> 38
 <212> DNA
 <213> Canis lupus familiaris

 <400> 390
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 <210> 391
 <211> 38
 <212> DNA
 <213> Canis lupus familiaris

 <400> 391
 tatggtattc ggcagaggga cccagctgac catcctcg 38

 <210> 392
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 <212> DNA
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 <400> 392
 tagtgtgttc ggcggaggca cccatctgac cgtcctcg 38

 <210> 393
 <211> 38
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 <400> 394
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 <210> 395
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 <210> 397
 <211> 38
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<400> 397
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<210> 398
 <211> 38
 <212> DNA
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<400> 398
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<210> 399
 <211> 306
 <212> DNA
 <213> Canis lupus familiaris

<220>
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 <222> (1)..(1)
 <223> a, c, t, g, unknown or other

<400> 399
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 tacgtgggtca tcggctgcct ggtgcaggga ttcttccac cggagcctgt gaacgtgacc 120
 tggaatgccg gcaaggacag cacatctgtc aagaacttcc ccccatgaa ggctgctacc 180
 ggaagcctat acaccatgag cagccagttg accctgccag ccgcccagtg ccctgatgac 240
 tcgtctgtga aatgccaaagt gcagcatgct tccagcccca gcaaggcagt gtctgtgccc 300
 tgcaaa 306

<210> 400
 <211> 342
 <212> DNA
 <213> Canis lupus familiaris

<400> 400
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 agtggcctga aagaccccaa gggtgccacc ttcacctgga acccctcaa agggaaggaa 180
 cccatccaga agaatcctga gcgtgactcc tgtggctgct acagtgtgtc cagtgtccta 240
 ccaggctgtg ctgatccatg gaaccatggg gacaccttct cctgcacagc caccaccct 300
 gaatccaaga gcccgatcac tgtcagcatc accaaaacca ca 342

<210> 401
 <211> 387
 <212> DNA
 <213> Canis lupus familiaris

<400> 401
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gagcctgacc agaccaacat gtttgccgtg accagcatgc tgagggtgac agccgaagac	240
tggaagcagg gggagaagtt ctcttgcacg gtgggccacg aggctctgcc catgtccttc	300
accagaaga ccatcgaccg cctggcgggt aaaccaccc acgtcaacgt gtctgtggtc	360
atggcagagg tggacggcat ctgctac	387

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 <211> 213
 <212> DNA
 <213> Canis lupus familiaris

<400> 402	
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caggaggacc tggaggagga tgccccagga gccagcctgt ggcccactac cgtcaccctt	120
ctcaccctct tcctactgag tctcttctac agcacagcac tgactgtgac aagcgtgcgg	180
ggcccaactg acagcagaga gggcccccag tac	213

<210> 403
 <211> 285
 <212> DNA
 <213> Canis lupus familiaris

<400> 403	
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ataaccctgg cctgcttggc aaaaggaccc ttcttagatt ctgtgcgggt cacgacaggc	120
ccagagtcac aggcccagat ggaaaagacc aactgaaga tgctaaagat accggaccac	180
actcaggtgt ctctcctgtc cccccctgg aaaccaggcc tgcactactg cgaagccatc	240
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<210> 404
 <211> 90
 <212> DNA
 <213> Canis lupus familiaris

<400> 404	
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acccaagccc ccagcatggc cagggtctca	90

<210> 405
 <211> 69
 <212> DNA
 <213> Canis lupus familiaris

<400> 405	
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atcctcaga	69

<210> 406
 <211> 327
 <212> DNA
 <213> Canis lupus familiaris

<400> 406

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gcccacctgt cctgggaggt agccggggcg cccccagcg aggctgtgga ggagaggcca	180
ctgcaggagc atgagaatgg ctcccagagc tggagcagcc gcctggtctt gcccatatcc	240
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gtggtgtccg cagcagccag agagcat	327

<210> 407
 <211> 312
 <212> DNA
 <213> Canis lupus familiaris

<400> 407 gctgccagag caccagcag cctcaatgtc catgccctga ccatgccag agcagcctcc	60
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gaccagattg aggtggaccc ttcttggttc gccactgcac ccccatggc ccagccgggc	180
agtggcacgt tccagacctg gagtctcctg cgtgtcctcg ctccccaggg ccctcaccg	240
cccacctaca cgtgtgtagt caggcacgag gcctcccgga agctgctcaa caccagctgg	300
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<210> 408
 <211> 150
 <212> DNA
 <213> Canis lupus familiaris

<400> 408 ggtctgacca tgaccccccc agcccctcag agccacgacg agagcagcgg ggactccatg	60
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<210> 409
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<400> 409 gtgaag	6
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<210> 410
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acctgggaca cggggtctct aaataagaat gtcacgacct tccccaccac cttccacgag	180
acctacggcc tccacagcat cgctagccag gtgaccgcct cgggcgagtg ggccaaacag	240
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<210> 411
 <211> 324
 <212> DNA
 <213> Canis lupus familiaris

<400> 411 gcatgtgcct taaacttcat tccgcctacc gtgaagctct tccactcctc ctgcaacccc	60
gtcggtgata cccacaccac catccagctc ctgtgcctca tctctggcta cgtcccaggt	120
gacatggagg tcatctggct ggtggatggg caaaaggcta caaacatatt cccatacact	180
gcacccggca caaaggaggg caacgtgacc tctaccaca gcgagctcaa catcaccag	240
ggcgagtggg tatcccaaaa aacctacacc tgccagggtca cctatcaagg ctttaccttt	300
aaagatgagg ctgcaagtg ctca	324

<210> 412
 <211> 321
 <212> DNA
 <213> Canis lupus familiaris

<400> 412 gagtccgacc cccgaggcgt gagcagctac ctgagccac ccagccccct tgacctgtat	60
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aacctgacct ggtaccggga gagcaaagaa cccgtgaacc cgggcccttt gaacaagaag	180
gatcattca atgggacgat cacagtcacg tctaccctgc cagtgaacac caatgactgg	240
atcgagggcg agacctacta ttgcagggtg acccaccgc acctgccc aa ggacatcgtg	300
cgctccattg ccaaggcccc t	321

<210> 413
 <211> 339
 <212> DNA
 <213> Canis lupus familiaris

<400> 413 ggcaagcgtg ccccccgga tgtgtacttg ttctgccac cggaggagga gcaggggacc	60
aaggacagag tcacctcac gtgcctgatc cagaacttct tccccgcgga catttcagt	120
caatggctgc gaaacgacag cccatccag acagaccagt acaccaccac ggggccccac	180
aaggtctcgg gctccaggcc tgccttcttc atcttcagcc gcctggaggt tagccgggtg	240
gactgggagc agaaaaacaa attcacctgc caagtgtgc atgaggcgct gtccggctct	300
aggatcctcc agaaatgggt gtccaaaacc cccggtaaa	339

<210> 414
 <211> 129
 <212> DNA
 <213> Canis lupus familiaris

<400> 414
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agcctgtctca tcttcatcac cctcttcctg ctcagcgtga gctacggcgc caccagcacc 120
ctcttcaag 129

<210> 415
<211> 81
<212> DNA
<213> Canis lupus familiaris

<400> 415
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aacatcgtgc ggccggcaca g 81

<210> 416
<211> 291
<212> DNA
<213> Canis lupus familiaris

<400> 416
gcctccacca cggccccctc ggttttccca ctggccccca gctgcgggtc cacttccggc 60
tccacgggtg ccctggcctg cctgggtgtca ggctacttcc ccgagcctgt aactgtgtcc 120
tggaattccg gctccttgac cagcgggtgtg cacaccttcc cgtccgtcct gcagtcctca 180
gggcttcact ccctcagcag catggtgaca gtgccctcca gcaggtggcc cagcgagacc 240
ttcacctgca acgtgggtcca cccagccagc aacactaaag tagacaagcc a 291

<210> 417
<211> 42
<212> DNA
<213> Canis lupus familiaris

<400> 417
gtgttcaatg aatgcagatg cactgataca ccccatgcc ca 42

<210> 418
<211> 330
<212> DNA
<213> Canis lupus familiaris

<400> 418
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ctcaggatta cccgaacacc cgaggtcacc tgtgtggtgt tagatctggg ccgtgaggac 120
cctgaggtgc agatcagctg gttcgtggat ggtaaggagg tgcacacagc caagaccag 180
tctcgtgagc agcagttcaa cggcacctac cgtgtggtca gcgtcctccc cattgagcac 240
caggactggc tcacagggaa ggagttcaag tgcagagtca accacataga cctcccgctc 300
cccatcgaga ggaccatctc taaggccaga 330

<210> 419
<211> 330
<212> DNA
<213> Canis lupus familiaris

<400> 419
 gggagggccc ataagcccag tgtgtatgtc ctgccgcat ccccaaagga gttgtcatcc 60
 agtgacacag tcagcatcac ctgcctgata aaagacttct acccacctga cattgatgtg 120
 gagtggcaga gcaatggaca gcaggagccc gagaggaagc accgcatgac cccgccccag 180
 ctggacgagg acgggtccta cttcctgtac agcaagctct ctgtggacaa gagccgctgg 240
 cagcaggag accccttcac atgtgcggtg atgcatgaaa ctctacagaa ccactacaca 300
 gatctatccc tctccattc tccgggtaaa 330

<210> 420
 <211> 291
 <212> DNA
 <213> Canis lupus familiaris

<220>
 <221> modified_base
 <222> (1)..(1)
 <223> a, c, t, g, unknown or other

<400> 420
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 tccacggtgg ccctggcctg cctggtgtca ggctacttcc ccgagcctgt aactgtgtcc 120
 tggaattccg gctccttgac cagcgggtgtg cacaccttcc cgtccgtcct gcagtcctca 180
 gggctctact ccctcagcag catggtgaca gtgccctcca gcaggtggcc cagcgagacc 240
 ttcacctgca acgtggccca cccggccagc aaaactaaag tagacaagcc a 291

<210> 421
 <211> 57
 <212> DNA
 <213> Canis lupus familiaris

<400> 421
 gtgccccaaa gagaaaatgg aagagttcct cgcccactg attgtcccaa atgcca 57

<210> 422
 <211> 330
 <212> DNA
 <213> Canis lupus familiaris

<400> 422
 gcccctgaaa tgctgggagg gccttcggtc ttcattttt ccccgaaacc caaggacacc 60
 ctcttgattg cccgaacacc tgaggtcaca tgtgtggtgg tggatctgga cccagaagac 120
 cctgaggtgc agatcagctg gttcgtggac ggtaagcaga tgcaaacagc caagactcag 180
 cctcgtgagg agcagttcaa tggcacctac cgtgtggtca gtgtcctccc cattgggcac 240
 caggactggc tcaaggggaa gcagttcacg tgcaaagtca acaacaaagc cctcccatcc 300
 ccgatcgaga ggaccatctc caaggccaga 330

<210> 423
 <211> 327
 <212> DNA

<213> Canis lupus familiaris

<400> 423

gggcaggccc atcaaccag tgtgtatgtc ctgccgcat cccgggagga gttgagcaag	60
aacacagtca gcttgacatg cctgatcaaa gacttcttcc cacctgacat tgatgtggag	120
tggcagagca atggacagca ggagcctgag agcaagtacc gcacgacccc gccccagctg	180
gacgaggacg ggtcctactt cctgtacagc aagctctctg tggacaagag ccgctggcag	240
cggggagaca cttcatatg tgcggtgatg catgaagctc tacacaacca ctacacacag	300
aatccctct cccattctcc gggtaaa	327

<210> 424

<211> 132

<212> DNA

<213> Canis lupus familiaris

<400> 424

gagctgatcc tggatgacag ctgtgctgag gaccaggacg gggagctgga cgggctgtgg	60
accaccatct ccatcttcat caccctcttc ctgctcagcg tgtgctacag cgccactgtc	120
accctcttca ag	132

<210> 425

<211> 81

<212> DNA

<213> Canis lupus familiaris

<400> 425

gtgaagtgga tcttctcatc agtgggtggag ctgaagcgca cgattgtccc cgactacagg	60
aatatgatcg ggcagggggc c	81

<210> 426

<211> 291

<212> DNA

<213> Canis lupus familiaris

<400> 426

gcctccacca cggccccctc ggttttccca ctggccccca gctgtgggtc ccaatccggc	60
tccacggtgg ccctggcctg cctggtgtca ggctacatcc ccgagcctgt aactgtgtcc	120
tggaaattccg tctccttgac cagcgggtgtg cacaccttcc cgtccgtcct gcagtcctca	180
gggctctact ccctcagcag catggtgaca gtgccctcca gcaggtggcc cagcgagacc	240
ttcacctgca atgtggccca cccggccacc aacactaaag tagacaagcc a	291

<210> 427

<211> 51

<212> DNA

<213> Canis lupus familiaris

<400> 427

gtggccaaag aatgcgagtg caagtgtaac tgtaacaact gcccatgccc a	51
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<210> 428

<211> 330

<212> DNA

<213> Canis lupus familiaris

<400> 428

ggttggtggcc tgctgggagg gccttcggtc ttcattcttc ccccaaaacc caaggacatc	60
ctcgtgactg cccggacacc cacagtcact tgtgtggtgg tggatctgga ccagaaaaac	120
cctgagggtgc agatcagctg gttcgtggat agtaagcagg tgcaaacagc caacacgcag	180
cctcgtgagg agcagtccaa tggcacctac cgtgtggtca gtgtcctccc cattgggcac	240
caggactggc tttcagggaa gcagttcaag tgcaaagtca acaacaaagc cctcccatcc	300
cccattgagg agatcatctc caagacccca	330

<210> 429

<211> 327

<212> DNA

<213> Canis lupus familiaris

<400> 429

gggcaggccc atcagcctaa tgtgtatgtc ctgccgccat cgcgggatga gatgagcaag	60
aatacgggtca ccctgacctg tctggtcaaa gacttcttcc cacctgagat tgatgtggag	120
tggcagagca atggacagca ggagcctgag agcaagtacc gcatgacccc gccccagctg	180
gatgaagatg ggtcctactt cctatacagc aagctctccg tggacaagag ccgctggcag	240
cggggagaca cttcatatg tgcggtgatg catgaagctc tacacaacca ctacacacag	300
atatccctct cccattctcc gggtaaa	327

<210> 430

<211> 291

<212> DNA

<213> Canis lupus familiaris

<400> 430

gcctccacca cggccccctc ggttttccca ctggccccca gctgcgggtc cacttccggc	60
tccacgggtg ccctggcctg cctggtgtca ggctacttcc ccgagcctgt aactgtgtcc	120
tggaattccg gtccttgac cagcgggtgtg cacaccttcc cgtccgtcct gcagtcctca	180
gggctctact ccctcagcag cacggtgaca gtgccctcca gcaggtggcc cagcgagacc	240
ttcacctgca acgtggtcca cccggccagc aacactaaag tagacaagcc a	291

<210> 431

<211> 42

<212> DNA

<213> Canis lupus familiaris

<400> 431

gtgccccaaag agtccacctg caagtgtata tccccatgcc ca	42
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<210> 432

<211> 330

<212> DNA

<213> Canis lupus familiaris

<400> 432

gtccctgaat cactgggagg gccttcggtc ttcattcttc ccccgaaacc caaggacatc	60
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ctcaggatta cccgaacacc cgagatcacc tgtgtggtgt tagatctggg ccgtgaggac	120
cctgaggtgc agatcagctg gttcgtggat ggtaaggagg tgcacacagc caagacgcag	180
cctcgtgagc agcagttcaa cagcacctac cgtgtggtca gcgtcctccc cattgagcac	240
caggactggc tcaccggaaa ggagttcaag tgcagagtca accacatagg cctcccgtcc	300
cccatcgaga ggactatctc caaagccaga	330

<210> 433
 <211> 330
 <212> DNA
 <213> Canis lupus familiaris

<400> 433 gggcaagccc atcagcccag tgtgtatgtc ctgccacat ccccaaagga gttgtcatcc	60
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gagtggcaga gcaatggaca gccggagccc gagagcaagt accacacgac tgcgccccag	180
ctggacgagg acgggtccta cttcctgtac agcaagctct ctgtggacaa gagccgctgg	240
cagcagggag acaccttcac atgtgcggtg atgcatgaag ctctacagaa ccactacaca	300
gatctatccc tctccattc tccgggtaaa	330

<210> 434
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<220>
 <221> modified_base
 <222> (1)..(1)
 <223> a, c, t, g, unknown or other

<400> 434 nagagtccat cccctccaaa cctcttcccc ctcatcacct gtgagaactc cctgtccgat	60
gagaccctcg tggccatggg ctgcctggcc cgggacttcc tgcctggctc catcaccttc	120
tcctggaagt acgagaacct cagtgcatac aacaaccagg acattaagac cttcccttca	180
gttctgagag agggcaagta tgtggcgacc tctcaggtgt tcctgccctc cgtggacatc	240
atccagggtt cagacgagta catcacatgc aacgtcaagc actccaatgg tgacaaatct	300
gtgaacgtgc ccatcaca	318

<210> 435
 <211> 339
 <212> DNA
 <213> Canis lupus familiaris

<400> 435 gggcctgtac caacgtctcc caacgtgact gtcttcatcc caccgcga cgccttctct	60
ggcaatggcc agcgaagtc ccagctcatc tgccaggctg caggtttcag cccaagcag	120
atttccgtgt cttggttccg tgatggaaag cagattgagt ctggcttcaa cacagggaag	180
gcagaggccg aggagaaaga gcatgggcct gtgacctaca gcacctcag catgctgacc	240

atcaccgaga gtgcctggct cagccagagc gtgttcacct gccacgtgga gcacaatggg 300

atcatcttcc agaagaacgt gtcctccatg tgcacctcc 339

<210> 436

<211> 318

<212> DNA

<213> Canis lupus familiaris

<400> 436

aatacacccg ttggcatcag catcttcacc atccccccct cctttgccag catcttcaac 60

accaagtcag ccaagctgtc ctgcctggtc actgacctgg ccacttatga cagcctgacc 120

atctcctgga cccgtcagaa tggcgaggct ctgaaaaccc acaccaacat ctctgagagc 180

catcccaaca acaccttcag tgccatgggg gaagccactg tctgcgtgga ggaatgggag 240

tcaggcgagc agttcacctg cacagtgacc cacacagatc tgccctcacc gctgaagaag 300

accatctcca ggccaag 318

<210> 437

<211> 393

<212> DNA

<213> Canis lupus familiaris

<400> 437

gatgtcaaca agcacatgcc ttctgtctac gtcctgcccc cgagccggga gcagctgagc 60

ctgcgggaat cggcctcact cacctgcctg gtgaaaggct tctcaccccc agatgtgttc 120

gtgcagtggc tgcagaaggg ccagcccgtg cccctgaca gctacgtgac cagcgccccg 180

atgcccagagc cccaagcccc cggcctctac tttgtccaca gcacacctgac cgtgagttag 240

gaggactgga atgccgggga gacctacacc tgtgtttag gccatgaggc cctgccccat 300

gtggtgaccg agaggagcgt ggacaagtcc accggtaaac ccaccttgta caacgtgtcc 360

ctggtcttat ctgacacagc cagcacctgc tac 393

<210> 438

<211> 117

<212> DNA

<213> Canis lupus familiaris

<400> 438

gggggggagg tgagtccga ggaggaaggc ttcgagaacc tgaataccat ggcattcacc 60

ttcatcgtcc tcttcctcct cagtgtcttc tacagcacca cagtcactct gttcaag 117

<210> 439

<211> 6

<212> DNA

<213> Canis lupus familiaris

<400> 439

gtgaaa 6

<210> 440

<211> 330

<212> DNA

<213> Canis lupus familiaris

<400> 440
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 ggaagtgcct ctgttgtgtg cttgtgaat agcttctacc ccaaagacat caatgtcaag 120
 tggaaagtgg atggtgtcat ccaagacaca ggcatccagg aaagtgtcac agagcaggac 180
 aaggacagta cctacagcct cagcagcacc ctgacgatgt ccagtactga gtacctaagt 240
 catgagttgt actcctgtga gatcactcac aagagcctgc cctccaccct catcaagagc 300
 ttccaaagga gcgagtgtca gagagtggac 330

<210> 441
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 441
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 gccacaagg ctaccctggt gtgcctcatc agcgacttct acccagtggt cctgaaagtg 120
 gcttgaagg cagatggcag caccatcatc cagggcgtgg aaaccacaa gccctccaag 180
 cagagcaaca acaagtacac ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
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 gccctgcag agtgctct 318

<210> 442
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 442
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 cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
 tctcacagca gcttcagctg cctggtcacg catgagggga gcaccgtgga gaagaagggtg 300
 gccccgcag agtgctct 318

<210> 443
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 443
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 gccacaagg ccaccctggt gtgcctcatc agcgacttct acccagtggt cgtgacgggtg 120
 gcctggaagg cagacggcag cccgctacc cagggcgtgg agaccacaa gccctccaag 180
 cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
 tctcacagca gcttcagctg cctggtcaca cagagggga gcaccgtgga gaagaagggtg 300

gccccgcag agtgctct 318

<210> 444
<211> 289
<212> DNA
<213> Canis lupus familiaris

<400> 444
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gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg tgtgacggtg 120
gcctggaagg cagacggcag ccccgtcacc cagggcgtgg agaccaccaa gccctccaag 180
cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
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<210> 445
<211> 318
<212> DNA
<213> Canis lupus familiaris

<400> 445
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gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg cgtgacagtg 120
gcctggaagg cagacggcag ccccatcacc caggggtgtgg agaccaccaa gccctccaag 180
cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
tctcacagca gcttcagctg cctggtcacg cacgagggga gcaccgtgga gaagaagggtg 300
gccccgcag agtgctct 318

<210> 446
<211> 318
<212> DNA
<213> Canis lupus familiaris

<400> 446
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gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg tgtgacggtg 120
gcctggaagg cagacggcag ccccgtcacc cagggcgtgg agaccaccaa gccctccaag 180
cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa 240
tctcacagca gcttcagctg cctggtcacg cacgagggga gcaccgtgga gaagaagggtg 300
gccccgcag agtgctct 318

<210> 447
<211> 318
<212> DNA
<213> Canis lupus familiaris

<400> 447
ggtcagccca aggcctcccc ctcggtcaca ctcttccgc cctcctctga ggagctcggc 60
gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg cgtgacggtg 120
gcctggaagg cagacggcag ccccgtcacc cagggcgtgg agaccaccaa gccctccaag 180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa	240
tctcacagca gcttcagctg cctggtcacg cacgagggga gcaccgtgga gaagaagggtg	300
gccccgcag agtgctct	318

<210> 448
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 448	
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gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg cgtgacgggtg	120
gcctggaagg cagacggcag ccccgtcacc cagggcgtgg agaccaccaa gccctccaag	180
cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa	240
tctcacagca gcttcagctg cctggtcacg cacgagggga gcaccgtgga gaagaagggtg	300
gccccgcag agtgctct	318

<210> 449
 <211> 318
 <212> DNA
 <213> Canis lupus familiaris

<400> 449	
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gccaacaagg ccaccctggt gtgcctcatc agcgacttct accccagcgg cgtgacgggtg	120
gcctggaagg cagacggcag ccccatcacc cagggcgtgg agaccaccaa gccctccaag	180
cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga caagtggaaa	240
tctcacagca gcttcagctg cctggtcacg cacgagggga gcactgtgga gaagaagggtg	300
gccccgcag agtgctct	318

<210> 450
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> source
 <223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 450	
acataataca ctgaaatgga gccc	24

<210> 451
 <211> 20
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> source
 <223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 451 gtccttggtc aacgtgaggg	20
<210> 452 <211> 24 <212> DNA <213> Artificial Sequence	
<220> <221> source <223> /note="Description of Artificial Sequence: Synthetic primer"	
<400> 452 cataatacac tgaaatggag ccct	24
<210> 453 <211> 20 <212> DNA <213> Artificial Sequence	
<220> <221> source <223> /note="Description of Artificial Sequence: Synthetic primer"	
<400> 453 gcaacagtgg taggtcgctt	20
<210> 454 <211> 100 <212> DNA <213> Mus musculus	
<400> 454 atttctgtac ctgatctatg tcaatatctg taccatggct ctagcagaga tgaaatatga	60
gacagtctga tgtcatgtgg ccatgcctgg tccagacttg	100
<210> 455 <211> 100 <212> DNA <213> Mus musculus	
<400> 455 gtcaatcagc agaaatccat catacatgag acaaagttat aatcaagaaa tgttgcccat	60
aggaaacaga ggatatctct agcactcaga gactgagcac	100
<210> 456 <211> 1103 <212> DNA <213> Artificial Sequence	
<220> <221> source <223> /note="Description of Artificial Sequence: Synthetic polynucleotide"	
<400> 456 gcattgaata aaccagtata aacaagcaag caaagataga tagatagata gatagataga	60
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agattttttac gtataataca ataaaaacat tcattgtccc tctattgggtg actactcaag	180
gaaaaaaatg ttcatatgca agaaaaaatg ttatcattac cagatgatcc agcaatctag	240
caatatatat attgtttatt cacaaaacat gaatgaacct tttaagaagc tgttacagtg	300
taaaaattaa gttaaatac tgaagaacat atactgtgtg atttcattca aatgaaattt	360
gagaagtaaa tatatatgta tatatatata tatgtaaaaa atataagtct gaactacaaa	420
aattcaattt gtttgatatg taagaataag aaaaattgac ccccaaaatt tgtaataat	480
taggtatgtg tatttttatg aatatataag tataataatg cttatagtat acactattct	540
gaatcacatt tattccctaa gtgtgttccc ttgattataa ttaaaagtat attttttaaa	600
tacagagtca gagtacagtc aataaggcga aaatatagtt gaatgatttg cttcagcttt	660
tgtaatgtac tagagattgt gagtacaaag tctcagagct ctttttatcc ctgacaataa	720
ccagctctgt gcttcaagta cttttccatc tttctctgaa atttagtctt atatagatag	780
acaaaattta agtaaatttc aaactacaca gaacaactaa gttgttggtt catattgata	840
atggatttga actgcattaa cagaacttta acatcctgct tattctccct tcagccatca	900
tattttgctt tattattttc actttttgag ttatttttca cattcagaaa gtcacataa	960
ttgtcacttc tttgtatact ggtatacaga ccagaacatt tgcatattgt tccctgggga	1020
ggtctttgcc ctgttgccct gagataaaac ctcaagtgtc ctcttgccct cactgatcac	1080
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<210> 457

<211> 46

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 457

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<210> 458

<211> 377

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 458

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gtgctgtttc tctccctgtg tattctgtgc atgggacaga ttgccctcca acagggggaa	120
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tttaattttt agactgtgag aattaagaag aatataaaat atttgatgaa cagtacttta	180
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gtgagatgct aaagaagaaa gaagtcactc tgtcttgcta tcttggttt tccatgataa	240
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ttgaatagat ttaaaatata aatcaaaatc aaaatatgat ttagcctaaa atatacaaaa	300
cccaaaatga ttgaaatgtc ttatactggt tctaacacaa cttgtactta tctctcatta	360
ttttaggatc cagtggg	377
<210> 459	
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<400> 459	
aggatccagt ggg	13
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<211> 297	
<212> DNA	
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ttccgacaga agccaggcca gtctccacag cgtttaatct ataaggtctc caacagagac	180
cctgggggtcc cagacagggt cagtggcagc gggtcaggga cagatttcac cctgagaatc	240
agcagagtgg aggctgacga tactggagtt tattactgcg ggcaaggat acaagat	297
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<211> 7	
<212> DNA	
<213> Artificial Sequence	
<220>	
<221> source	
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> 461	
cacagtg	7
<210> 462	
<211> 142	
<212> DNA	
<213> Artificial Sequence	
<220>	
<221> source	
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"	
<400> 462	
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aagaggagca gagagcatct tgtgtctgtg tgagaaggag gggctgggat acatgagtaa 120

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<210> 463

<211> 1103

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 463

gcattgaata aaccagtata aacaagcaag caaagataga tagatagata gatagataga 60

tagatagata catagataga tagatagata gatagatgat agatagatag atagatagat 120

agatttttac gtataatata ataaaaacat tcattgtccc tctattgggtg actactcaag 180

gaaaaaatg ttcatatgca agaaaaatg ttatcattac cagatgatcc agcaatctag 240

caatatatat attgtttatt cacaaaacat gaatgaacct tttaagaagc tgttacagtg 300

taaaaattaa gttaaatacac tgaagaacat atactgtgtg atttcattca aatgaaattt 360

gagaagtaaa tatatatgta tatatatata tatgtaaaaa atataagtct gaactacaaa 420

aattcaattt gtttgatatg taagaataag aaaaattgac ccccaaaatt tgттаатаат 480

taggtatgtg tatttttatg aatatataag tataataatg cttatagtat acactattct 540

gaatcacatt tattccctaa gtgtgttccc ttgattataa ttaaaagtat attttttaaa 600

tacagagtca gagtacagtc aataaggcga aaatatagtt gaatgatttg cttcagcttt 660

tgtaatgtac tagagattgt gagtacaaag tctcagagct cattttatcc ctgacaataa 720

ccagctctgt gcttcaagta catttccatc tttctctgaa atttagtctt atatagatag 780

acaaaattta agtaaatttc aaactacaca gaacaactaa gttgttgttt catattgata 840

atggatttga actgcattaa cagaacttta acatcctgct tattctccct tcagccatca 900

tattttgctt tattattttc actttttgag ttatttttca cattcagaaa gctcacataa 960

ttgtcacttc ttgtataact ggtatacaga ccagaacatt tgcatattgt tccctgggga 1020

ggtctttgcc ctgttggcct gagataaaac ctcaagtgtc ctcttgccct cactgatcac 1080

tctcctatgt ttatttcctc aaa 1103

<210> 464

<211> 49

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 464

atgatgagtc ctgccagtt cctgtttctg ttagtgctct ggattcagg 49

<210> 465
<211> 386
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 465
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catcctaag agatattcca catggaacag tatctgtact aagatcagta ttctgacata 180
gattggatgg agtggatatag actccatcta taatggatga tgtttagaaa cttcaacact 240
tgttttatga caaagcattt gatataata atttttaaat ctgaaaaact gctaggatct 300
tacttgaaag gaatagcata aaagatttca caaagggtgc tcaggatctt tgcacatgat 360
tttcactat tgtattgtaa tttcag 386

<210> 466
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 466
aaaccaacgg t 11

<210> 467
<211> 297
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 467
gatattgtca tgacacagac ccactgtcc ctgtctgtca gccctggaga gactgcctcc 60
atctcctgca aggccagtca gagcctcctg cacagtgatg gaaacacgta tttgaactgg 120
ttccgacaga agccaggcca gtctccacag cgtttaaatct ataaggtctc caacagagac 180
cctgggggtcc cagacagggt cagtggcagc gggtcaggga cagatttcac cctgagaatc 240
agcagagtgg aggctgacga tactggagtt tattactgcg ggcaaggat acaagat 297

<210> 468
<211> 7
<212> DNA
<213> Artificial Sequence

<220>

<221> source	
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> 468	
cacagtg	7
<210> 469	
<211> 142	
<212> DNA	
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<221> source	
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aagaggagca gagagcatct tgtgtctgtg tgagaaggag gggctgggat acatgagtaa	120
ttctttgcag ctgtgagctc tg	142
<210> 470	
<211> 13	
<212> DNA	
<213> Mus musculus	
<400> 470	
cttccttcct cag	13
<210> 471	
<211> 13	
<212> DNA	
<213> Artificial Sequence	
<220>	
<221> source	
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> 471	
aaattaatta acc	13