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(54) Title: CANINIZED ANTIBODIES TO CANINE INTERLEUKIN-31 RECEPTOR *ALPHA*

(57) Abstract: The present invention provides caninized rat antibodies to canine IL-31 receptor *alpha* that have a high binding affinity for canine IL-31 receptor *alpha*, and that can block the binding of canine IL-31 to canine IL-31 receptor *alpha*. The present invention further provides the use of the antibodies for the treatment of atopic dermatitis in dogs.

WO 2022/079139 A1

CANINIZED ANTIBODIES TO CANINE INTERLEUKIN-31 RECEPTOR *ALPHA***CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims priority under 35 U.S.C. § 119(e) of provisional applications:

5 U.S. Serial 63/092,294, filed October 15, 2020, U.S. Serial 63/092,296, filed October 15, 2020, U.S. Serial 63/127,184, filed December 18, 2020, U.S. Serial 63/235,258, filed August 20, 2021, U.S. Serial 63/235,257, filed August 20, 2021, the contents of which are hereby incorporated by reference in their entireties.

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SEQUENCE LISTING

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 October 1, 2021, is named 25071-WO-PCT_SL.txt and is 103,453 bytes in size.

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FIELD OF THE INVENTION

The present invention relates to antibodies to canine IL-31 receptor *alpha* that have a high binding affinity for the canine IL-31 receptor *alpha* and that can block the binding of canine IL-31 to the canine IL-31 receptor *alpha*. The present invention also relates to use of the antibodies of the present invention in the treatment of atopic dermatitis in dogs.

20

BACKGROUND OF THE INVENTION

The immune system comprises a network of resident and recirculating specialized cells that function collaboratively to protect the host against infectious diseases and cancer. The ability of the immune system to perform this function depends to a large extent on the biological activities of a group of proteins secreted by leukocytes and collectively referred to as interleukins. Among the well-studied interleukins are four important molecules identified as interleukin-31 (IL-31), interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-22 (IL-22). Although IL-4, IL-13, IL-22, and IL-31, are critical cytokines for the development of immune responses that are required for protection against extracellular pathogens (*e.g.*, tissue or lumen dwelling parasites), these cytokines also have been implicated in the pathogenesis of allergic diseases in humans and animals, including atopic dermatitis.

Atopic dermatitis (AD) is a relapsing pruritic and chronic inflammatory skin disease, that is characterized by immune system dysregulation and epidermal barrier abnormalities in humans. The pathological and immunological attributes of atopic dermatitis have been the subject of extensive investigations [reviewed in Rahman *et al.* *Inflammation & Allergy-drug target* 10:486-496 (2011) and Harskamp *et al.*, *Seminar in Cutaneous Medicine and Surgery* 32:132-139 (2013)]. Atopic dermatitis is also a common condition in companion animals, especially dogs, where its prevalence has been estimated to be approximately 10-15% of the canine population. The pathogenesis of atopic dermatitis in dogs and cats [reviewed in Nuttall *et al.*, *Veterinary Records* 172(8):201-207 (2013)] shows significant similarities to that of atopic dermatitis in man including skin infiltration by a variety of immune cells and CD4⁺ Th2 polarized cytokine milieu including the preponderance of IL-31, IL-4, and IL-13. In addition, IL-22 has been implicated in the exaggerated epithelial proliferation leading to epidermal hyperplasia that is characteristic of atopic dermatitis.

For example, antibodies against canine IL-31 have been shown to have an effect on pruritus associated with atopic dermatitis in dogs [US 8,790,651 B2; US 10,093,731 B2]. In addition, an antibody against human IL-31 receptor *alpha* (IL-31RA) has been tested and found to have an effect on pruritus associated with atopic dermatitis in humans [Ruzicka, *et al.*, *New England Journal of Medicine*, 376(9),826–835 (2017)].

IL-4 and IL-13 are closely related proteins that can be secreted by many cell types including CD4⁺ Th2 cells, natural killer T cells (NKT), macrophages, mast cells, and basophils. IL-4 and IL-13 display many overlapping functions and are critical to the development of T cell-dependent humoral immune responses. It is known that IL-4 binds with high affinity to two receptors *i.e.*, type-I and type-II IL-4 receptors. Monoclonal antibodies raised against human IL-4 receptor *alpha* (IL-4 R_α) have been developed and some of these antibodies have been extensively tested for their therapeutic effects for treating atopic dermatitis in humans [see, *e.g.*, US2015/0017176 A1]. More recently, caninized antibodies to canine IL-4 R_α that block the binding of canine IL-4 to canine IL-4 R_α also have been disclosed [US2018/0346580A1, hereby incorporated by reference in its entirety].

Because the Type II IL-4 receptor consists of the IL-4 receptor α chain and the IL-13 receptor $\alpha 1$ chain, antibodies to canine IL-4 R_α have been obtained that can block both canine IL-4 and canine

IL-13 from binding the Type II canine IL-4 receptor, thereby serving to help block the inflammation associated with atopic dermatitis [US2018/0346580A1].

Interleukin-22 (IL-22), also known as IL-10-related T cell-derived inducible factor (IL-TIF), belongs to the IL-10 cytokine family. IL-22 is produced by normal T cells upon anti-CD3
5 stimulation in humans. Mouse IL-22 expression is also induced in various organs upon lipopolysaccharide injection, suggesting that IL-22 may be involved in inflammatory responses. IL-22 binds specifically to, and signals through, a receptor complex consisting of a heterodimeric complex of IL-10R2 (also known as IL-10R *beta*) and the Interleukin-22 receptor (IL-22R) [see, Lee *et al.*, *Pharmacology Research & Perspectives*, Pages 1-13 (2018:e00434)]. The
10 Interleukin-22 receptor is also known as Interleukin-22R, *alpha* 1; IL-22RA1; IL-22R1; zcytor11; and CRF2-9 [Xu *et al.*, *Proc. Nat. Acad. Sci.* 98 (17) 9511-9516 (2001); Gelebart and Lai, *Atlas of Genetics and Cytogenetics* 14(12):1106-1110 (2010)]. IL-22 induces epithelial cell proliferation during wound healing, and its deficiency can enable uncontrolled proliferation and enhance tumor development [Huber *et al.*, *Nature* 491:259-263 (2012)]. IL-22 has been shown to activate STAT-1
15 and STAT-3 in several hepatoma cell lines and upregulate the production of acute phase proteins. Antibodies to Interleukin-22 and IL-22R act as anti-proliferative agents by blocking the interaction of IL-22 with IL-22R and thereby the related signaling pathway that leads to the epithelial proliferation.

Pharmaceuticals that have either proven to aid in the treatment of atopic dermatitis and/or have
20 shown promise to do so include: Janus kinase (JAK) inhibitors [see *e.g.*, U.S. 8,133,899; U.S. 8,987,283; WO 2018/108969], spleen tyrosine kinase (SYK) inhibitors [see *e.g.*, U.S. 8,759,366], and antagonists to a chemoattractant receptor-homologous molecule expressed on TH2 cells [see *e.g.*, U.S. 7,696,222, U.S. 8,546,422, U.S. 8,637,541, and U.S. 8,546,422].

25 However, despite some success in treating atopic dermatitis, there remains a need to design alternative and/or better therapies that can address one or more of the symptoms of canine atopic dermatitis.

The citation of any reference herein should not be construed as an admission that such reference is available as "prior art" to the instant application.

SUMMARY OF THE INVENTION

5 The present invention provides new mammalian antibodies, including caninized antibodies, to IL-31 receptor *alpha* (IL-31RA) from canines. In certain embodiments, the mammalian antibodies to canine IL-31 receptor *alpha* (cIL-31RA) are isolated antibodies. In preferred embodiments, the mammalian antibodies or antigen binding fragments thereof bind canine IL-31RA. In more particular embodiments, the mammalian antibodies or antigen binding fragments also block the
10 binding of canine IL-31RA to canine interleukin-31. In particular embodiments, the antibodies are rat antibodies to canine IL-31RA. In more particular embodiments, the mammalian antibodies are caninized rat antibodies to canine IL-31RA.

Accordingly, the present invention provides mammalian antibodies or antigen binding fragments
15 thereof that bind canine IL-31RA and that comprise a heavy chain that comprises a set of three heavy chain complementary determining regions (CDRs), a CDR heavy 1 (HCDR1), a CDR heavy 2 (HCDR2), and a CDR heavy 3 (HCDR3) and a set of three light chain CDRs: CDR light 1 (LCDR1), CDR light 2 (LCDR2), and CDR light 3 (LCDR3).

20 In certain embodiments, the mammalian antibody or antigen binding fragment comprises an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 13, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 14, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 15; and further comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 16, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 17, and a LCDR3 that
25 comprises the amino acid sequence of SEQ ID NO: 18. In specific embodiments, when bound to canine IL-31RA, the antibody binds to an epitope comprised by the amino acid of SEQ ID NO: 102, or SEQ ID NO: 103, or to both SEQ ID NO: 102 and SEQ ID NO: 103. In related embodiments, when bound to canine IL-31RA, the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more
30 preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 103, or both SEQ ID NO: 102 and SEQ ID NO: 103.

In other embodiments, the mammalian antibody or antigen binding fragment comprises an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 19, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 20, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 21; and further comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 22, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 23, and a LCDR3 that comprises the amino acid sequence of SEQ ID NO: 24.

In still other embodiments, the mammalian antibody or antigen binding fragment comprises an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 25, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 26, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 27; and further comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 28, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 29, and a LCDR3 that comprises the amino acid sequence of SEQ ID NO: 30. In specific embodiments, when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid sequence of SEQ ID NO: 101. In related embodiments, when bound to canine IL-31RA the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 101.

In specific embodiments, the mammalian antibody to canine IL-31RA is a rat antibody. In particular embodiments, the mammalian antibody to canine IL-31RA is a caninized rat antibody. In certain embodiments, the caninized antibody comprises a heavy chain that comprises an IgG-D cFc, but the naturally occurring IgG-D hinge region is replaced by a hinge region comprising the amino acid sequence of SEQ ID NO: 79. In other embodiments, the caninized antibody comprises a heavy chain that comprises an IgG-D cFc, but the naturally occurring IgG-D hinge region is replaced by a hinge region comprising the amino acid sequence of SEQ ID NO: 80. In still other embodiments, the caninized antibody comprises a heavy chain that comprises an IgG-D cFc, but the naturally occurring IgG-D hinge region is replaced by a hinge region comprising the amino acid sequence of SEQ ID NO: 81. In yet other embodiments, the caninized antibody comprises a heavy chain that

comprises an IgG-D cFc, but the naturally occurring IgG-D hinge region is replaced by a hinge region comprising the amino acid sequence of SEQ ID NO: 82.

In certain embodiments, the caninized antibody comprises a heavy chain comprising a modified canine IgG-B (IgG-Bm) that comprises the amino acid sequence of SEQ ID NO: 78. In alternative
5 embodiments, the caninized antibody comprises a heavy chain comprising a non-modified canine IgG-B that comprises the amino acid sequence of SEQ ID NO: 77.

In certain embodiments of the compositions, the caninized antibody against canine IL-31RA
10 (cIL-31RA) comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 or SEQ ID NO: 89 and a light chain comprising the amino acid sequence of SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, or SEQ ID NO: 93. In specific embodiments, when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid sequence of SEQ ID
15 NO: 101. In related embodiments, when bound to canine IL-31RA the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 101. The present invention further provides antigen binding fragments of these caninized antibodies.

20 In particular embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 90 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88. In other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 91 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88. In still other embodiments, the caninized antibody comprises a light chain
25 comprising the amino acid sequence of SEQ ID NO: 92 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 93 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88. In other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 90 and a heavy chain
30 comprising the amino acid sequence of SEQ ID NO: 89. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 91 and a

heavy chain comprising the amino acid sequence of SEQ ID NO: 89. In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 92 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 89. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of
5 SEQ ID NO: 93 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 89. In specific embodiments when bound to canine IL-31RA the antibody binds to at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or even more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 101.

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In certain embodiments of the compositions, the caninized antibody against cIL-31RA comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, or SEQ ID NO: 100, and a light chain comprising the amino acid sequence of SEQ ID NO: 97, SEQ ID NO: 98, or SEQ ID NO: 99. In specific embodiments, when bound to canine
15 IL-31RA, the antibody binds to an epitope comprised by the amino acid of SEQ ID NO: 102, or SEQ ID NO: 103, or to both SEQ ID NO: 102 and SEQ ID NO: 103. In related embodiments, when bound to canine IL-31RA, the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 102 or SEQ ID
20 NO: 103, or both SEQ ID NO: 102 and SEQ ID NO: 103.

The present invention further provides antigen binding fragments of these caninized antibodies.

In other embodiments, the caninized antibody comprises a light chain comprising the amino acid
25 sequence of SEQ ID NO: 97 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 94. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95. In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising the amino
30 acid sequence of SEQ ID NO: 96. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising

the amino acid sequence of SEQ ID NO: 100. In specific embodiments, when bound to canine IL-31RA, the antibody binds to an epitope comprised by the amino acid of SEQ ID NO: 102, or SEQID NO: 103, or to both SEQ ID NO: 102 and SEQID NO: 103. In related embodiments, when bound to canine IL-31RA, the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 103, or both SEQ ID NO: 102 and SEQ ID NO: 103.

In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 94. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95. In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 96. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 100. In specific embodiments, when bound to canine IL-31RA, the antibody binds to an epitope comprised by the amino acid of SEQ ID NO: 102, or SEQID NO: 103, or to both SEQ ID NO: 102 and SEQID NO: 103. In related embodiments, when bound to canine IL-31RA, the antibody binds at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 103, or both SEQ ID NO: 102 and SEQ ID NO: 103.

In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 94. In yet other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95. In still other embodiments, the caninized antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 96. In yet other embodiments, the caninized antibody comprises a

light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 100. In specific embodiments when bound to canine IL-31RA the antibody binds to at least one amino acid residue, preferably two to five amino acid residues, and/or more preferably three to eight amino acid residues or more within the amino acid
5 sequence of SEQ ID NO: 102 or SEQ ID NO: 103, or both SEQ ID NO: 102 and SEQ ID NO: 103.

The present invention further provides antigen binding fragments of all of these caninized antibodies.

10 The present invention further provides isolated mammalian antibodies or antigen binding fragments thereof (including caninized antibodies, canine antibodies, or antigen binding fragments thereof) that bind to canine interleukin-31 receptor *alpha* (canine IL-31RA) and that when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid sequence of SEQ ID NO: 101, or SEQ ID NO: 102, or SEQ ID NO: 103, or SEQ ID NO: 104, or SEQ ID NO: 105, or
15 any combination thereof, in which the antibody binds to canine IL-31RA and blocks the binding of canine IL-31RA to canine IL-31.

In certain embodiments the isolated mammalian antibodies or antigen binding fragments thereof (including caninized antibodies, canine antibodies, or antigen binding fragments thereof)
20 bind canine IL-31RA with specificity, and when bound to canine IL-31RA, the antibody binds to at least one amino acid residue, preferably one to three amino acid residues, more preferably two to five amino acid residues, and/or even more preferably three to eight amino acid residues or more amino acid residues within the amino acid sequence of SEQ ID NO: 101, or SEQ ID NO: 102, or SEQ ID NO: 103, or SEQ ID NO: 104, or SEQ ID NO: 105, or any combination thereof. In
25 particular embodiments, the antibody or antigen binding fragment thereof binds canine IL-31RA and blocks the binding of canine IL-31RA to canine IL-31.

The present invention also provides nucleic acids, including isolated nucleic acids, that encode the CDRs, the heavy chains of the caninized antibodies or antigen binding fragments thereof, and/or the
30 light chains of the caninized antibodies or antigen binding fragments thereof.

Accordingly, the present invention further provides a nucleic acid that encodes a set of the three heavy chain complementary determining regions (CDRs), a CDR heavy 1 (HCDR1), a CDR heavy 2 (HCDR2), and a CDR heavy 3 (HCDR3) of a mammalian antibody or an antigen binding fragment thereof of the present invention. In preferred embodiments a nucleic acid encodes a set of the three heavy chain complementary determining regions (CDRs), a CDR heavy 1 (HCDR1), a CDR heavy 2 (HCDR2), and a CDR heavy 3 (HCDR3) of a caninized antibody or an antigen binding fragment thereof of the present invention.

In certain embodiments of this type, the nucleic acid encodes an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 13, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 14, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 15. In another embodiment of this type, the nucleic acid encodes an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 19, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 20, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 21. In still another embodiment of this type, the nucleic acid encodes an HCDR1 that comprises the amino acid sequence of SEQ ID NO: 25, an HCDR2 that comprises the amino acid sequence of SEQ ID NO: 26, and an HCDR3 that comprises the amino acid sequence of SEQ ID NO: 27.

The present invention also provides a nucleic acid that encodes a set of the three light chain complementary determining regions (CDRs), a CDR light 1 (LCDR1), a CDR light 2 (LCDR2), and a CDR light 3 (LCDR3) of a mammalian antibody or an antigen binding fragment thereof of the present invention. In a more specific embodiment of this type, the nucleic acid encodes an LCDR1 comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 16, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 17, and a LCDR3 that comprises the amino acid sequence of SEQ ID NO: 18. In a another embodiment of this type, the nucleic acid encodes an LCDR1 comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 22, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 23, and a LCDR3 that comprises the amino acid sequence of SEQ ID NO: 24. In yet another embodiment of this type, the nucleic acid encodes an LCDR1 comprises a LCDR1 that comprises the amino acid sequence of SEQ ID NO: 28, a LCDR2 that comprises the amino acid sequence of SEQ ID NO: 29, and a LCDR3 that comprises the amino acid sequence of SEQ ID NO: 30.

The present invention further provides a nucleic acid that encodes the heavy chain of a mammalian antibody or an antigen binding fragment thereof of the present invention. The present invention also provides a nucleic acid that encodes the light chain of a mammalian antibody or an antigen binding fragment thereof of the present invention. In addition, the present invention provides expression
5 vectors that comprise one or more of the nucleic acids of the present invention, and host cells that comprise such expression vectors.

The present invention also provides pharmaceutical compositions that comprise the caninized antibodies and antigen binding fragments thereof of the present invention along with a
10 pharmaceutically acceptable carrier and/or diluent. The present invention further provides methods of treating atopic dermatitis comprising administering one of the aforesaid compositions to a canine that has atopic dermatitis. In particular embodiments, the present invention provides methods of aiding in blocking of the pruritus associated with atopic dermatitis, comprising administering to a canine in need thereof a therapeutically effective amount of a pharmaceutical composition of the
15 present invention.

These and other aspects of the present invention will be better appreciated by reference to the following Brief Description of the Drawings and the Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1. The extracellular domain (ECD) of canine IL-31RA was tested for its ability to bind to canine IL-31. The results indicate that canine IL-31RA ECD binds in a dose-dependent manner to biotinylated canine IL-31.

25 Figures 2A-2E. The selected rat mAbs to canine IL-31RA were tested for their reactivity to canine IL-31RA. The results indicate that the selected rat mAbs bind to canine IL-31RA in a dose-dependent manner. All the 14 rat monoclonal antibodies tested have strong binding reactivity to canine IL-31RA. Figure 2A: 4G7 (●), 20B8 (■), 22B4 (▲), 27A10 (▼), and the Rat IgG2a/*Kappa* (◆) control. Figure 2B: 38B6 (●), 48B1 (■), 49D3 (▲), and the Rat IgG2a/*Kappa* (◆) control.

30 Figure 2C: 10A12 (■), 44E2 (▼) and the Rat IgG2a/*Kappa* (◆) control. Figure 2D: 47F3 (●), 51G4

(■), and the Rat IgG2a/*Kappa* (▼) control. Figure 2E: 7D7(●), 28F12 (■), 53B3 (▲), and the Rat IgG2a/*Kappa* (×) and Rat IgG2b/*Kappa* (◆) controls.

Figure 3. The selected rat mAbs were tested for their ability to block the binding of canine IL-31 to canine IL-31RA by ELISA. The results indicated that some of the selected mAbs can block the binding of canine IL-31 to canine IL-31RA in a dose-dependent manner, whereas others could not: Figure 3 shows the antibodies: 4G7(●), 28F12 (▲), 44E2(▼), 48B1 (■); and the Rat IgG2a/*Kappa* (Δ) and Rat IgG2b/*Kappa* (▽) controls.

Figure 4. Ba/f3-OI cells expressing the IL-31 receptor complex were tested for IL-31-induced STAT-3 phosphorylation. The results indicate that STAT-3 phosphorylation was induced by IL-31 in the Ba/f3-OI cells (■) in a dose-dependent manner, implying that: (i) the canine IL-31 receptor complex is successfully expressed on cell surface; (ii) that the binding of canine IL-31 to the IL-31 receptor can stimulate the endogenous STAT3 phosphorylation; and (iii) then initiate its downstream signaling pathway. Ba/f3 cells (●) were used as the control.

Figures 5. Inhibition of IL-31-mediated STAT-3 phosphorylation in Ba/f3-OI cells. The results show the inhibition of IL-31-mediated STAT-3 phosphorylation by the antibodies 4G7(●) and 44E2(▲). The media with (×) or without cIL-31 (+) were used as controls.

Figures 6A-6C show the binding of caninized anti-canine IL-31RA antibodies containing either lambda (L) or kappa (k) light chains as evaluated by ELISA.

Figure 6A depicts the binding of caninized anti-canine IL-31RA antibodies (cA12) containing lambda (L) light chains as evaluated by ELISA. Chimeric rat/caninized: chimeric 10A12 [●], caninized 10A12VH1VL5 [▽], caninized 10A12VH1VL6 [■], caninized 10A12VH2VL5[▲], and caninized 10A12VH2VL6 [▼].

Figure 6B depicts the binding of caninized anti-canine IL-31RA antibodies (28F12) containing kappa (k) light chains as evaluated by ELISA. Chimeric rat/caninized: chimeric 28F12 [●], caninized 28F12VH1VK3 [■], caninized 28F12VH1VK4 [▲], caninized 28F12VH2VK2 [▼], caninized 28F12VH2VK3[▽], and caninized 28F12VH2VK4 [Δ].

Figure 6C depicts the binding of caninized anti-canine IL-31RA antibodies (44E2) containing kappa (k) light chains as evaluated by ELISA. Chimeric rat/caninized: chimeric 44E2 [●], caninized 44E2VH2VK1[■], caninized 44E2VH2VK2 [▲], caninized 44E2VH5VK1[▼], caninized 44E2VH5VK2 [▽], and caninized 44E2VH4VK1[Δ]. The results show that caninized anti-canine IL-31RA antibodies bind to canine IL-31RA.

Figure 7A-7C are graphs showing the inhibition of cIL-31-mediated STAT-3 phosphorylation by cIL-31RA antibodies. Three different caninized monoclonal anti-canine IL-31RA antibodies designated caninized 10A12, caninized c28F12, and caninized 44E2 were evaluated for their ability to inhibit STAT-3 phosphorylation.

Figure 7A depicts the inhibition of cIL-31-mediated STAT-3 phosphorylation by cIL-31RA antibodies (c10A12). Chimeric rat/caninized: chimeric 10A12 [●] and caninized 10A12VH2VL6 [■].

Figure 7B depicts the inhibition of cIL-31-mediated STAT-3 phosphorylation by cIL-31RA antibodies (c28F12). Chimeric rat/caninized: chimeric 28F12 [●], caninized 28F12VH2K2[■] and caninized 28F12VH2VK3 [▲].

Figure 7C depicts the inhibition of cIL-31-mediated STAT-3 phosphorylation by cIL-31RA antibodies (c44E2). Chimeric rat/caninized: chimeric c44E2 [●], caninized 44E2VH2VK1[■], caninized 44E2VH2VK2 [▲], and caninized 44E2VH5VK2 [▼]. The data show that all three antibodies result in a dose dependent inhibition of STAT-3 phosphorylation in the presence of IL-31.

Figures 8A-8C show the epitopes on canine IL-31RA for the antibodies 10A12, 28F12 and 44E2, respectively. Figure 8A depicts the amino acid sequences of SEQ ID NO: 104 and SEQ ID NO: 105 respectively. Figure 8B depicts the amino acid sequence of SEQ ID NO: 101. Figure 8C depicts the amino acid sequences of SEQ ID NO: 102 and SEQ ID NO: 103, respectively.

DETAILED DESCRIPTION OF THE INVENTION

In response to need for better therapies for atopic dermatitis, the present invention provides formulations and methodology that can achieve a significant effect on the skin inflammation associated with atopic dermatitis.

5

ABBREVIATIONS

Throughout the detailed description and examples of the invention the following abbreviations will be used:

	ADCC	Antibody-dependent cellular cytotoxicity
10	CDC	Complement-dependent cytotoxicity
	CDR	Complementarity determining region in the immunoglobulin variable regions, defined using the Kabat numbering system
	EC50	concentration resulting in 50% efficacy or binding
	ELISA	Enzyme-linked immunosorbant assay
15	FR	Antibody framework region: the immunoglobulin variable regions excluding the CDR regions.
	IC50	concentration resulting in 50% inhibition
	IgG	Immunoglobulin G
	Kabat	An immunoglobulin alignment and numbering system pioneered by Elvin
20		A. Kabat [<i>Sequences of Proteins of Immunological Interest</i> , 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)]
	mAb	Monoclonal antibody (also Mab or MAb)
	V region	The segment of IgG chains which is variable in sequence between different antibodies.
25	VH	Immunoglobulin heavy chain variable region
	VL	Immunoglobulin <i>lambda</i> light chain variable region
	VK	Immunoglobulin <i>kappa</i> light chain variable region

DEFINITIONS

30 So that the invention may be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other

technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

"Administration" and "treatment", as it applies to an animal, *e.g.*, a canine subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal *e.g.*, a canine subject, cell, tissue, organ, or biological fluid.

Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

"Administration" and "treatment" also mean *in vitro* and *ex vivo* treatments, *e.g.*, of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term "subject" includes any organism, preferably an animal, more preferably a mammal (*e.g.*, canine, feline, or human) and most preferably a canine.

"Treat" or "treating" means to administer a therapeutic agent, such as a composition containing any of the antibodies of the present invention, internally or externally to *e.g.*, a canine subject or patient having one or more symptoms, or being suspected of having a condition, for which the agent has therapeutic activity. Typically, the agent is administered in an amount effective to alleviate and/or ameliorate one or more disease/condition symptoms in the treated subject or population, whether by inducing the regression of or inhibiting the progression of such symptom(s) by any clinically measurable degree. The amount of a therapeutic agent that is effective to alleviate any particular disease/condition symptom (also referred to as the "therapeutically effective amount") may vary according to factors such as the disease/condition state, age, and weight of the patient (*e.g.*, canine), and the ability of the pharmaceutical composition to elicit a desired response in the subject.

Whether a disease/condition symptom has been alleviated or ameliorated can be assessed by any clinical measurement typically used by veterinarians or other skilled healthcare providers to assess the severity or progression status of that symptom. While an embodiment of the present invention (*e.g.*, a treatment method or article of manufacture) may not be effective in alleviating the target

disease/condition symptom(s) in every subject, it should alleviate the target disease/condition symptom(s) in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student's t-test, the chi²-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

5

"Treatment," as it applies to a human, veterinary (*e.g.*, canine), or research subject, refers to therapeutic treatment, as well as research and diagnostic applications. "Treatment" as it applies to a human, veterinary (*e.g.*, canine), or research subject, or cell, tissue, or organ, encompasses contact of the antibodies of the present invention to *e.g.*, a canine or other animal subject, a cell, tissue, physiological compartment, or physiological fluid.

10

As used herein, the term "canine" includes all domestic dogs, *Canis lupus familiaris* or *Canis familiaris*, unless otherwise indicated.

15

As used herein, the term "feline" refers to any member of the *Felidae* family. Members of this family include wild, zoo, and domestic members, including domestic cats, pure-bred and/or mongrel companion cats, show cats, laboratory cats, cloned cats, and wild or feral cats.

20

As used herein the term "canine frame" refers to the amino acid sequence of the heavy chain and light chain of a canine antibody other than the hypervariable region residues defined herein as CDR residues. With regard to a caninized antibody, in the majority of embodiments the amino acid sequences of the native canine CDRs are replaced with the corresponding foreign CDRs (*e.g.*, those from a mouse or rat antibody) in both chains. Optionally the heavy and/or light chains of the canine antibody may contain some foreign non-CDR residues, *e.g.*, so as to preserve the conformation of the foreign CDRs within the canine antibody, and/or to modify the Fc function, as exemplified below and/or disclosed in U.S. 10,106,607 B2, hereby incorporated by reference herein in its entirety.

25

The "Fragment crystallizable region" abbreviated as "Fc" corresponds to the CH3-CH2 portion of an antibody that interacts with cell surface receptors called Fc receptors. The canine fragment crystallizable region (cFc) of each of the four canine IgGs were first described by Tang *et al.* [*Vet.*

30

Immunol. Immunopathol. 80: 259-270 (2001); *see also*, Bergeron *et al.*, *Vet. Immunol. Immunopathol.* 157: 31-41 (2014) and U.S. 10,106,607 B2].

As used herein the canine Fc (cFc) “IgG-Bm” is canine IgG-B Fc comprising two (2) amino acid
 5 residue substitutions, D31A and N63A, as in the amino acid sequence of SEQ ID NO: 78 of IgG-B
 (see below) and without the c-terminal lysine (“K”). Both the aspartic acid residue (D) at position
 31 of SEQ ID NO: 77 and the asparagine residue (N) at position 63 of SEQ ID NO: 77, are
 substituted by an alanine residue (A) in IgG-Bm. These two amino acid residue substitutions serve
 to significantly diminish the antibody-dependent cytotoxicity (ADCC) and complement-dependent
 10 cytotoxicity (CDC) of the naturally occurring canine IgG-B [see, U.S. 10,106,607 B2, the contents
 of which are hereby incorporated by reference in their entirety]. Further amino acid substitutions to
 the IgG-Bm are also envisioned, which parallel those which can be made in IgG-B and may include
 amino acid substitutions to favor heterodimer formation in bispecific antibodies.

15 The amino acid sequence of IgG-B, SEQ ID NO: 77 is:

```

1                               50
LGGPSVFIFP PKPKDTLLIA RTPEVTCVVV DLDPEDPEVQ ISWFVDGKQM
└─ CH2
51                               100
20 QTAKTQPREE QFNGTYRVVS VLPIGHQDWL KGKQFTCKVN NKALPSPIER

101                               150
TISKARGQAH QPSVYVLPPS REELSKNTVS LTCLIKDFFP PDIDVEWQSN
└─ CH3
25 151                               200
GQQEPESKYR TTPPQLDEDG SYFLYSKLSV DKSRWQRGDT FICAVMHEAL

201                               215
30 HNHYTQKSLS HSPGK

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The amino acid sequence of IgG-Bm, SEQ ID NO: 78, is provided below.

```

LGGPSVFIFP PKPKDTLLIARTPEVTCVVVALDPEDPEVQISWFVDGKQM QTAKTQPREEQFAGTYR
VSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTISKARGQAHQPSVYVLPPSREELSKNTVSLTCL
IKDFFPPDIDVEWQSN GQQEPESKYRTTPPQLDEDG SYFLYSKLSV DKSRWQRGDT FICAVMHEALH
35 NHYTQESLSHSPG

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As used herein, a “substitution of an amino acid residue” with another amino acid residue in an
 amino acid sequence of an antibody for example, is equivalent to “replacing an amino acid residue”
 with another amino acid residue and denotes that a particular amino acid residue at a specific

position in the amino acid sequence has been replaced by (or substituted for) by a different amino acid residue. Such substitutions can be particularly designed *i.e.*, purposefully replacing an alanine with a serine at a specific position in the amino acid sequence by *e.g.*, recombinant DNA technology. Alternatively, a particular amino acid residue or string of amino acid residues of an antibody can be replaced by one or more amino acid residues through more natural selection processes *e.g.*, based on the ability of the antibody produced by a cell to bind to a given region on that antigen, *e.g.*, one containing an epitope or a portion thereof, and/or for the antibody to comprise a particular CDR that retains the same canonical structure as the CDR it is replacing. Such substitutions/replacements can lead to “variant” CDRs and/or variant antibodies.

As used herein, the term "antibody" refers to any form of antibody that exhibits the desired biological activity. An antibody can be a monomer, dimer, or larger multimer. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multi-specific antibodies (*e.g.*, bispecific antibodies), caninized antibodies, fully canine antibodies, chimeric antibodies and camelized single domain antibodies. "Parental antibodies" are antibodies obtained by exposure of an immune system to an antigen prior to modification of the antibodies for an intended use, such as caninization of an antibody for use as a canine therapeutic antibody.

As used herein, antibodies of the present invention that "block" or is “blocking” or is “blocking the binding” of *e.g.*, a canine receptor to its binding partner (ligand), is an antibody that blocks (partially or fully) the binding of the canine receptor to its canine ligand and *vice versa*, as determined in standard binding assays (*e.g.*, BIACore[®], ELISA, or flow cytometry).

Typically, an antibody or antigen binding fragment of the invention retains at least 10% of its canine antigen binding activity (when compared to the parental antibody) when that activity is expressed on a molar basis. Preferably, an antibody or antigen binding fragment of the invention retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the canine antigen binding affinity as the parental antibody. It is also intended that an antibody or antigen binding fragment of the invention can include conservative or non-conservative amino acid substitutions (referred to as "conservative

variants" or "function conserved variants" of the antibody) that do not substantially alter its biologic activity.

"Isolated antibody" refers to the purification status and in such context means the molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to a complete absence of such material or to an absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

As used herein, an antibody is said to bind specifically to a polypeptide comprising a given antigen sequence (in this case a portion of the amino acid sequence of canine IL-31RA) if it binds to polypeptides comprising the portion of the amino acid sequence of canine IL-31RA, but does not bind to other canine proteins lacking that portion of the sequence of canine IL-31RA. For example, an antibody that specifically binds to a polypeptide comprising canine IL-31RA, may bind to a FLAG[®]-tagged form of canine IL-31RA, but will not bind to other FLAG[®]-tagged canine proteins. An antibody, or binding compound derived from the antigen-binding site of an antibody, binds to its canine antigen, or a variant or mutein thereof, "with specificity" when it has an affinity for that canine antigen or a variant or mutein thereof which is at least ten-times greater, more preferably at least 20-times greater, and even more preferably at least 100-times greater than its affinity for any other canine antigen tested.

As used herein, a "chimeric antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, where the first and second antibodies are from different species. [U.S. 4,816,567; and Morrison *et al.*, *Proc. Natl. Acad. Sci. USA* 81: 6851-6855 (1984)]. Typically the variable domains are obtained from an antibody from an experimental animal (the "parental antibody"), such as a rodent, and the constant domain sequences are obtained from the animal subject antibodies, *e.g.*, human or canine so that the resulting chimeric antibody will be less likely to elicit an adverse immune response in a human or canine subject respectively, than the parental (*e.g.*, rodent) antibody.

As used herein, the term "caninized antibody" refers to forms of antibodies that contain sequences from both canine and non-canine (*e.g.*, rat) antibodies. In general, the caninized antibody will comprise substantially all of at least one or more typically, two variable domains in which all or substantially all of the hypervariable loops correspond to those of a non-canine immunoglobulin (*e.g.*, comprising 6 CDRs as exemplified below), and all or substantially all of the framework (FR) regions (and typically all or substantially all of the remaining frame) are those of a canine immunoglobulin sequence. As exemplified herein, a caninized antibody comprises both the three heavy chain CDRs and the three light chain CDRS from a rat anti-canine antigen antibody together with a canine frame or a modified canine frame. A modified canine frame comprises one or more amino acids changes as exemplified herein that further optimize the effectiveness of the caninized antibody, *e.g.*, to increase its binding to its canine antigen and/or its ability to block the binding of that canine antigen to the canine antigen's natural binding partner.

The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same. Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of *Sequences of Proteins of Immunological Interest*, Kabat, *et al.*; National Institutes of Health, Bethesda, Md. ; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat, *Adv. Prot. Chem.* 32:1-75 (1978); Kabat, *et al.*, *J. Biol. Chem.* 252:6609-6616 (1977); Chothia, *et al.*, *J. Mol. Biol.* 196:901-917 (1987) or Chothia, *et al.*, *Nature* 342:878-883 (1989)].

As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (*i.e.* LCDR1, LCDR2 and LCDR3 in the light chain variable domain and HCDR1, HCDR2 and HCDR3 in the heavy chain variable domain). [See Kabat *et al. Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991), defining the CDR regions of an antibody by

sequence; *see also* Chothia and Lesk, *J. Mol. Biol.* 196: 901-917 (1987) defining the CDR regions of an antibody by structure]. As used herein, the term "framework" or "FR" residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

5

There are four known IgG heavy chain subtypes of dog IgG and they are referred to as IgG-A, IgG-B, IgG-C, and IgG-D. The two known light chain subtypes are referred to as *lambda* and *kappa*. In specific embodiments of the invention, besides binding canine IL-31RA, a canine or caninized antibody against its antigen of the present invention optimally has two attributes:

- 10 1. Lack of effector functions such as antibody-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and
2. be readily purified on a large scale using industry standard technologies such as that based on protein A chromatography.

15 None of the naturally occurring canine IgG isotypes satisfy both criteria. For example, IgG-B can be purified using protein A, but has high level of ADCC activity. On the other hand, IgG-A binds weakly to protein A, but also displays ADCC activity. Moreover, neither IgG-C nor IgG-D can be purified on protein A columns, although IgG-D displays no ADCC activity. (IgG-C has considerable ADCC activity). One way the present invention addresses these issues is by providing

20 modified canine IgG-B antibodies of the present invention specific to an antigen of the present invention that lack the effector functions such as ADCC and can be easily purified using industry standard protein A chromatography.

As used herein an "antipruritic agent" is a compound, macromolecule, and/or formulation that tends

25 to inhibit, relieve, and/or prevent itching. Antipruritic agents are colloquially referred to as anti-itch drugs.

As used herein an "antipruritic antibody" is an antibody that can act as an antipruritic agent in an animal, including a mammal such as a human, a canine, and/or a feline, particularly with respect to

30 atopic dermatitis. In particular embodiments, the antipruritic antibody binds to specific proteins in the IL-31 signaling pathway, such as IL-31 or its receptor IL-31RA. The binding of the antipruritic

antibody to its corresponding antigen (*e.g.*, IL-31 or IL-31RA) inhibits the binding of *e.g.*, IL-31 with IL-31RA, and interferes with and/or prevents the successful signaling of this pathway, and thereby inhibits, relieves, and/or prevents the itching that is otherwise caused by the IL-31 signaling pathway.

5

"Homology", as used herein, refers to sequence similarity between two polynucleotide sequences or between two polypeptide sequences when they are optimally aligned. When a position in both of the two compared sequences is occupied by the same base or amino acid residue, *e.g.*, if a position in each of two DNA molecules is occupied by adenine, then the molecules are homologous at that position. The percent of homology is the number of homologous positions shared by the two sequences divided by the total number of positions compared $\times 100$. For example, if 6 of 10 of the positions in two sequences are matched or homologous when the sequences are optimally aligned then the two sequences are 60% homologous. Generally, the comparison is made when two sequences are aligned to give maximum percent homology. Sequence identity refers to the degree to which the amino acids of two polypeptides are the same at equivalent positions when the two sequences are optimally aligned. As used herein one amino acid sequence is 100% "identical" to a second amino acid sequence when the amino acid residues of both sequences are identical.

Accordingly, an amino acid sequence is 50% "identical" to a second amino acid sequence when 50% of the amino acid residues of the two amino acid sequences are identical. The sequence comparison is performed over a contiguous block of amino acid residues comprised by a given protein, *e.g.*, a protein, or a portion of the polypeptide being compared. In particular embodiments, selected deletions or insertions that could otherwise alter the correspondence between the two amino acid sequences are taken into account. Sequence similarity includes identical residues and nonidentical, biochemically related amino acids. Biochemically related amino acids that share similar properties and may be interchangeable.

"Conservatively modified variants" or "conservative substitution" refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (*e.g.* charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.), such that the changes can frequently be made without altering the biological activity of the protein. Those of skill in this art

recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity [see, e.g., Watson *et al.*, *Molecular Biology of the Gene*, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.; 1987)]. In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth in Table A directly below.

TABLE A
Exemplary Conservative Amino Acid Substitutions

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys; His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala; Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Function-conservative variants of the antibodies of the invention are also contemplated by the present invention. "Function-conservative variants," as used herein, refers to antibodies or fragments in which one or more amino acid residues have been changed without altering a desired property, such as an antigen affinity and/or specificity. Such variants include, but are not limited to, replacement of an amino acid with one having similar properties, such as the conservative amino acid substitutions of Table A above.

"Isolated nucleic acid molecule" means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it should be understood that "a nucleic acid molecule comprising" a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules "comprising" specified nucleic acid sequences may include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty or more other proteins or portions or fragments thereof, or may include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or may include vector sequences.

The present invention provides isolated caninized antibodies of the present invention, methods of use of the antibodies in the treatment of a condition *e.g.*, the treatment of atopic dermatitis in canines. In canine, there are four IgG heavy chains referred to as A, B, C, and D. These heavy chains represent four different subclasses of dog IgG, which are referred to as IgG-A (or IgGA), IgG-B (or IgGB), IgG-C (or IgGC) and IgG-D (or IgGD). Each of the two heavy chains consists of one variable domain (VH) and three constant domains referred to as CH-1, CH-2, and CH-3. The CH-1 domain is connected to the CH-2 domain *via* an amino acid sequence referred to as the "hinge" or alternatively as the "hinge region".

The nucleic acid and amino acid sequences of these four heavy chains were first identified by Tang *et al.* [*Vet. Immunol. Immunopathol.* 80: 259-270 (2001)]. The amino acid and nucleic sequences for these heavy chains are also available from the GenBank data bases. For example, the amino acid sequence of IgGA heavy chain has accession number AAL35301.1, IgGB has accession number

AAL35302.1, IgGC has accession number AAL35303.1, and IgGD has accession number (AAL35304.1). Canine antibodies also contain two types of light chains, *kappa* and *lambda*. The DNA and amino acid sequence of these light chains can be obtained from GenBank Databases. For example, the *kappa* light chain amino acid sequence has accession number ABY 57289.1 and the
5 *lambda* light chain has accession number ABY 55569.1.

In the present invention, the amino acid sequence for each of the four canine IgG Fc fragments is based on the identified boundary of CH1 and CH2 domains as determined by Tang *et al, supra*.

Caninized rat anti-canine antibodies that bind canine IL-31RA include, but are not limited to:

10 antibodies of the present invention that comprise canine IgG-A, IgG-B, IgG-C, and IgG-D heavy chains and/or canine *kappa* or *lambda* light chains together with rat anti-canine IL-31RA CDRs.

Accordingly, the present invention provides caninized rat anti-canine antibodies of the present invention, including isolated caninized rat anti-canine antibodies, that bind to canine IL-31RA and that preferably also block the binding of that canine IL-31RA to canine IL-31.

15 Accordingly, the present invention further provides caninized rat antibodies and methods of use of the antibodies of the present invention in the treatment of a condition *e.g.*, the treatment of atopic dermatitis in canines.

20 The present invention further provides full length canine heavy chains that can be matched with corresponding light chains to make a caninized antibody. Accordingly, the present invention further provides caninized rat anti-canine antigen antibodies (including isolated caninized rat anti-canine antibodies) of the present invention and methods of use of the antibodies of the present invention in the treatment of a condition *e.g.*, the treatment of atopic dermatitis in canines.

25 The present invention also provides antibodies of the present invention that comprise a canine fragment crystallizable region (cFc region) in which the cFc has been genetically modified to augment, decrease, or eliminate one or more effector functions. In one aspect of the present invention, the genetically modified cFc decreases or eliminates one or more effector functions. In
30 another aspect of the invention the genetically modified cFc augments one or more effector function. In certain embodiments, the genetically modified cFc region is a genetically modified canine IgGB

Fc region. In another such embodiment, the genetically modified cFc region is a genetically modified canine IgGC Fc region. In a particular embodiment the effector function is antibody-dependent cytotoxicity (ADCC) that is augmented, decreased, or eliminated. In another embodiment the effector function is complement-dependent cytotoxicity (CDC) that is augmented, decreased, or eliminated. In yet another embodiment, the cFc region has been genetically modified to augment, decrease, or eliminate both the ADCC and the CDC.

In order to generate variants of canine IgG that lack effector functions, a number of mutant canine IgGB heavy chains were generated. These variants may include one or more of the following single or combined substitutions in the Fc portion of the heavy chain amino acid sequence: P4A, D31A, N63A, G64P, T65A, A93G, and P95A. Variant heavy chains (*i.e.*, containing such amino acid substitutions) are cloned into expression plasmids and are transfected into HEK 293 cells along with a plasmid containing the gene encoding a light chain. Intact antibodies are expressed and purified from HEK 293 cells and then can be evaluated for binding to Fc γ RI and C1q to assess their potential for mediation of immune effector functions. [See, U.S. 10,106,607 B2, the contents of which are hereby incorporated by reference in its entirety.]

The present invention also provides modified canine IgG-Ds which in place of its natural IgG-D hinge region they comprise a hinge region from:

IgG-A:	FNECRCTDTPPCPVPEP	SEQ ID NO: 79
IgG-B:	PKRENGRVPRPPDCPKCPAPEM	SEQ ID NO: 80; or
IgG-C:	AKECECKCNCNNCPGCGGL	SEQ ID NO: 81.

Alternatively, the IgG-D hinge region can be genetically modified by replacing a serine residue with a proline residue, *i.e.*, PKESTCKC**I**PPCPVPES, SEQ ID NO: 82 (with the proline residue (P) underlined and in bold substituting for the naturally occurring serine residue). Such modifications can lead to a canine IgG-D lacking fab arm exchange. The modified canine IgG-Ds can be constructed using standard methods of recombinant DNA technology [*e.g.*, Maniatis *et al.*, *Molecular Cloning, A Laboratory Manual* (1982)]. In order to construct these variants, the nucleic acids encoding the amino acid sequence of canine IgG-D can be modified so that it encodes the

modified IgG-Ds. The modified nucleic acid sequences are then cloned into expression plasmids for protein expression.

The six complementary determining regions (CDRs) of a caninized rat anti-canine antibody, as described herein can comprises a canine antibody *kappa* (*k*) or *lambda* (*l*) light chain comprising a rat light chain LCDR1, LCDR2, and LCDR3 and a canine antibody heavy chain IgG comprising a rat heavy chain HCDR1, HCDR2, and HCDR3.

Nucleic Acids

The present invention further comprises the nucleic acids encoding the antibodies of the present invention (*see e.g.*, Examples below).

Also included in the present invention are nucleic acids that encode immunoglobulin polypeptides comprising amino acid sequences that are at least about 70% identical, preferably at least about 80% identical, more preferably at least about 90% identical and most preferably at least about 95% identical (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to the amino acid sequences of the caninized antibodies, with the exception of the CDRs which do not change, provided herein when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. The present invention further provides nucleic acids that encode immunoglobulin polypeptides comprising amino acid sequences that are at least about 70% similar, preferably at least about 80% similar, more preferably at least about 90% similar and most preferably at least about 95% similar (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to any of the reference amino acid sequences when the comparison is performed with a BLAST algorithm, wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences, are also included in the present invention.

As used herein, nucleotide and amino acid sequence percent identity can be determined using C, MacVector (MacVector, Inc. Cary, NC 27519), Vector NTI (Informax, Inc. MD), Oxford Molecular Group PLC (1996) and the Clustal W algorithm with the alignment default parameters, and default

parameters for identity. These commercially available programs can also be used to determine sequence similarity using the same or analogous default parameters. Alternatively, an Advanced Blast search under the default filter conditions can be used, *e.g.*, using the GCG (Genetics Computer Group, Program Manual for the GCG Package, Version 7, Madison, Wisconsin) pileup program
 5 using the default parameters.

The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., *et al.*, *J. Mol. Biol.* 215:403-410 (1990); Gish, W., *et al.*, *Nature Genet.* 3:266-272 (1993); Madden, T.L., *et al.*, *Meth. Enzymol.* 266:131-141(1996); Altschul, S.F.,
 10 *et al.*, *Nucleic Acids Res.* 25:3389-3402 (1997); Zhang, J., *et al.*, *Genome Res.* 7:649-656 (1997); Wootton, J.C., *et al.*, *Comput. Chem.* 17:149-163 (1993); Hancock, J.M. *et al.*, *Comput. Appl. Biosci.* 10:67-70 (1994); ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in *Atlas of Protein Sequence and Structure*, vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, (1978); *Natl. Biomed. Res. Found.*, Washington, DC; Schwartz, R.M., *et al.*,
 15 *"Matrices for detecting distant relationships."* in *Atlas of Protein Sequence and Structure*, vol. 5, suppl. 3." (1978), M.O. Dayhoff (ed.), pp. 353-358 (1978), *Natl. Biomed. Res. Found.*, Washington, DC; Altschul, S.F., *J. Mol. Biol.* 219:555-565 (1991); States, D.J., *et al.*, *Methods* 3:66-70(1991); Henikoff, S., *et al.*, *Proc. Natl. Acad. Sci. USA* 89:10915-10919 (1992); Altschul, S.F., *et al.*, *J. Mol. Evol.* 36:290-300 (1993); ALIGNMENT STATISTICS: Karlin, S., *et al.*, *Proc. Natl. Acad. Sci. USA* 87:2264-2268 (1990); Karlin, S., *et al.*, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993); Dembo, A., *et al.*, *Ann. Prob.* 22:2022-2039 (1994); and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in *Theoretical and Computational Methods in Genome Research* (S. Suhai, ed.), pp. 1-14, Plenum, New York (1997).

25 *Antibody Protein Engineering*

By way of example, and not limitation, the canine heavy chain constant region can be from IgG-B or a modified cFc, such as the IgG-Bm used herein [*see*, U.S. 10,106,607 B2, hereby incorporated by reference in its entirety] and the canine light chain constant region can be from *kappa* or *lambda*.

The antibodies can be engineered to include modifications to the canine framework and/or the canine frame residues within the variable domains of a parental (*i.e.*, rat) monoclonal antibody, *e.g.* to improve the properties of the antibody.

- 5 The construction of caninized anti-canine IL-31 receptor *alpha* monoclonal antibodies can be performed by determining a DNA sequence that encodes the heavy and light chains of canine IgG were determined. The DNA and protein sequence of the canine heavy and light chains are known in the art and can be obtained by searching of the NCBI gene and protein databases. As indicated above, for canine antibodies there are four known IgG subtypes: IgG-A, IgG-B, IgG-C, and IgG-D,
10 and two types of light chains, *i.e.*, *kappa* and *lambda*.

A caninized rat anti-canine IL-31 antibody can be produced recombinantly by methods that are known in the field. Mammalian cell lines available as hosts for expression of the antibodies or fragments disclosed herein are well known in the art and include many immortalized cell lines
15 available from the American Type Culture Collection (ATCC). These include, *inter alia*, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are
20 selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. When recombinant expression vectors encoding the heavy chain or antigen-binding portion or fragment thereof, the light chain and/or antigen-binding fragment thereof are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time
25 sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown.

Antibodies can be recovered from the culture medium using standard protein purification methods. Further, expression of antibodies of the invention (or other moieties therefrom) from production cell
30 lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under

certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0 216 846, 0 256 055, and 0 323 997 and European Patent Application No. 89303964.4.

5 In certain embodiments, the antibody or antigen binding fragment comprises a heavy chain constant region, *e.g.*, a canine constant region, such as IgG-A, IgG-B, IgG-C and IgG-D canine heavy chain constant region or a variant thereof. In certain embodiments, the antibody or antigen binding fragment comprises a light chain constant region, *e.g.*, a canine light chain constant region, such as *lambda* or *kappa* canine light chain region or variant thereof. By way of example, and not
10 limitation, the canine heavy chain constant region can be from IgG-B and the canine light chain constant region can be from *kappa*.

Epitope Mapping

The interaction of antibodies with their cognate protein antigens is mediated through the binding of specific amino acids of the antibodies (paratopes) with specific amino acids (epitopes) of target
15 antigens. An epitope is an antigenic determinant that causes a specific reaction by an immunoglobulin. An epitope consists of a group of amino acids on the surface of the antigen. A protein of interest may contain several epitopes that are recognized by different antibodies. The epitopes recognized by antibodies are classified as linear or conformational epitopes. Linear epitopes are formed by a stretch of a continuous sequence of amino acids in a protein, while
20 conformational epitopes are composed of amino acids that are discontinuous (*e.g.*, far apart) in the primary amino acid sequence, but are brought together upon three-dimensional protein folding.

Epitope mapping refers to the process of identifying the amino acid sequences (*i.e.*, epitopes) that are recognized by antibodies on their target antigens. Identification of epitopes recognized by monoclonal antibodies (mAbs) on target antigens has important applications. For example, it can
25 aid in the development of new therapeutics, diagnostics, and vaccines. Epitope mapping can also aid in the selection of optimized therapeutic mAbs and help elucidate their mechanisms of action. Epitope information on IL-31 receptor *alpha* can also elucidate unique epitopes and define the protective or pathogenic effects of vaccines. Epitope identification also can lead to development of subunit vaccines based on chemical or genetic coupling of the identified peptide epitope to a carrier
30 protein or other immunostimulating agents.

Epitope mapping can be carried out using polyclonal or monoclonal antibodies and several methods are employed for epitope identification depending on the suspected nature of the epitope (*i.e.*, linear *versus* conformational). Mapping linear epitopes is more straightforward and relatively, easier to perform. For this purpose, commercial services for linear epitope mapping often employ peptide scanning. In this case, an overlapping set of short peptide sequences of the target protein are chemically synthesized and tested for their ability to bind antibodies of interest. The strategy is rapid, high-throughput, and relatively inexpensive to perform. On the other hand, mapping of a discontinuous epitope is more technically challenging and requires more specialized techniques such as x-ray co-crystallography of a monoclonal antibody together with its target protein, Hydrogen-Deuterium (H/D) exchange, Mass Spectrometry coupled with enzymatic digestion as well as several other methods known to those skilled in the art.

Epitope Binding and Cross-Blocking Antibodies

An anti-canine IL-31RA antibody or antigen-binding fragment thereof of the present invention includes any antibody or antigen-binding fragment thereof that binds to the same epitope in canine IL-31RA as the one of the antibodies, disclosed herein, bind, *e.g.*, as the 28F12 antibody which binds to the epitope comprising the amino acid sequence of SEQ ID NO: 101, including caninized antibodies, and any antibody or antigen-binding fragment that cross-blocks (partially or fully) or is cross-blocked (partially or fully) by an antibody or fragment discussed herein for canine IL-31RA binding; as well as any variant thereof.

The cross-blocking antibodies and antigen-binding fragments can be identified based on their ability to cross-compete with *e.g.*, the 28F12 antibody in standard binding assays (*e.g.*, BIAcore[®], ELISA, as exemplified below, or flow cytometry). For example, standard ELISA assays can be used in which a recombinant canine IL-31RA protein is immobilized on the plate, one of the antibodies is fluorescently labeled and the ability of non-labeled antibodies to compete off the binding of the labeled antibody is evaluated. Additionally or alternatively, BIAcore[®] analysis can be used to assess the ability of the antibodies to cross-compete. The ability of a test antibody to inhibit the binding of the 28F12 antibody, to canine IL-31RA demonstrates that the test antibody can compete with the

28F12 antibody for binding to canine IL-31RA and thus, may, in some cases, bind to the same epitope on canine IL-31RA as the 28F12 antibody binds. Antibodies and fragments thereof that bind to the same epitope as any of the anti-canine IL-31RA antibodies or fragments of the present invention also form part of the present

5

Pharmaceutical Compositions and Administration

To prepare pharmaceutical or sterile compositions comprising the antibodies of the present invention, these antibodies can be admixed with a pharmaceutically acceptable carrier or excipient. [See, e.g., *Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary*,
10 Mack Publishing Company, Easton, PA (1984)].

Formulations of therapeutic and diagnostic agents may be prepared by mixing with acceptable carriers, excipients, or stabilizers in the form of, e.g., lyophilized powders, slurries, aqueous solutions or suspensions [see, e.g., Hardman, *et al.* (2001) *Goodman and Gilman's The*
15 *Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams, and Wilkins, New York, NY; Avis, *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems*, Marcel Dekker,
20 NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety*, Marcel Dekker, Inc., New York, NY]. In one embodiment, the antibodies of the present invention are diluted to an appropriate concentration in a sodium acetate solution pH 5-6, and NaCl or sucrose is added for tonicity. Additional agents, such as polysorbate 20 or polysorbate 80, may be added to enhance stability.

25 Toxicity and therapeutic efficacy of the antibody compositions, administered alone or in combination with another agent, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD₅₀/ ED₅₀). In particular
30 aspects, antibodies exhibiting high therapeutic indices are desirable. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in

canines. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

- 5 The mode of administration can vary. Suitable routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal, or intra-arterial. In particular embodiments, the antibodies of the present invention can be administered by an invasive route such as by injection. In
10 further embodiments of the invention, the antibodies of the present invention, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially, or by inhalation, aerosol delivery. Administration by non-invasive routes (*e.g.*, orally; for example, in a pill, capsule or tablet) is also within the scope of the present invention.
- 15 Compositions can be administered with medical devices known in the art. For example, a pharmaceutical composition of the invention can be administered by injection with a hypodermic needle, including, *e.g.*, a prefilled syringe or autoinjector. The pharmaceutical compositions disclosed herein may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos.: 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335;
20 5,064,413; 4,941,880; 4,790,824 or 4,596,556.

- The pharmaceutical compositions disclosed herein may also be administered by infusion. Examples of well-known implants and modules for administering pharmaceutical compositions include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing
25 medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those
30 skilled in the art.

Alternatively, one may administer the antibodies of the present invention in a local rather than systemic manner, often in a depot or sustained release formulation.

5 The administration regimen depends on several factors, including the serum or tissue turnover rate of the therapeutic antibodies, the level of symptoms, the immunogenicity of the therapeutic antibodies and the accessibility of the target cells in the biological matrix. Preferably, the administration regimen delivers sufficient therapeutic antibodies to effect improvement in the target disease/condition state, while simultaneously minimizing undesired side effects. Accordingly, the amount of biologic delivered depends in part on the particular therapeutic antibodies and the severity of the condition being treated. Guidance in selecting appropriate doses of therapeutic antibodies is available [see, e.g., Wawrzynczak *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK (1996); Kresina (ed.) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY (1991); Bach (ed.) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY (1993); Baert, *et al. New Engl. J. Med.* 348:601-608 (2003); Milgrom *et al. New Engl. J. Med.* 341:1966-1973 (1999); Slamon *et al. New Engl. J. Med.* 344:783-792 (2001); Beniaminovitz *et al. New Engl. J. Med.* 342:613-619 (2000); Ghosh *et al. New Engl. J. Med.* 348:24-32 (2003); Lipsky *et al. New Engl. J. Med.* 343:1594-1602 (2000)].

20 Determination of the appropriate dose is made by the veterinarian, e.g., using parameters or factors known or suspected in the art to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of the symptoms.

25 Antibodies provided herein may be provided by continuous infusion, or by doses administered, e.g., daily, 1-7 times per week, weekly, bi-weekly, monthly, bimonthly, quarterly, semiannually, annually etc. Doses may be provided, e.g., intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, intraspinally, or by inhalation. A total weekly dose is generally at least 0.05 µg/kg body weight, more generally at least 0.2 µg/kg, 0.5 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 0.25 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 5.0 mg/ml, 10 mg/kg, 25 mg/kg, 50 mg/kg or more [see,

e.g., Yang, *et al.* *New Engl. J. Med.* 349:427-434 (2003); Herold, *et al.* *New Engl. J. Med.* 346:1692-1698 (2002); Liu, *et al.* *J. Neurol. Neurosurg. Psych.* 67:451-456 (1999); Portielji, *et al.* *Cancer Immunol. Immunother.* 52:133-144 (2003)]. Doses may also be provided to achieve a pre-determined target concentration of antibodies of the present invention in the canine's serum, such as
5 0.1, 0.3, 1, 3, 10, 30, 100, 300 µg/ml or more. In other embodiments, antibodies of the present invention is administered subcutaneously or intravenously, on a weekly, biweekly, "every 4 weeks," monthly, bimonthly, or quarterly basis at 10, 20, 50, 80, 100, 200, 500, 1000 or 2500 mg/subject.

As used herein, "inhibit" or "treat" or "treatment" includes a postponement of development of the
10 symptoms associated with a disorder and/or a reduction in the severity of the symptoms of such disorder. The terms further include ameliorating existing uncontrolled or unwanted symptoms, preventing additional symptoms, and ameliorating or preventing the underlying causes of such symptoms. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject (*e.g.*, a canine) with a disorder, condition and/or symptom, or with the potential to develop such a
15 disorder, disease or symptom.

As used herein, the terms "therapeutically effective amount", "therapeutically effective dose" and "effective amount" refer to an amount of antibodies of the present invention that, when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, *e.g.*, canine,
20 is effective to cause a measurable improvement in one or more symptoms of a disease or condition or the progression of such disease or condition. A therapeutically effective dose further refers to that amount of the antibodies sufficient to result in at least partial amelioration of symptoms, *e.g.*, treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to a
25 combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. An effective amount of a therapeutic will result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least about 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in
30 an improvement in a subjective measure in cases where subjective measures are used to assess severity of the condition.

EXAMPLES**EXAMPLE 1****IL-31 RECEPTOR *alpha****Nucleotide Sequence*

5 The nucleotide sequence of SEQ ID NO: 1 encodes the extracellular domain of the canine IL-31 receptor *alpha* (cIL-31RA) fused to a HIS tag. Canine IL-31RA ECD HIS-tagged protein comprises the amino acid sequence of SEQ ID NO: 2. The nucleotide sequence was prepared by chemical synthesis and then cloned into expression plasmids that are suitable for production of the corresponding proteins in eukaryotic cells, either HEK-293 or CHO cells.

10

Canine IL-31RA ECD-10His: [SEQ ID NO: 1]

gtgctgccccgccaagccccgagaacatcagctgcatcttctactacgaggagaacttcacctgcacctggagcc
 ccgagaaggaggccagctacacctggtacaaggtgaagagaacctacagctacggctacaagagcgacatctg
 cagcaccgacaacagcaccagaggcaaccacgccagctgcagcttctgccccccaccatcaccaacccccgac
 15 aactacaccatccaggtggaggcccagaacgccgacggcatcatgaagagcgacatcacctactggaacctgg
 acgccatcatgaagatcgagccccccgagatcttcagcgtgaagagcgtgctgggcatcaagagaatgctgca
 gatcaagtggatcagacccgtgctggccccccacagcagcaccctgaagtacaccctgagattcagaacctc
 aacagcgcctactggatggaggtgaacttcaccaaggaggacatcgacagagacgagacctacaacctgaccg
 agctgcaggccttcaccgagtacgtgatgaccctgagatgcgccccccgagagcatgttctggagcggctg
 20 gagccaggagaaggtgggcaccaccgaggaggagggccccctacggcctggacctgtggagagtgtggaagccc
 gccatggtggacggcagaagacctgtgcagctgatgtggaagaaggccaccggcgcccccgctgctggagaagg
 ccctgggctacaacatctggtacttccccgagaacaacaccaacctgaccgagaccgtgaacaccaccaacca
 gaccacgagctgtacctgggcggaagacctactgggtgtacgtggtgagctacaacagcctgggcgagagc
 cccgtggccaccctgagaatccccgccctgaacgagaagaccttccagtgcacgaggccatgcaggcctgcc
 25 tgaccacaggaccagctggtggtggagtggcagagcagcgcccccgaggtggacacctggatggtggagtgggtt
 ccccgacgtggacagcgagcccagcagcttcagctgggagagcgtgagccaggccagaaactggaccatccag
 aaggacgagctgaagccccctgtggtgctacaacatcagcgtgtacccccgtgctgagagacagagtgggccagc
 cctacagcaccacaggcctacgtgcaggagggcatccccagcgcggcccccgctgaccacaggccgacagcatcgg
 cgtgaagaccgtgaccatcacctggaaggagatccccaagagcaagagaaacggcttcatcaagaactacacc
 30 atcttctaccaggccgaggacggcaaggagttcagcaagaccgtgaacagcaacatcctgcagtacagactgg
 agagcctgaccagaagaaccagctacagcctgcaggtgatggccagcaccaacgccggcgccaccaacggcac
 caagatcaacttcaagacctgagcatcagccaccaccaccaccaccaccaccaccaccac

EXAMPLE 2

35 **EXPRESSION AND PURIFICATION OF IL-31 RECEPTOR *alpha* ECD**

Plasmids comprising the nucleotide sequence of SEQ ID NO: 1 were transfected into HEK-293 or CHO cells using electroporation *via* the MaxCyte instrument as per the manufacturer's recommendation. Several days following transfection, the supernatants of transfected cells and untransfected controls were harvested and spun down to remove cellular debris. IL-31RA with the HIS tag was purified from cell culture fluids by passing the clarified harvested fluid from transfected cells over nickel columns as per the manufacturer's recommendation. Purified proteins were quantified by measuring their absorbance of ultraviolet light at 280 nm.

Canine IL-31RA ECD-10His: [SEQ ID NO: 2]

VLP A K P E N I S C I F Y Y E E N F T C T W S P E K E A S Y T W Y K V K R T Y S Y G Y K S D I C S T D N S T R G N H A S C S F L P P
 10 T I T N P D N Y T I Q V E A Q N A D G I M K S D I T Y W N L D A I M K I E P P E I F S V K S V L G I K R M L Q I K W I R P V L A P H S
 S T L K Y T L R F R T I N S A Y W M E V N F T K E D I D R D E T Y N L T E L Q A F T E Y V M T L R C A P A E S M F W S G W S Q E K V G
 T T E E E A P Y G L D L W R V L K P A M V D G R R P V Q L M W K K A T G A P V L E K A L G Y N I W Y F P E N N T N L T E T V N T T N Q
 T H E L Y L G G K T Y W V Y V V S Y N S L G E S P V A T L R I P A L N E K T F Q C I E A M Q A C L T Q D Q L V V E W Q S S A P E V D T
 W M V E W F P D V D S E P S S F S W E S V S Q A R N W T I Q K D E L K P L W C Y N I S V Y P V L R D R V G Q P Y S T Q A Y V Q E G I P
 15 S A G P V T Q A D S I G V K T V T I T W K E I P K S K R N G F I K N Y T I F Y Q A E D G K E F S K T V N S N I L Q Y R L E S L T R R T
 S Y S L Q V M A S T N A G G T N G T K I N F K T L S I S H H H H H H H H H H

EXAMPLE 3

BINDING OF CANINE IL-31RA TO BIOTINYLATED CANINE IL-31

20 Protocol

1. Coat immunoplate(s) with IL-31RA proteins by diluting to 1 µg/mL in phosphate-buffered saline solution (PBS). Add 100 µL/well. Incubate the plate(s) at 2-7° overnight.
2. Wash the plates 3 times with 275 µL/well of phosphate-buffered saline solution plus TWEEN 20 (PBST).
- 25 3. Block the plates with 200 µL/well of blocking buffer [1% nonfat dried milk (NFDM) in PBST] for 30-45 minutes at 36 ± 2°C with gentle shaking (120 ± 20 RPM).
4. Wash the plates 3 times with 275 µL/well of PBST.
5. 3-fold dilute biotinylated IL-31 (at 10 µg/mL) in 1% NFDM in PBST on a dilution plate, and transfer 100 µL/well to the immunoplate(s). Incubate for 30-45 minutes at 36 ± 2°C with gentle shaking (120 ± 20 RPM).
- 30 6. Wash the plates 3 times with 275 µL/well of PBST.

7. Dilute horse raddish peroxidase-Streptavidin (HRP-Streptavidin) to a final dilution of 1:1000 in 1% NFDM in PBST.
8. Add 100 μ L/well of HRP-Streptavidin to the immunoplate(s) and incubate for 30-45 minutes at $36 \pm 2^\circ\text{C}$ with gentle shaking (120 ± 20 RPM).
- 5 9. Wash the plates 3 times with 275 μ L/well of PBST.
10. Combine equal volumes of pre-warmed TMP 2-Component substrate immediately before use.
11. Add 100 μ L/well of prepared 3,3',5,5'-tetramethylbenzidine (TMP) substrate to the immunoplate(s) and incubate in the dark for 10 to 15 minutes at $36 \pm 2^\circ\text{C}$ with gentle shaking (120 ± 20 RPM).
- 10 12. Stop the reaction by addition of 100 μ L/well of 1 M H_3PO_4 .
13. Read the plates using a microplate reader at a wavelength of 450 nm with a reference wavelength of 540 nm.

EXAMPLE 4

15 MONOCLONAL ANTIBODIES AGAINST CANINE IL-31 RECEPTOR *alpha*

Monoclonal antibodies (mAbs) against canine IL-31RA were produced by the immunization of two Lewis rats multiple times with canine IL-31RA ECD (using 10 μ g or 25 μ g of antigen/rat each time) over a 3 to 4 week period. Following immunization, sera was collected from each rat and tested against canine IL-31RA by ELISA. The lymph node cells of the rat with the highest IL-31RA ECD reactivity were fused with the myeloma SP2/0 cell line to produce hybridomas. Approximately 10 days after the fusion, supernatants from growing hybridomas were screened on IL-31RA ECD protein coated plates by ELISA using the protocol described below. There were approximately 260 clones selected that showed potential binding to IL-31RA in this ELISA, as exemplified in Figures 2A-2E below with the rat IgG2a/*Kappa* used as the negative control. The majority of clones had an OD₄₅₀ > 1.

The procedure for the ELISA:

1. Coat 96-well half area plates with IL-31RA (1 μ g/mL in PBS buffer), 25 μ L/well.
2. Incubate the plates at 4°C overnight.
- 30 3. Wash the plates 3 times with PBST (PBS +0.05% Tween 20)

4. Block the plates with blocking buffer (PBS with 5% fetal bovine serum (FBS)], 25ul/well for 30 minutes at room temperature.
5. Transfer 25 ul/well hybridoma supernatant to the 96-well plates, incubate 60 minutes at room temperature.
- 5 6. Wash the plates 3 times with PBST.
7. Add 25ul/well anti-rat HRP, 1:4000 dilution in blocking buffer, to the plates and incubate 60 minutes at room temperature.
8. Wash the plates 5 times by PBST.
9. Add TMB based reagent to the plates for colorimetric reaction for 2-3 minutes.
- 10 10. Stop the reactions with 0.16M sulfuric acid.
11. Read the plates by plate reader.

Fourteen rat antibodies raised against canine IL-31RA that bind IL-31 were selected. The heavy and light chain variable regions of the rat antibodies are provided below. These antibodies were further tested in Example 5 below for their ability to block the binding of canine IL-31RA to canine IL-31.

15 49D3VH [SEQ ID NO: 49]
EVQLVESGGGLVQPGRSMKLSCAASGFTFSNYMAWVRQAPTKGLEWVASISTGGGNTYYRDSVKGR
FTISRDNASTLYLQMDSLRSEDTATYYCARHGTLYFDYWGQGVMVTVSS

20 49D3VL [SEQ ID NO: 50]
QFTLTQPKSVSGSLRSTITIPCERSSGDIGDSYVSWYQQHLGRPPINVIYADDQRPSEVSDRFSGSI
DSSSNSASLTITNLQMDDEADYFCQSYDSNIDGPVFGGGTKLTVL

25 10A12VH [SEQ ID NO: 51]
EVQLVESGGGLVKPGRSMKLSCAASGFTFSNYMAWVRQAPTKGLEWVASISTGGGNTYYRDSVKGR
FTISRDNAKRTLTLQMDSLRSEDTATYYCGRHGTLYFDYWGQGVMVTVSS

30 10A12VL [SEQ ID NO: 52]
QFTLTQPKSVSGSLRSTITIPCERSSGDIGDSYVSWYQQHLGRPPINVIYVDDQRPSEVSDRFSGSI
DSSSNSASLTITDLQMDDEADYFCQSYDSNIDGPVFGGGTKLTVL

47F3VH [SEQ ID NO: 53]
EVQLVESGGGLVQPGRSMKLSCVASGFTFSNYMAWVRQAPTKGLEWVASISTGGGNTYYRDSVKGR
FTISRDNASTLYLQMDSLRSEDTATYYCARHGTLYFDYWGQGVMVTVS

35 47F3VL [SEQ ID NO: 54]

QFTLTQPKSVSGSLRSTITIPCERSSGDIGNTYVSWYQQHLGRPPINVIYADDQRPSEVSDRFSGSI
DSSSNSASLTITNLQMDDEADYFCQSYDSNIDGPVFGGGTKLTVL

5 51G4VH [SEQ ID NO: 55]

EVQLVESGGGLVQPGRSMKLSCAALGFTFSNYYMAWVRQAPTKGLEWVASISTGGGNTYYRDSVKGR
FTISRDNKNTLYLQMDSLRSEDATATYYCARHGTIAAMDYWGQGVMVTVSS

51G4VL [SEQ ID NO: 56]

10 QFTLTQPKSVSGSLRSTITIPCERNNGDIGDSYVSWYQQHLGRPPIIVIIYADDQRPSEVSDRFSGSI
DSSSNSASLTITNLQMDDEADYFCQSYDSNIDGPVFGGGTKLTVL

53B3VH [SEQ ID NO: 57]

15 EVQLVESGGGLVQPGRSMKLSCAAFGFTFNNYYMAWVRQAPTKGLEWVASISTGGGNTFYRDSVKGR
FTISRDNVKSILSLQMDSLRSEDATATYYCARHGTIAAMDYWGQGVMVTVSS

53B3VL [SEQ ID NO: 58]

20 QFTLTQPKSVSGSLRSTITIPCERTSGDIGDNYVSWYQQHLGRPPINVIYADDQRPSEVSDRFSGSI
DSSSNSASLTITNLQMDDEADYFCQSYDSNIDGPVFGGGTKLTVL

27A10VH [SEQ ID NO: 59]

EVQLVESGGGLVQPGRSMKLSCTASGFTFSNYYMAWVRQAPTKGLEWVASISTGGGNTYYRDSVKGR
FTISRDNKSTLYLQMDSLRAEDATATYYCARHTMGYFDYWGQGVMVTVSS

25 27A10VL [SEQ ID NO: 60]

QFTLTQPKSVSGSLRSTITIPCERSSGDIGDNYVSWYQQHLGRPPINVIYADDQRPSEVSDRFSGSI
DSSSNSASLTITNLQMDDEADYFCQSYDGKIEIPVFGGGTKLTVL

44E2VH [SEQ ID NO: 61]

30 QVQLKESGPGGLVQPSQTLSTCTVSGFSLTSNGVSWVRQPPGKGLEWIAAIISSGGSTYYNSVLKSRL
SISRDTSKSQVFLKMNSLQTEDTAIYFCTRRLSGYNYVPFAYWGQGTLLTVSS

44E2VK [SEQ ID NO: 62]

35 DIQMTQSPSLLSASVGDRTVLNCKASQNIYKHLAWCQQKLGEPPNLLISNANSLQTGIPSRFSGSGS
GTDFTLTISLQPEDVATYFCQQYYSGDTFGAGTKLELK

4G7VH [SEQ ID NO: 63]

40 EVQLQQYGAELGKPGTSVKLSCKVSGYNIRSTFMHWVNQRPGKGLEWIGRIDPVNGNTIYSEKFKSK
ATLTADTSSNTAYMQLSQLKSDDTAIYFCAMFNYAGHSGDYWGQGVMVTVSS

4G7VK [SEQ ID NO: 64]

DIQMTQSPSSMSVSLGDTVITICRASQDVGIYVNWFFQQPGKSPRRMIYRATNLADGVPSRFSGSRS
GSDYSLTISSELESEDVADYHCLQYDEYPYTFGAGTKLELK

28F12VH [SEQ ID NO: 65]

5 EVQLVESDGGGLAQPGRSLKLSCAASGFTFSDYYMAWVRQAPTKGLEWVATISYDGSSTYYRDSVRGR
FTISRDNAAKSTLYLQMDSLRS EDTATYYCARGPLTDWAPNWFAYWGQGTLVTVSS

28F12VK [SEQ ID NO: 66]

10 DIQMTQSPASLSASLGETVTIQCQTSEDIYSGLAWYQQKPGKSPQFLIYGASRLEDGVPSRFSGSGS
GTQYSLKISSMQTEDEGVYFCQQGLKYPNTFGAGTKLELK

38A6VH [SEQ ID NO: 67]

15 EVQLVESGGGLVQPGRSLKLSCVASGFTFN NYWMTWIRQAPGKGLEWVASITNTGGTTYYPDSVKGR
FTISRDNAAKSTLYLQMNSLRSEDTATYYCTRGPTTVVGGWFAYWGQGTLVTVSS

38A6VK [SEQ ID NO: 68]

DIVMTQSPTSMSISVGDRVTMNCKASQNVGSNVDWYQQKTGQSPKVL IYRASSRSTGVPDRFTGSGS
GTDFTFTISNMQAEDLAVYYCMQSNSYPPTFGGGTKLELK

20 **20B8VH [SEQ ID NO: 69]**

EVQLVESGGGLVQPGRSLKLSCVASGFTFN NYWMTWIRQAPGKGLEWVASITNTGGSTYYPD SVKGR
FTISRDNAAKSTLYLQMNSLRSEDTATYYCTRGPTTVVGGWFAYWGQGTLVTVSS

20B8VK [SEQ ID NO: 70]

25 DIVMTQSPTSMSISVGDRVTMNCKASQNVGSNVDWYQQKTGQSPKLLIYRPSNRYTGVPDRFTGSGS
GTDFTFTISNMQAEDLAVYYCMQSNSYPPTFGGGTKLELK

7D7VH [SEQ ID NO: 71]

30 EVQLVESGGGLVQPGRSLKLSCVASGFTFN NYWMTWIRQAPGKGLEWVASITNTGGSTFY PD SVKGR
FTISRDNAAKSTLYLQMNSLRSEDTATYYCTRGPDYGGHLNWFAYWGQGTLVTVSS

7D7VK [SEQ ID NO: 72]

35 DIVMTQSPTSMSISAGDRVTMNCKASQNVGSNVDWYQQKTGQSPKLLIYKASNRYTGVPDRCTGSGS
GTDFTFTISNMQAEDLAVYYCMQSNSYPPTFGGGTKLELK

22B4VH [SEQ ID NO: 73]

EVQLVESGGGLVQPGRSLKLSCVASGFTFN KYWMTWIRQAPGKGLEWVASITNTGGSSYYSD SVKGR
FTISRDNAAKSTLYLQMNSLRSEETATYYCTRGPDYGGHLNWFAYWGQGTLVTVSS

40 **22B4VK [SEQ ID NO: 74]**

DIVMTQSPTSMSISVGDRVTMNCKASQNVGSNVDWYQEKTGQSPKLV IYKASNRYTGVPDRFTGSGS
GTDFTFTISNMQAEDLAVYYCMQSNSYPPTFGGGTKLELK

48B1VH [SEQ ID NO: 75]

EVQLVESGGGLVQPGRTLKLFQCVASGFTFNNYWMTWIRQAPGKGLEWVASITNTGGSTYYPD
SVKGRFTISRDNKSTLYLQMNSLRSEDATYYCTRGPDYGGHLNWFVYWGQGTLLVTVSS

5 48B1VK [SEQ ID NO: 76]

DIVMTQSPTSMISVGDRVTMNCKASQNVGSNVDWYQQKTGQSPKLLIYKASNRYTGVPDRFTGSGS
GTDFTFTISNMQAEDLAVYYCMQSNSYPPTFGGGTKLELK

EXAMPLE 5

10 BLOCKING ACTIVITY OF ANTI-IL-31 RECEPTOR *alpha* ANTIBODIES

The ability of anti-canine IL-31RA hybridoma supernatants to block the binding of IL-31 to IL-31RA were evaluated in the blocking ELISA described below.

Protocol

1. Coat 96-well half area plates with IL-31RA (1 µg/mL in PBS buffer), 25 µL/well.
- 15 2. Incubate the plates at 4°C overnight.
3. Wash the plates 3 times by PBST (PBS +0.05% Tween 20)
4. Block the plates with blocking buffer (PBS with 5% FBS), 25ul/well, for 30 minutes at room temperature.
5. Transfer 25 ul/well hybridoma supernatant to the 96-well plates, incubate 60 minutes at
- 20 room temperature.
6. Wash the plates 3 times with PBST.
7. Transfer 25 µL/well of biotinylated IL31 (0.5 µg/mL in blocking buffer,) incubate 60 minutes at room temperature.
8. Wash the plates 3 times with PBST.
- 25 9. Add 25 µl/well Streptavidin-HRP, 1:5000 dilution in blocking buffer, to the plates and incubate 60 minutes at room temperature.
10. Wash the plates five times with PBST.
11. Add TMB based reagent to the plates for colorimetric reaction for 2-3 minutes.
12. Stop the reactions with 0.16M sulfuric acid.
- 30 13. Read the plates by plate reader.

Results:

Out of the approximately 260 clones that showed binding to IL-31RA, only 20 to 25 clones also showed potential blocking of canine IL-31 binding to canine IL-31RA. Of these, a particular group of three rat anti-canine IL-31RA antibodies (44E2, 4G7, and 28F12) that both bind IL-31RA and block the binding of IL-31 to IL-31RA were identified. See, Figure 3, in which rat IgG2a and IgG2b was used as negative controls. These three antibodies appear to show some modest homology in the amino acid sequences of their respective CDRs. These amino acid sequences also are provided in Table 3 below.

HEAVY CHAIN:

<u>AB</u>	<u>HCDR1</u>	<u>SEQ ID</u>	<u>HCDR2</u>	<u>SEQ ID</u>
44E2	SNGVS	NO:13	AISSGGSTYYNSVLKS	NO:14
4G7	STFMH	NO:19	RIDPVNGNTIYSEKFKS	NO:20
28F12	DYYMA	NO:25	TISYDGSSTYYRDSVRG	NO:26

<u>AB</u>	<u>HCDR3</u>	<u>SEQ ID</u>
44E2	RLSGYNYVPFAY	NO:15
4G7	FNYAGHSGDY	NO:21
28F12	GPLTDWAPNWFAY	NO:27

LIGHT CHAIN:

<u>AB</u>	<u>LCDR1</u>	<u>SEQ ID</u>	<u>LCDR2</u>	<u>SEQ ID</u>
44E2	KASQNIYKHLA	NO:16	NANSLQT	NO:17
4G7	RASQDVGIYVN	NO:22	RATNLAD	NO:23
28F12	QTSEDIYSGLA	NO:28	GASRLED	NO:29

<u>AB</u>	<u>LCDR3</u>	<u>SEQ ID</u>
44E2	QQYYSGDT	NO:18
4G7	LQYDEYPYT	NO:24

28F12 QQGLKYPNT NO: 30

A second group of six rat anti-canine IL-31RA antibodies that both bind canine IL-31RA and block the binding of canine IL-31 to canine IL-31RA were identified as comprising sets of CDRs that have a striking amino acid sequence similarity. These amino acid sequences also are provided in Table 3 below.

HEAVY CHAIN:

10	<u>AB</u>	<u>HCDR1</u>	<u>SEQ ID</u>	<u>HCDR2</u>	<u>SEQ ID</u>
	49D3	NY YMA	NO: 31	SISTGGGNTYYRDSVKG	NO: 32
	10A12	NY YMA	NO: 31	SISTGGGNTYYRDSVKG	NO: 32
	47F3	NY YMA	NO: 31	SISTGGGNTYYRDSVKG	NO: 32
	27A10	NY YMA	NO: 31	SISTGGGNTYYRDSVKG	NO: 32
15	51G4	NY YMA	NO: 31	SISTGGGNTYYRDSVKG	NO: 32
	53B3	NY YMA	NO: 31	SISTGGGNTFYRDSVKG	NO: 41

	<u>AB</u>	<u>HCDR3</u>	<u>SEQ ID</u>
	49D3	HGTLYFDY	NO: 33
20	10A12	HGTLYFDY	NO: 33
	47F3	HGTLYFDY	NO: 33
	27A10	H TM G YFDY	NO: 43
	51G4	HGT IA AMDY	NO: 39
	53B3	HGT IA AMDY	NO: 39

25

LIGHT CHAIN:

	<u>AB</u>	<u>LCDR1</u>	<u>SEQ ID</u>	<u>LCDR2</u>	<u>SEQ ID</u>
	49D3	ERSSGDIGDSYVS	NO: 34	ADDQRPS	NO: 35
	10A12	ERSSGDIGDSYVS	NO: 34	V DDQRPS	NO: 37
30	47F3	ERSSGDIG N TYVS	NO: 38	ADDQRPS	NO: 35

27A10	ERSSGDIGD NYVS	NO: 44	ADDQRPS	NO: 35
51G4	ER NN GDIGDSYVS	NO: 40	ADDQRPS	NO: 35
53B3	ER T SGDIGD NYVS	NO: 42	ADDQRPS	NO: 35

5	<u>AB</u>	<u>LCDR3</u>	<u>SEQ ID</u>
	49D3	QSYDSNIDGPV	NO: 36
	10A12	QSYDSNIDGPV	NO: 36
	47F3	QSYDSNIDGPV	NO: 36
	27A10	QSYD GKIE IPV	NO: 45
10	51G4	QSYDSNIDGPV	NO: 36
	53B3	QSYDSNIDGPV	NO: 36

EXAMPLE 6
CANINIZED ANTIBODIES

- 15 The overall process of producing caninized heavy and light chains that can be mixed in different combinations to produce caninized anti-canine IL-31 receptor *alpha* mAbs involves the following scheme:
- i) Identify the DNA sequence of VH and VL domains comprising the CDRs of desired anti-IL-31 receptor *alpha* mAbs
 - 20 ii) Identify the H and L chain CDRs of desired anti-IL-31RA mAbs
 - iii) Identify a suitable sequence for H and L chain of canine IgG
 - iv) Identify the DNA sequence encoding the endogenous CDRs of canine IgG H and L chains of the above sequence.
 - v) Replace the DNA sequence encoding endogenous canine H and L chain CDRs with
25 DNA sequences encoding the desired anti-IL-31RA CDRs. In addition, optionally replace some canine framework residues with selected residues from the desired anti-IL-31 receptor *alpha* mAb framework regions.
 - vi) Synthesize the DNA from step (v), clone it into a suitable expression plasmid, and
30 transfect the plasmids containing desired caninized H and L chains into HEK 293 cells.

- vii) Purify expressed caninized antibody from HEK 293 supernatant.
- viii) Test purified caninized antibody for binding to canine IL-31 receptor *alpha* chain.

The application of the above outlined steps can result in a set of caninized H and L chain sequences provided below. The corresponding SEQ ID NOs. are listed in Table 5 below.

Figures 6A-6C show the binding of caninized anti-canine IL-31RA antibodies containing either lambda (L) or kappa (K) light chains as evaluated by ELISA. The results show that caninized anti-canine IL-31RA antibodies bind to canine IL-31RA.

10

Figures 7A-7C are plots showing the inhibition of cIL-31-mediated STAT-3 phosphorylation by cIL-31RA antibodies employing the assay described in Example 6 below. Three different caninized monoclonal anti-canine IL-31RA antibodies designated c10A12, c28F12, and c44E2 were evaluated for their ability to inhibit STAT-3 phosphorylation. The data show that all three antibodies result in a dose dependent inhibition of STAT-3 phosphorylation in the presence of IL-31.

15

Caninized Antibodies to Canine IL-31 Receptor alpha (cIL-31RA)

c10A12VL5-cCL [SEQ ID NO: 83]

QPVLTPPPSLASLGTTARLTCERSSGDIGDSYVSWYQQKPGSPPRDLLYVDDQRP SGVSKSFSGSK
 20 DTSANAGLLLLISGLQPEDEADYYCQSYDSNIDGPVFGGGTHLTVLGQPKASPSVTLPFPPSSEELGAN
 KATLVCLISDFYPSGVTVAWKADGSPVTQGVETTKPSKQSNNKYAASSYLSLTPDKWKSHSSFCLV
 THEGSTVEKKVAPAECS

c10A12VH1-cIgGBm [SEQ ID NO: 84]

EVQLVESGGDLVKPGGSLRLSCVASGFTFSNYMAWVRQAPGKGLQWVASISTGGGNTYYRDSVKGR
 25 FTISRDN AKNTLYLQMNSLRAEDTAMYYCAKHGTL YFDYWGQGT LVTVSSASTTAPSVFPLAPSCGS
 TSGSTVALACLVSGYFPEPVT VSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETFTCN
 VAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFIFPPKPKDTLLIARTPEVTCVVVA
 LDPEDPEVQISWFDGKQMQTAKTQPREEQFAGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPI
 30 ERTISKARGQAHQPSVYVLP PSREELSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTTPPQ
 LDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

c10A12VH2-cIgGBm [SEQ ID NO: 85]

EVQLVESGGDLVKPGGSLRLSCAASGFTFSNYMAWVRQAPGKGLQWVASISTGGGNTYYRDSVKGR
 35 FTISRDN AKNTLYLQMNSLRAEDTAMYYCARHGTLYFDYWGQGT LVTVSSASTTAPSVFPLAPSCGS
 TSGSTVALACLVSGYFPEPVT VSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETFTCN
 VAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFIFPPKPKDTLLIARTPEVTCVVVA

LDPEDPEVQISWFVDGKQMOTAKTQPREEQFAGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPI
ERTISKARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDVEWQSNNGQQEPESKYRTTPPQ
LDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

5 **c10A12VL4-cCL [SEQ ID NO: 86]**

QSVLTQPASVSGSLGQRVTISCERSSGDIGDSYVSWYQQLP GKAPSLLIYVDDQRP SGVPERFSGSK
SGSSNSATLTITGLQAEDEADYYCQSYDSNIDGPVFGGGTHLTVLGQPKASPSVTLFPPSSEELGAN
KATLVCLISDFYPSGVTVAWKADGSPVTQGVETTKPSKQSNNKYAASSYLSLTPDKWKSHSSFCLV
THEGSTVEKKVAPAECS

10

c10A12VL6-cCL [SEQ ID NO: 87]

QPVLTQPPSLASLGTTARLTICERSSGDIGDSYVSWYQQKPGSPPRDVIYVDDQRPSEVSKSFSGSK
DTSANAGLLISGLQPEDEADYFCQSYDSNIDGPVFGGGTHLTVLGQPKASPSVTLFPPSSEELGAN
KATLVCLISDFYPSGVTVAWKADGSPVTQGVETTKPSKQSNNKYAASSYLSLTPDKWKSHSSFCLV
THEGSTVEKKVAPAECS

15

c28F12VH1-cIgGBm [SEQ ID NO: 88]

EVQLVESGGDLVKPGGSLRLSCVASGFTFSDYYMAWVRQAPGKGLQWVATISYDGSSTYYRDSVRGR
FTISRDN AKNTLYLQMNSLRAEDTAMYYCAKGPLTDWAPNWFAYWGQGT LVTVSSASTTAPSVFPLA
PSCGSTSGSTVALACLVS GYFPEPVT VSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSE
TFTCNVAHPASKTKVDKPV PKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVT
CVVVALDPEDPEVQISWFVDGKQMOTAKTQPREEQFAGTYRVVSVLPIGHQDWLKGKQFTCKVNNKA
LPSPIERTISKARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDVEWQSNNGQQEPESKYR
TTPPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

25

c28F12VH2-cIgGBm [SEQ ID NO: 89]

EVQLVESGGDLVKPGGSLRLSCAASGFTFSDYYMAWVRQAPGKGLQWVATISYDGSSTYYRDSVRGR
FTISRDN AKNTLYLQMNSLRAEDTAMYYCARGPLTDWAPNWFAYWGQGT LVTVSSASTTAPSVFPLA
PSCGSTSGSTVALACLVS GYFPEPVT VSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSE
TFTCNVAHPASKTKVDKPV PKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVT
CVVVALDPEDPEVQISWFVDGKQMOTAKTQPREEQFAGTYRVVSVLPIGHQDWLKGKQFTCKVNNKA
LPSPIERTISKARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDVEWQSNNGQQEPESKYR
TTPPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

30

35 **c28F12VK1-cCK [SEQ ID NO: 90]**

DIVMTQTPLSLSVSPGETASISCQTSEDIYSGLAWFRQKPGQSPQR LIYGASRLEDGV PDRFSGSGS
GTDFTLRISTVEADDTGVYYCQQGLKYPNTFGAGTKVELKRND AQPAVYLFQPSPDQLHTGSASVVC
LLNSFY PKDINV KWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLP
STLIKS FQRSECQRVD

40

c28F12VK2-cCK [SEQ ID NO: 91]

EIVMTQSPASLSLSQEEKVTITCQTSEDIYSGLAWYQQKPGQAPKLLIYGASRLEDGVPSRFSGSGS
GTD FSFTISSLEPEDVAVYYCQQGLKYPNTFGAGTKVELKRND AQPAVYLFQPSPDQLHTGSASVVC
LLNSFY PKDINV KWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLP
STLIKS FQRSECQRVD

45

c28F12VK3-cCK [SEQ ID NO: 92]

DIVMTQSPASLSLSQEEKVTITCQTSEDIYSGLAWYQQKPGQAPKLLIYGASRLEDGVPSRFSGSGS
 GTDFSFTISSLEPEDVAVYFCQQGLKYPNTFGAGTKVELKRNDAPAVYLFQPSPDQLHTGSASVVC
 LLNSFYPKDINVKWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLP
 5 STLIKSFQRSECQRVD

c28F12VK4-cCK [SEQ ID NO: 93]

DIVMTQTPLSLSVSPGETASISCQTSEDIYSGLAWFRQKPGQSPQLLIYGASRLEDGVDPDRFSGSGS
 GTDFTLRISTVEADDTGVYFCQQGLKYPNTFGAGTKVELKRNDAPAVYLFQPSPDQLHTGSASVVC
 10 LLNSFYPKDINVKWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLP
 STLIKSFQRSECQRVD

c44E2VH1-cIgGBm [SEQ ID NO: 94]

EVQLVESGGDLVKPEGSLRLSCVVSQFTFSSNGVSWVRQAPGKGLQWVAAISSGGSTYYNSVLKSRF
 15 TISRDNAKNTLYLQMNSLRTEDTAVYYCAKRLSGYNYVPFAYWGQGTLLTVSSASTTAPSVFPLAPS
 CGSTSGSTVALACLVSGYFPEPVTVSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETF
 TCNVAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVTCV
 VVALDPEDPEVQISW FVDGKQMQTAKTQPREEQFAGTYRVVSVLP IGHQDWLKGKQFTCKVNNKALP
 SPIERTISKARGQAHQPSVYVLPSPSREELSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTT
 20 PPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

c44E2VH4-cIgGBm [SEQ ID NO: 95]

ELTLQESGPGLVKPSQTLSTLCVVSGGSVTSNGVSWIRQRPGRGLEWMGAISSGGSTYYNSVLKSRI
 SITADTAKNQFSLQLSSMTTEDTAVYYCARRLSGYNYVPFAYWGQGTLLTVSSASTTAPSVFPLAPS
 25 CGSTSGSTVALACLVSGYFPEPVTVSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETF
 TCNVAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVTCV
 VVALDPEDPEVQISW FVDGKQMQTAKTQPREEQFAGTYRVVSVLP IGHQDWLKGKQFTCKVNNKALP
 SPIERTISKARGQAHQPSVYVLPSPSREELSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTT
 PPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

c44E2VH5-cIgGBm [SEQ ID NO: 96]

ELTLQESGPGLVKPSQTLSTCTVSGFSLTSNGVSWIRQRPGRGLEWMGAISSGGSTYYNSVLKSRI
 SITADTAKNQFSLQLSSMTTEDTAVYYCARRLSGYNYVPFAYWGQGTLLTVSSASTTAPSVFPLAPS
 CGSTSGSTVALACLVSGYFPEPVTVSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETF
 35 TCNVAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVTCV
 VVALDPEDPEVQISW FVDGKQMQTAKTQPREEQFAGTYRVVSVLP IGHQDWLKGKQFTCKVNNKALP
 SPIERTISKARGQAHQPSVYVLPSPSREELSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTT
 PPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

c44E2VK1-cCK [SEQ ID NO: 97]

EIVMTQSPASLSLSQEEKVTITCKASQNIYKHLAWYQQKPGQAPKLLIYNANSLQTGVPSRFSGSGS
 GTDFSFTISSLEPEDVAVYYCQQYYSGDTFGAGTKVELKRNDAPAVYLFQPSPDQLHTGSASVVC
 LNSFYPKDINVKWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLPS
 40 TLIKSFQRSECQRVD

c44E2VK2-cCK [SEQ ID NO: 98]

EIVMTQSPASLSLSQEEKVTITCKASQNIYKHLAWYQQKPGQAPKLLIYNANSLQTGIPSRFSGSGS
 GTDFSFTISSLEPEDVAVYFCQQYYSGDTFGAGTKVELKRNDAPAVYLFQPSPDQLHTGSASVVCL
 LNSFYPKDINVKWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLPS
 TLIKSFQRSECQRVD

5

c44E2VK4-cCK [SEQ ID NO: 99]

EIVMTQSPGSLAGSAGESVSINCKASQNIYKHLAWYQQKPGERP KLLIYNANSLQTGVPARFSSSGS
 GTDFTLTINNLAEDVGDYYCQQYYSGDTFGAGTKVELKRNDAPAVYLFQPSPDQLHTGSASVVCL
 LNSFYPKDINVKWKVDGVIQDTGIQESVTEQDKDSTYSLSSTLTMSSTEYLSHELYSCEITHKSLPS
 TLIKSFQRSECQRVD

10

c44E2VH2-cIgGBm [SEQ ID NO: 100]

EVQLVESGGDLVKPEGSLRLSCVVS GFSLT SNGVSWVRQAPGKGLQWIAAIISSGGSTYYNSVLKSRL
 TISRDNANTLYLQMNSLRTEDTAVYYCARRLSGYNYPFAYWGQGT LVT VSSASTTAPSVFPLAPS
 CGSTSGSTVALACLVSGYFPEPVT VSWNSGSLTSGVHTFPSVLQSSGLYSLSSMVTVPSSRWPSETF
 TCNVAHPASKTKVDKPVPKRENGRVPRPPDCPKCPAPEMLGGPSVFI FPPKPKDTLLIARTPEVTCV
 VVALDPEDPEVQISWFVDGKQMOTAKTQPREEQFAGTYRVVSVLP IGHQDWLKGKQFTCKVNNKALP
 SPIERTISKARGQAHQPSVYVLPPSREELSKNTVSLTCLIKDFFPPDIDVEWQSNGQQEPESKYRTT
 PPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK

20

EXAMPLE 7

STAT-3 ASSAY

Stat-3 is known to be activated by IL-31 in cells comprising the the heterodimeric receptor for
 IL-31. In order to develop an assay to assess the activation of STAT-3 by canine IL-31, the
 nucleotide sequences encoding IL-31RA and OSMR, respectively, were prepared by chemical
 synthesis and then cloned into expression vectors pcDNA3.1. The vectors containing the IL-31RA
 and OSMR nucleotide sequences, respectively, were co-transfected into Ba/f3 cells and the
 transfected cells, denoted as “Ba/f3-OI”, were grown as a pool under antibiotic selection. The
 ability of canine IL-31 to induce STAT-3 activation was tested as follows.

Materials:

Cell line: Ba/f3-OI stable pool cells

Growth medium with mouse IL-3 or with canine IL-31 (cIL-31)

RPMI 1640 435 ml (ThermoFisher, 12633-020)

FBS 50 mL (SAFC cat# 12003c-500mL)

2-Mercaptoethanol (50 mM) 0.5 mL (Gibco 31350-010)

100X Pen Strep 5 mL (Gibco 15140-122 Lot1734040)

200mM L-Glu 10 ml (Gibco 25030-081 Lot1677185)

500 ng/mL Geneticin G418 (from Gibco or Sigma)

5 ng/mL mIL-3 or 100 ng/mL cIL-31

Starvation medium: the growth medium without mIL-3 and cIL-31

p-STAT3 (Tyr705) Assay Kit: PerkinElmer, ALSU-PST3-A-HV

5

Procedure

Cell culture

1. Thaw a vial of the Ba/f3-OI cells, and grow the cells in the growth medium with mIL-3 in 37°C CO₂ shaker with 125 rpm.
- 10 2. Passage the cells 2 – 3 passages to have the cells with $\geq 90\%$ viability before set a cell-based assay.
3. To setup assay, harvest and resuspend the cells in the starvation medium to 1×10^7 viable cells/mL.
4. Dispense cells into 96 well plate, 50 μ L/well (about 5×10^5 cells/well).
- 15 5. Three-fold dilute cIL-31 in starvation medium in a dilution plate, and then transfer 50 μ L of each of the serial diluted cIL-31 aliquots into the cell plate.
6. Incubate the cell plate for 15-30 min in 37°C CO₂ shaker with 125 rpm for 1-2 hrs.

AlphaLISA assay as per manufacturer's instruction:

7. Spin down the cells, aspirate the supernatant, and add 1x lysis buffer of 50 – 100 μ L/well.
- 20 Incubate at RT for 10 min with 1000rpm shaking.
8. Remove 30 μ L of the cell lysate into a $\frac{1}{2}$ area plate or freeze and store at -80°C for future test.
9. *SureFire Assay*: add 15 μ L /well acceptor mix to the cell lysate. Seal and agitate plate for 2 min at 1000 rpm and then incubate for 1-2 hours at RT.
- 25 10. Add 15 μ L/well donor mix to the cell lysate. Seal and agitate for 2 min at 1000 rpm, and then incubate for 1-2 hours at RT (the plate can be stored at 4°C overnight. Incubate at room temp for 1 hr before reading the plate next day)
11. Read the plate on Alpha plate reader at 520 – 620 nm.

30

Results:

As shown in Figure 4, canine IL-31 stimulates activation of STAT-3 in Ba/f3-OI cells in a dose dependent manner.

EXAMPLE 8**BIOLOGICAL ACTIVITY OF ANTI-CANINE IL-31RA ANTIBODIES**

The ability of the anti-canine IL-31RA mAbs to inhibit the activation of STAT-3 in Ba/f3-OI cells is assessed as follows:

1. Thaw a vial of the Ba/f3-OI cells, and grow the Ba/f3-OI cells in the growth medium with mIL-3 in 37°C CO₂ shaker with 125 rpm.
2. Passage the cells 2 – 3 passages to have the cells with $\geq 90\%$ viability before set a cell-based assay.
3. To setup assay, harvest and resuspend the cells in the starvation medium to 1×10^7 viable cells/mL.
4. Dispense cells into 96 well plate, 50 μ L/well (about 5×10^5 cells/well).
5. Three-fold dilute the antibody in starvation medium in a row on a 96 well plate, starting concentration at 200 μ g/mL. Then add 5-10 μ L cIL-31 in each well to get final concentration of 100 ng/mL.
6. Transfer 50 μ L of the diluted antibody and cIL-31 mix into each well of the cell plate, gently mix.
7. Incubate the cell plate in 37°C CO₂ shaker with 125 rpm for 1-2 hrs.

AlphaLISA assay as per manufacturer's instruction: (refer to Example 7)

Results:

As exemplified in Figure 5, both antibody 4G7 and 44E2 inhibit the ability of canine IL-31 to stimulate activation of STAT-3 in Ba/f3-OI cells.

EXAMPLE 9**MAPPING OF CANINE IL-31 RECEPTOR *alpha* EPITOPES
USING MASS SPECTROSCOPY**

A method based on chemical crosslinking and mass spectrometry detection was employed to identify epitopes recognized by anti-canine IL-31 receptor *alpha* mAbs [CovalX Instrument Incorporated, located at 999 Broadway, Suite 305, Saugus, MA 01906-4510]. The application of this technology to epitope mapping of canine IL-31 receptor *alpha* chain resulted in

5 identification of epitopes recognized by the mAbs listed in Table 6. The results from the epitope mapping of canine IL-31 receptor *alpha* with three antibodies disclosed herein indicates that the mAbs recognize specific peptide epitopes that are present within the extracellular domain of canine IL-31 receptor *alpha* (*see*, Table 6 below).

10 Notably, the epitopes identified for each of the three monoclonal antibodies (mAbs) tested were markedly different. As depicted in Table 6 below, the data indicates the 28F12 antibody binds to a single epitope comprising the amino acid sequence of SEQ ID NO: 101, where the antibody binds with arginine (R) residues at positions 215 and 225, and a lysine (K) residue at position 233 of the amino acid sequence SEQ ID NO: 2. The data further indicates the 44E2 antibody
15 binds to two different epitopes: the first comprising the amino acid sequence of SEQ ID NO: 102, where the antibody binds with a threonine (T) residue at position 408 of the amino acid sequence SEQ ID NO: 2 and a second epitope comprising the amino acid sequence of SEQ ID NO: 103, which has two separate parts, one of which the antibody binds with serine (S) residues at positions 464 and 472, and a tyrosine (Y) residue at position 471 of the amino acid
20 sequence SEQ ID NO: 2 and the other part, where the antibody binds with a threonine (T) residue at position 487 of the amino acid sequence SEQ ID NO: 2. The data further indicates the 10A12 antibody binds to two different epitopes the first comprising the amino acid sequence of SEQ ID NO: 104, where the antibody binds with tyrosine (Y) residues at positions 31, 34, and 42, and a threonine (T) residue at position 39 of the amino acid sequence SEQ ID NO: 2 and a
25 second epitope comprising the amino acid sequence of SEQ ID NO: 105, where the antibody binds with a lysine (K) residue at position 89, a serine (S) residue at position 90, a threonine (T) residue at position 93, and a tyrosine (Y) residue at position 94 of the amino acid sequence SEQ ID NO: 2.

SEQUENCE TABLES

TABLE 1

CANINE IL-31RA EXTRACELLULAR DOMAIN -HIS TAG

	SEQ ID NO:	Nucleic Acid	Amino Acid
canine IL-31RA ECD-10His	1	X	
canine IL-31RA ECD-10His	2		X

5

TABLE 2

CDRs of Non-BLOCKING ANTIBODIES

Amino Acid Sequence		SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:
	20B8		38A6	
HCDR1	NYWMT	3	NYWMT	3
HCDR2	SITNTGGSTYYPDSVKG	4	SITNTGGSTYYPDSVKG	4
HCDR3	GPTTVVGGWFAY	5	GPTTVVGGWFAY	5
LCDR1	KASQNVGSNVD	6	KASQNVGSNVD	6
LCDR2	RPSNRYT	7	RASSRST	9
LCDR3	MQSNSYPPT	8	MQSNSYPPT	8
	7D7		48B1	
HCDR1	NYWMT	3	NYWMT	3
HCDR2	SITNTGGSTFYPSVKG	10	SITNTGGSTYYPDSVKG	4
HCDR3	GPDYGGHLNWFAY	11	GPDYGGHLNWFVY	46
LCDR1	KASQNVGSNVD	6	KASQNVGSNVD	6
LCDR2	KASNRYT	12	KASNRYT	12
LCDR3	MQSNSYPPT	8	MQSNSYPPT	8
	22B4			
HCDR1	KYWMT	47		
HCDR2	SITNTGGSSYYSDSVKG	48		
HCDR3	GPDYGGHLNWFAY	11		
LCDR1	KASQNVGSNVD	6		
LCDR2	KASNRYT	12		
LCDR3	MQSNSYPPT	8		

TABLE 3

CDRs of BLOCKING ANTIBODIES

Amino Acid Sequence		SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:
	44E2		4G7	

HCDR1	SNGVS	13	STFMH	19
HCDR2	AISSGGSTYYNSVLKS	14	RIDPVNGNTIYSEKFKS	20
HCDR3	RLSGYNYVPFAY	15	FNYAGHSGDY	21
LCDR1	KASQNIYKHLA	16	RASQDVGIYVN	22
LCDR2	NANSLQT	17	RATNLAD	23
LCDR3	QQYYSGDT	18	LQYDEYPYT	24
	28F12			
HCDR1	DYYMA	25		
HCDR2	TISYDGSSTYYRDSVRG	26		
HCDR3	GPLTDWAPNWFAY	27		
LCDR1	QTSEDIYSGLA	28		
LCDR2	GASRLD	29		
LCDR3	QQGLKYPNT	30		
	49D3		10A12	
HCDR1	NYYMA	31	NYYMA	31
HCDR2	SISTGGGNTYYRDSVKG	32	SISTGGGNTYYRDSVKG	32
HCDR3	HGTLYFDY	33	HGTLYFDY	33
LCDR1	ERSSGDIGDSYVS	34	ERSSGDIGDSYVS	34
LCDR2	ADDQRPS	35	VDDQRPS	37
LCDR3	QSYDSNIDGPV	36	QSYDSNIDGPV	36
	47F3		51G4	
HCDR1	NYYMA	31	NYYMA	31
HCDR2	SISTGGGNTYYRDSVKG	32	SISTGGGNTYYRDSVKG	32
HCDR3	HGTLYFDY	33	HGTIAAMDY	39
LCDR1	ERSSGDIGNTYVS	38	ERNNGDIGDSYVS	40
LCDR2	ADDQRPS	35	ADDQRPS	35
LCDR3	QSYDSNIDGPV	36	QSYDSNIDGPV	36
	53B3		27A10	
HCDR1	NYYMA	31	NYYMA	31
HCDR2	SISTGGGNTFYRDSVKG	41	SISTGGGNTYYRDSVKG	32
HCDR3	HGTIAAMDY	39	HTMGYFDY	43
LCDR1	ERTSGDIGDNYVS	42	ERSSGDIGDNYVS	44
LCDR2	ADDQRPS	35	ADDQRPS	35
LCDR3	QSYDSNIDGPV	36	QSYDGKIEIPV	45

TABLE 4
RAT ANTI-CANINE IL-31RA VARIABLE REGIONS

SEQ ID NO:	Heavy Chain	SEQ ID NO:	Light Chain
49	49D3VH	50	49D3VL
51	10A12VH	52	10A12VL

53	47F3VH	54	47F3VL
55	51G4VH	56	51G4VL
57	53B3VH	58	53B3VL
59	27A10VH	60	27A10VL
61	44E2VH	62	44E2VK
63	4G7VH	64	4G7VK
65	28F12VH	66	28F12VK
67	38A6VH	68	38A6VK
69	20B8VH	70	20B8VK
71	7D7VH	72	7D7VK
73	22B4VH	74	22B4VK
75	48B1VH	76	48B1VK

TABLE 5
AMINO ACID SEQUENCES OF CANINIZED
ANTIBODIES TO CANINE IL-31RA

SEQ ID NO:	IL-31 Receptor <i>alpha</i>	Heavy Chain	Light Chain
83	c10A12VL5-cCL		√
84	c10A12VH1-cIgGBm	√	
85	c10A12VH2-cIgGBm	√	
86	c10A12VL4-cCL		√
87	c10A12VL6-cCL		√
88	c28F12VH1-cIgGBm	√	
89	c28F12VH2-cIgGBm	√	
90	c28F12VK1-cCK		√
91	c28F12VK2-cCK		√
92	c28F12VK3-cCK		√
93	c28F12VK4-cCK		√
94	c44E2VH1-cIgGBm	√	
95	c44E2VH4-cIgGBm	√	
96	c44E2VH5-cIgGBm	√	
97	c44E2VK1-cCK		√
98	c44E2VK2-cCK		√
99	c44E2VK4-CcK		√
100	c44E2VH2-cIgGBm	√	

5

TABLE 6
Epitope Sequences

Antibody	SEQ ID NO:	Amino Acid Sequences of Epitopes of cIL-31RA
28F12	101	GLDLWRVLKPAMVDGRRPVQLMWKKATGAPV
44E2	102	GIPSAGPVTQADSIGVKTVTITWKEI
44E2	103	SKTVNSNILQYRLESLTRRTSYSLQVMASTNAGGTNGTKINFKTL SIS
10A12	104	SYTWYKVKRTYSYGYKSDICS
10A12	105	EAQNADGIMKSDITYWNLDAIMKIEPPEIFSVKSVLGIKRMLQIKWIRPVL

We Claim:

1. An isolated mammalian antibody or antigen binding fragment thereof that binds canine interleukin-31 receptor *alpha* (canine IL-31RA), wherein said antibody comprises a set of six complementary determining regions (CDRs), three of which are heavy chain CDRs: CDR heavy 1 (HCDR1), CDR heavy 2 (HCDR2) and CDR heavy 3 (HCDR3) and three of which are light chain CDRs: CDR light 1 (LCDR1), CDR light 2 (LCDR2), and CDR light 3 (LCDR3); and

wherein the set of six CDRs are selected from the group of sets consisting of (i), (ii), and (iii); wherein for set (i):

HCDR1 comprises the amino acid sequence of SEQ ID NO: 13;

HCDR2 comprises the amino acid sequence of SEQ ID NO: 14;

HCDR3 comprises the amino acid sequence of SEQ ID NO: 15;

LCDR1 comprises the amino acid sequence of SEQ ID NO: 16;

LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and

LCDR3 comprises the amino acid sequence of SEQ ID NO: 18;

wherein for set (ii):

HCDR1 comprises the amino acid sequence of SEQ ID NO: 19;

HCDR2 comprises the amino acid sequence of SEQ ID NO: 20;

HCDR3 comprises the amino acid sequence of SEQ ID NO: 21;

LCDR1 comprises the amino acid sequence of SEQ ID NO: 22;

LCDR2 comprises the amino acid sequence of SEQ ID NO: 23; and

LCDR3 comprises the amino acid sequence of SEQ ID NO: 24; and

wherein for set (iii)

HCDR1 comprises the amino acid sequence of SEQ ID NO: 25;

HCDR2 comprises the amino acid sequence of SEQ ID NO: 26;

HCDR3 comprises the amino acid sequence of SEQ ID NO: 27;

LCDR1 comprises the amino acid sequence of SEQ ID NO: 28;

LCDR2 comprises the amino acid sequence of SEQ ID NO: 29; and

LCDR3 comprises the amino acid sequence of SEQ ID NO: 30.

2. The isolated mammalian antibody or antigen binding fragment thereof of Claim 1,
wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13;
wherein HCDR2 comprises the amino acid sequence of SEQ ID NO: 14;
wherein HCDR3 comprises the amino acid sequence of SEQ ID NO: 15;
5 wherein LCDR1 comprises the amino acid sequence of SEQ ID NO: 16;
wherein LDR2 comprises the amino acid sequence of SEQ ID NO: 17; and
wherein LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.
3. The isolated mammalian antibody or antigen binding fragment thereof of Claim 2,
10 that when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid
sequence selected from the group consisting of SEQ ID NO: 102, SEQID NO: 103, and both SEQ
ID NO: 102 and SEQID NO: 103.
4. The isolated mammalian antibody or antigen binding fragment thereof of Claim 1,
15 wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 19;
wherein HCDR2 comprises the amino acid sequence of SEQ ID NO: 20;
wherein HCDR3 comprises the amino acid sequence of SEQ ID NO: 21;
wherein LCDR1 comprises the amino acid sequence of SEQ ID NO: 22;
wherein LDR2 comprises the amino acid sequence of SEQ ID NO: 23; and
20 wherein LCDR3 comprises the amino acid sequence of SEQ ID NO: 24.
5. The isolated mammalian antibody or antigen binding fragment thereof of Claim 1,
wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25;
wherein HCDR2 comprises the amino acid sequence of SEQ ID NO: 26;
25 wherein HCDR3 comprises the amino acid sequence of SEQ ID NO: 27;
wherein LCDR1 comprises the amino acid sequence of SEQ ID NO: 28;
wherein LDR2 comprises the amino acid sequence of SEQ ID NO: 29; and
wherein LCDR3 comprises the amino acid sequence of SEQ ID NO: 30.
- 30 6. The isolated mammalian antibody or antigen binding fragment thereof of Claim 5,

that when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid sequence of SEQ ID NO: 101.

7. The isolated mammalian antibody or antigen binding fragment thereof of any one of Claims 1 to 6, wherein the antibody and antigen binding fragment thereof bind canine IL-31RA and block the binding of canine IL-31RA to canine interleukin-31.

8. The isolated mammalian antibody or antigen binding fragment thereof of Claim 7, that is a caninized antibody or a caninized antigen binding fragment thereof.

9. The caninized antibody or antigen binding fragment thereof of Claim 8, that comprises a hinge region that comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, and SEQ ID NO: 82.

10. The caninized antibody or antigen binding fragment thereof of Claim 8, that comprises a heavy chain comprising a modified canine IgG-B (IgG-Bm) comprising the amino acid sequence of SEQ ID NO: 78.

11. The caninized antibody or antigen binding fragment thereof of Claim 8, wherein the caninized IL-31RA antibody comprises a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, and SEQ ID NO: 93; and a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 88 and SEQ ID NO: 89.

12. The caninized antibody or antigen binding fragment thereof of Claim 11, wherein the caninized IL-31RA antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 92 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88; or

a light chain comprising the amino acid sequence of SEQ ID NO: 93 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 88; or

a light chain comprising the amino acid sequence of SEQ ID NO: 92 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 89; or

a light chain comprising the amino acid sequence of SEQ ID NO: 93 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 89.

5

13. The caninized antibody or antigen binding fragment thereof of Claim 8, wherein the caninized IL-31RA antibody comprises a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99; and SEQ ID NO: 100; and a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 95 and SEQ ID NO: 96.

10

14. The caninized antibody or antigen binding fragment thereof of Claim 13, wherein the caninized IL-31RA antibody comprises:

15

a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95; or

a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95; or

a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 95; or

20

a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 96; or

a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 96; or

25

a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 96 or

a light chain comprising the amino acid sequence of SEQ ID NO: 97 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; or

a light chain comprising the amino acid sequence of SEQ ID NO: 98 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; or

30

a light chain comprising the amino acid sequence of SEQ ID NO: 99 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 100.

15. A canine or caninized antibody or antigen binding fragment thereof that binds to canine interleukin-31 receptor *alpha* (canine IL-31RA) and that when bound to canine IL-31RA the antibody binds to an epitope comprised by the amino acid sequence selected from the group consisting of SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID
5 NO: 105, or any combination thereof; wherein the antibody binds to canine IL-31RA and blocks the binding of canine IL-31RA to canine IL-31.

16. An isolated nucleic acid that encodes the heavy chain of the caninized antibody or antigen binding fragment thereof of Claims 1-15.

17. An isolated nucleic acid that encodes the light chain of the caninized antibody or antigen binding fragment thereof of any one Claims 1-15.

18. An expression vector comprising the isolated nucleic acid of Claim 17.

19. An expression vector comprising the isolated nucleic acid of Claim 16.

20. A host cell comprising the expression vector of Claims 18 or 19 or both Claims 18 or 19.

21. A pharmaceutical composition comprising the caninized antibody or antigen binding fragment thereof of any one of Claims 8-15, and a pharmaceutically acceptable carrier or diluent.

22. A method of aiding in the blocking the pruritus associated with atopic dermatitis, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical
25 composition of Claim 21.

Figure 1

IL31Ra/IL31 ELISA

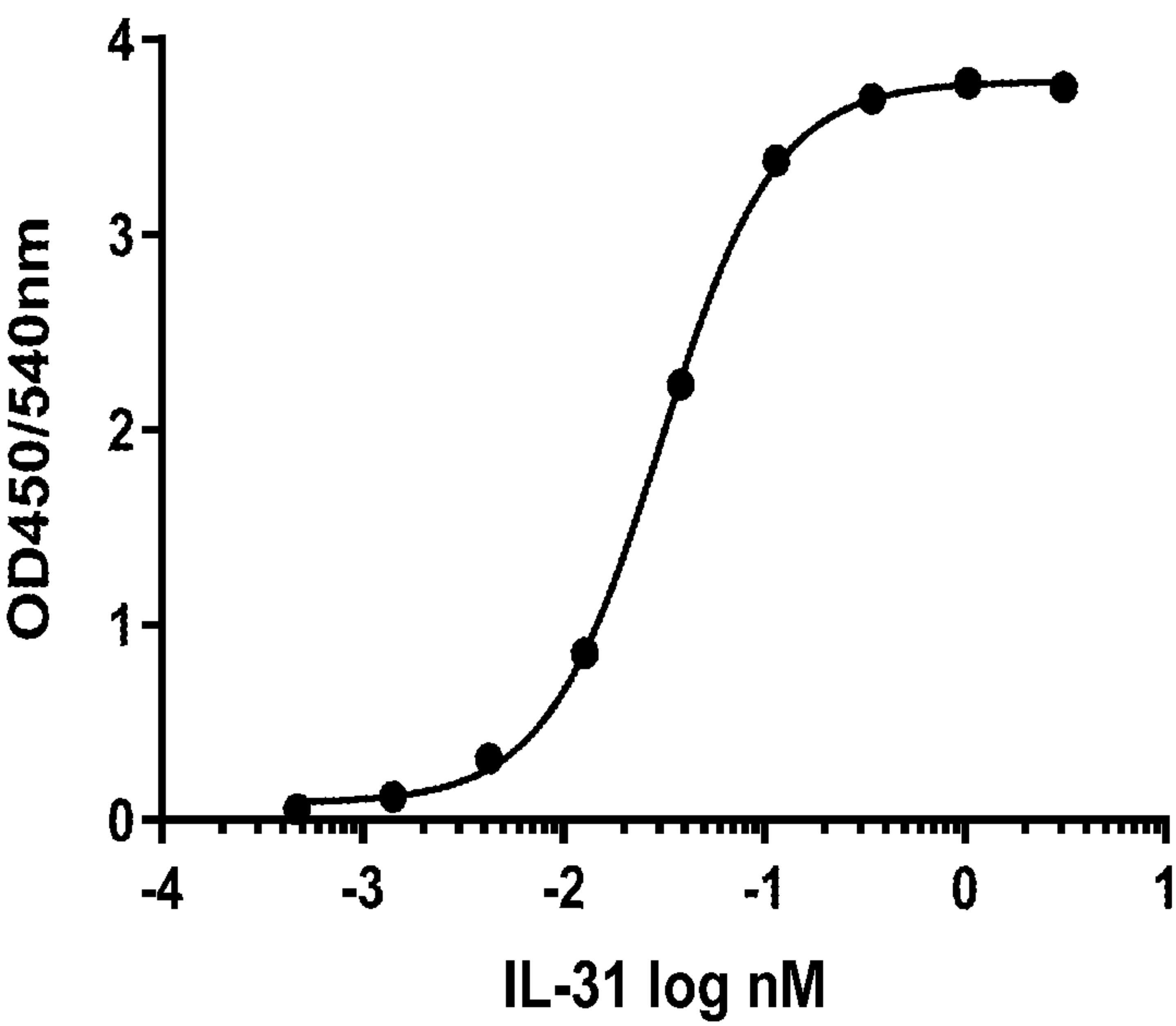


Figure 2A

Binding of xIL31R mAbs to IL31RA

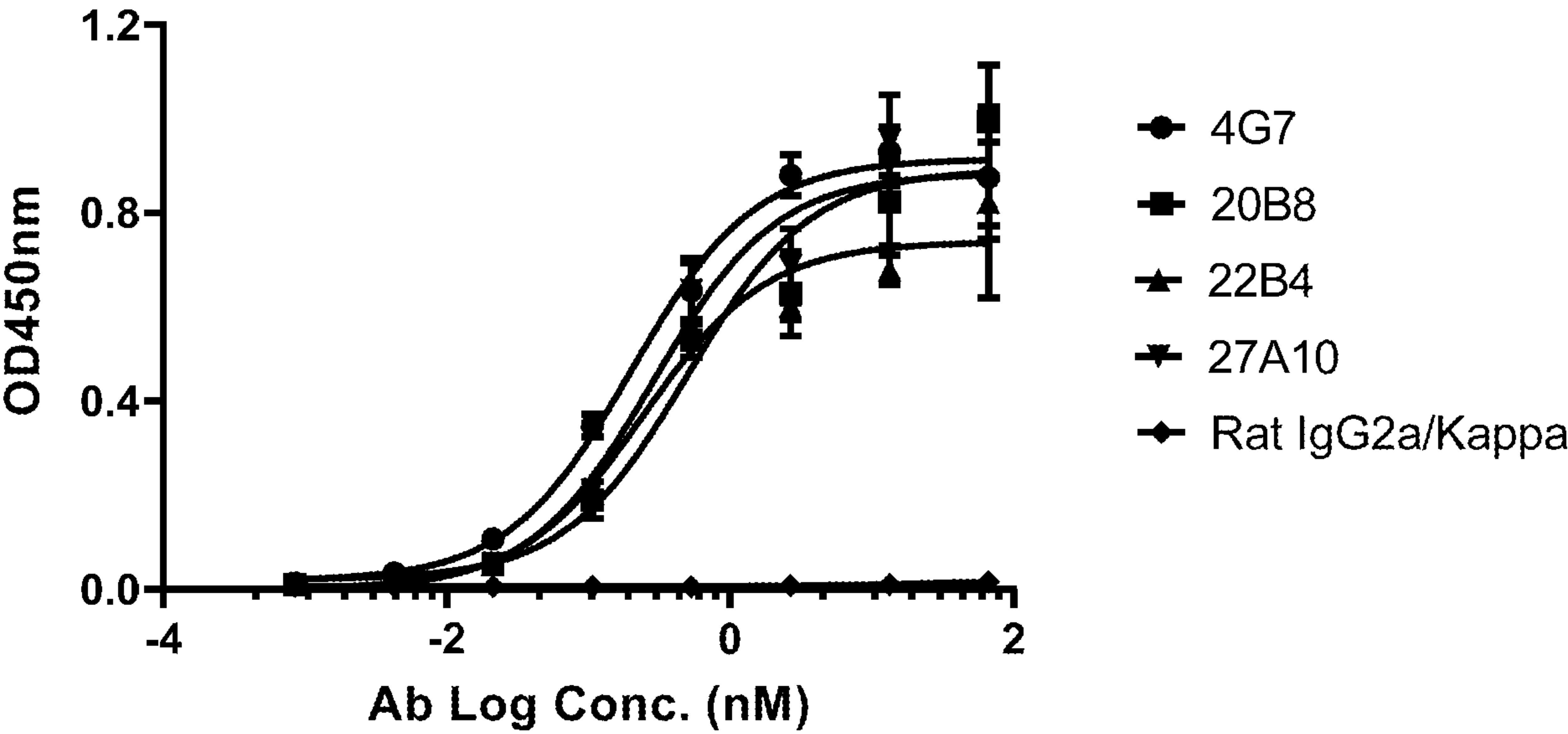


Figure 2B

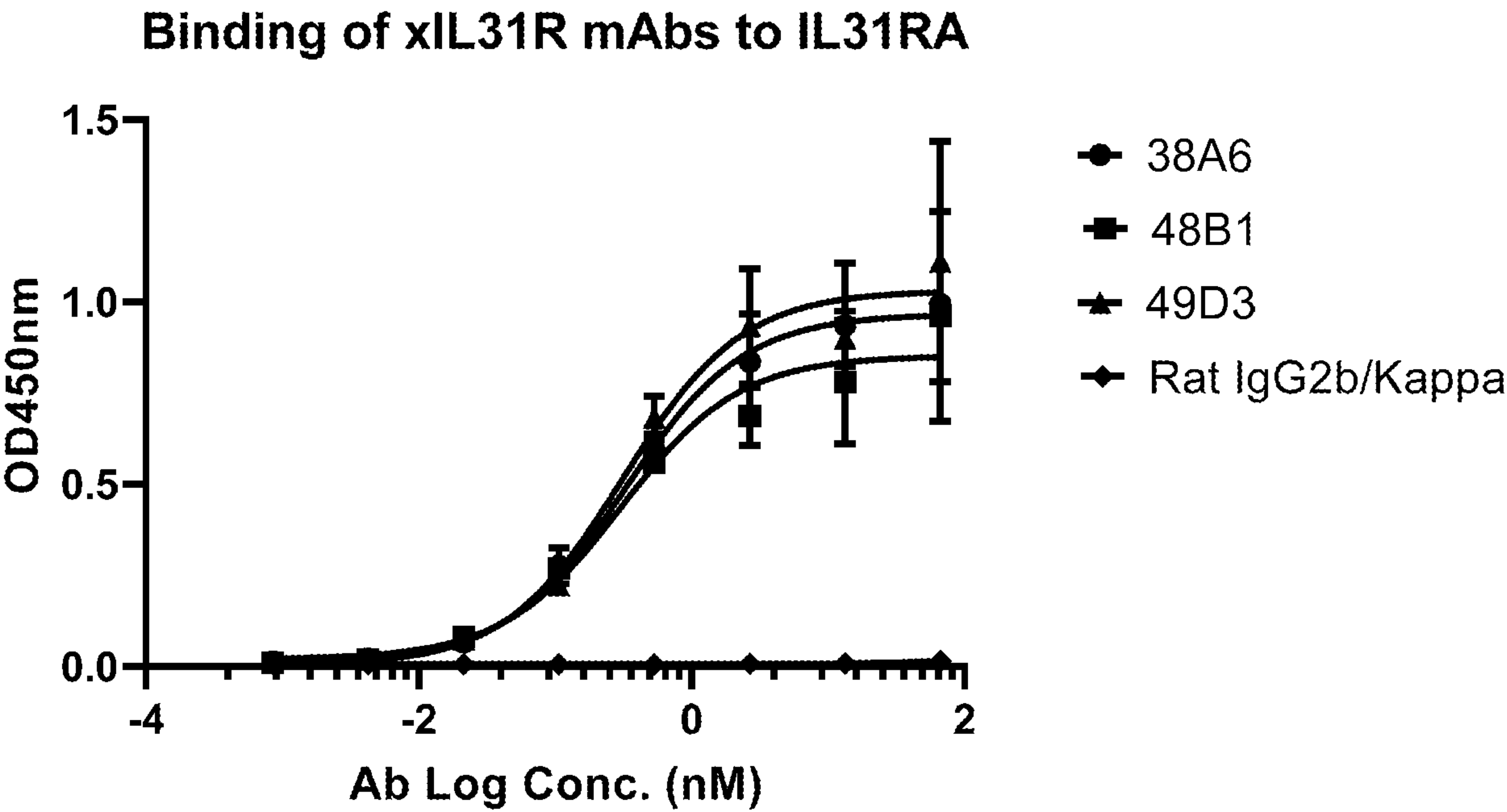


Figure 2C

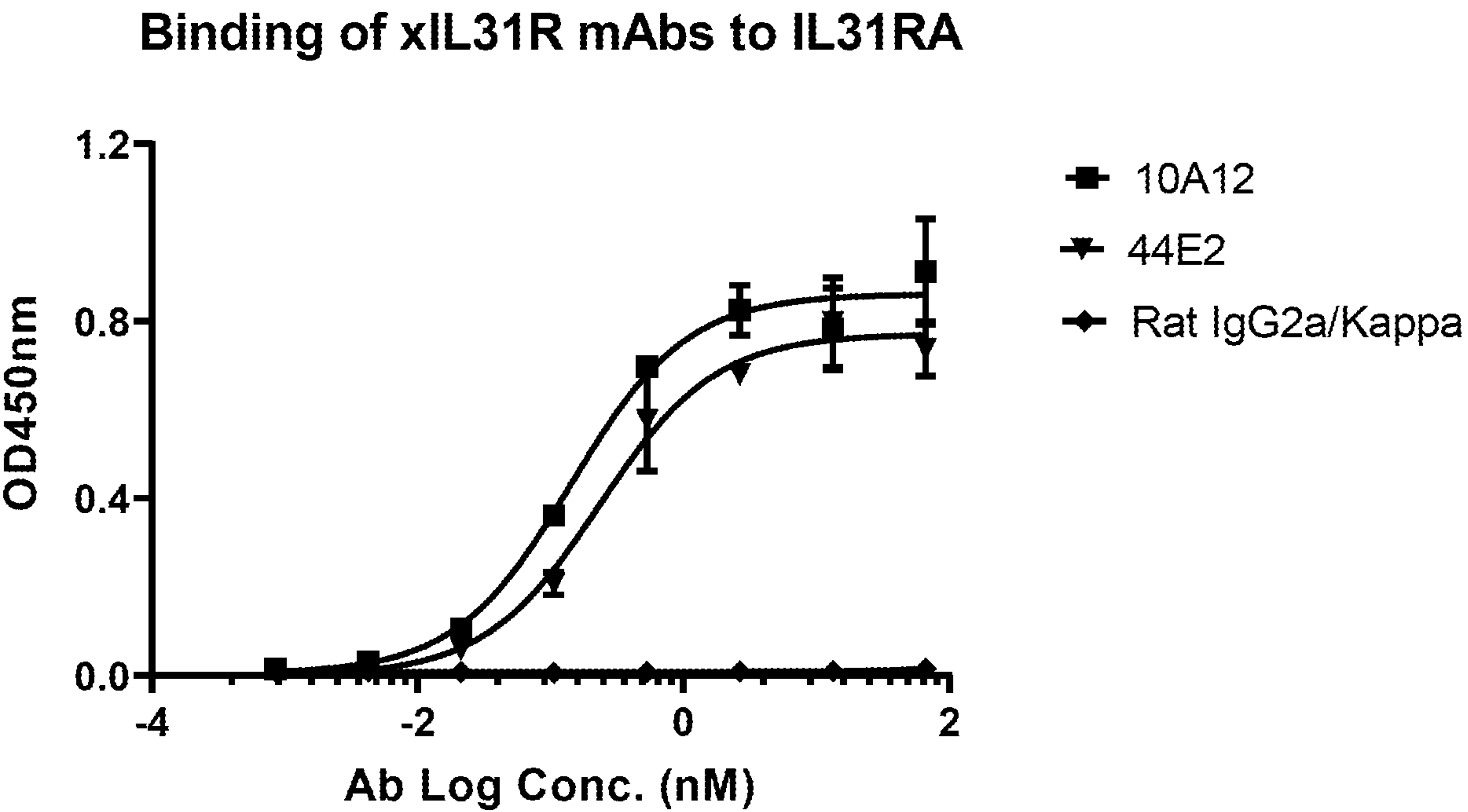


Figure 2D

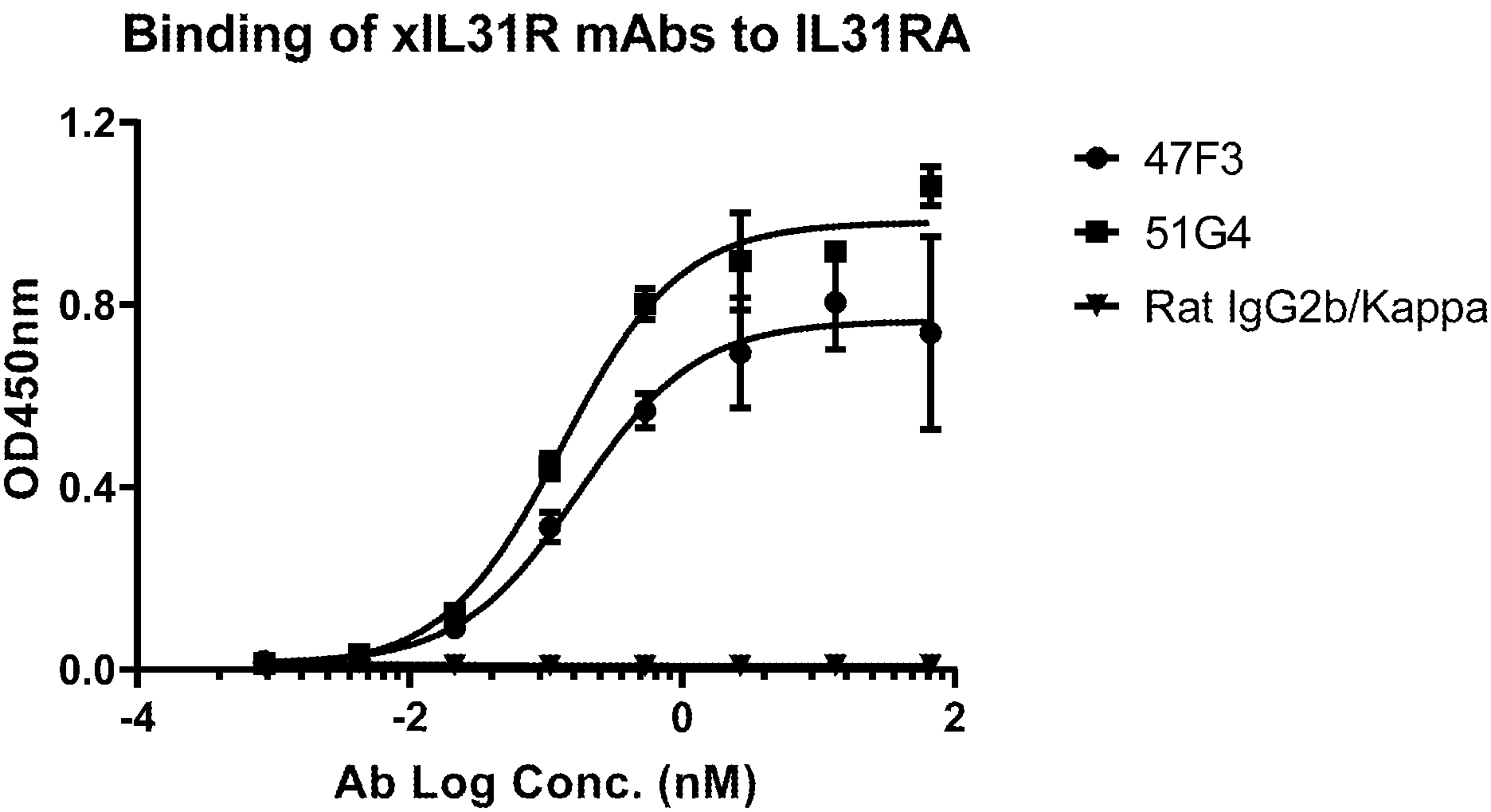


Figure 2E

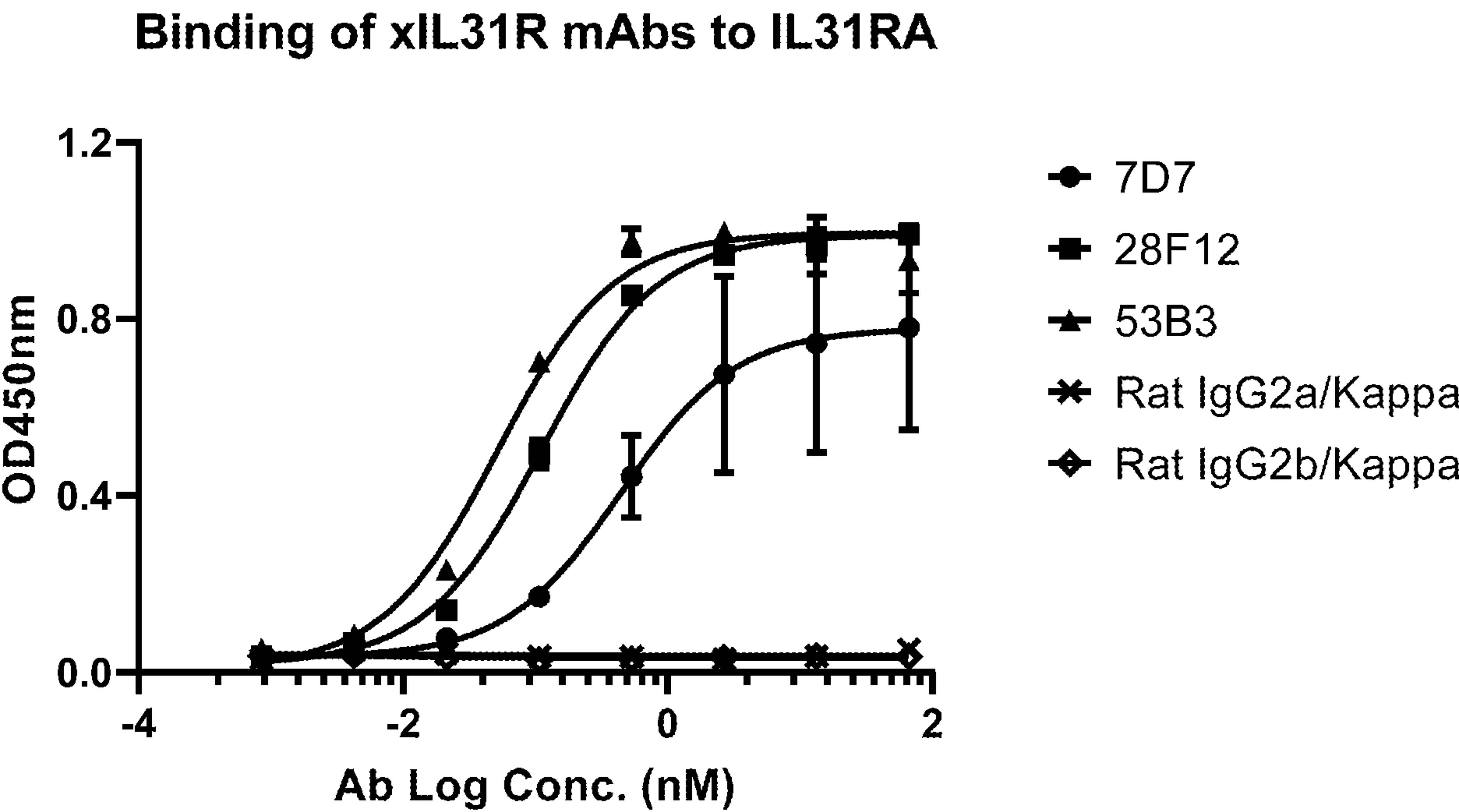


Figure 3

Blocking of IL-31 binding by anti-IL-31RA antibodies

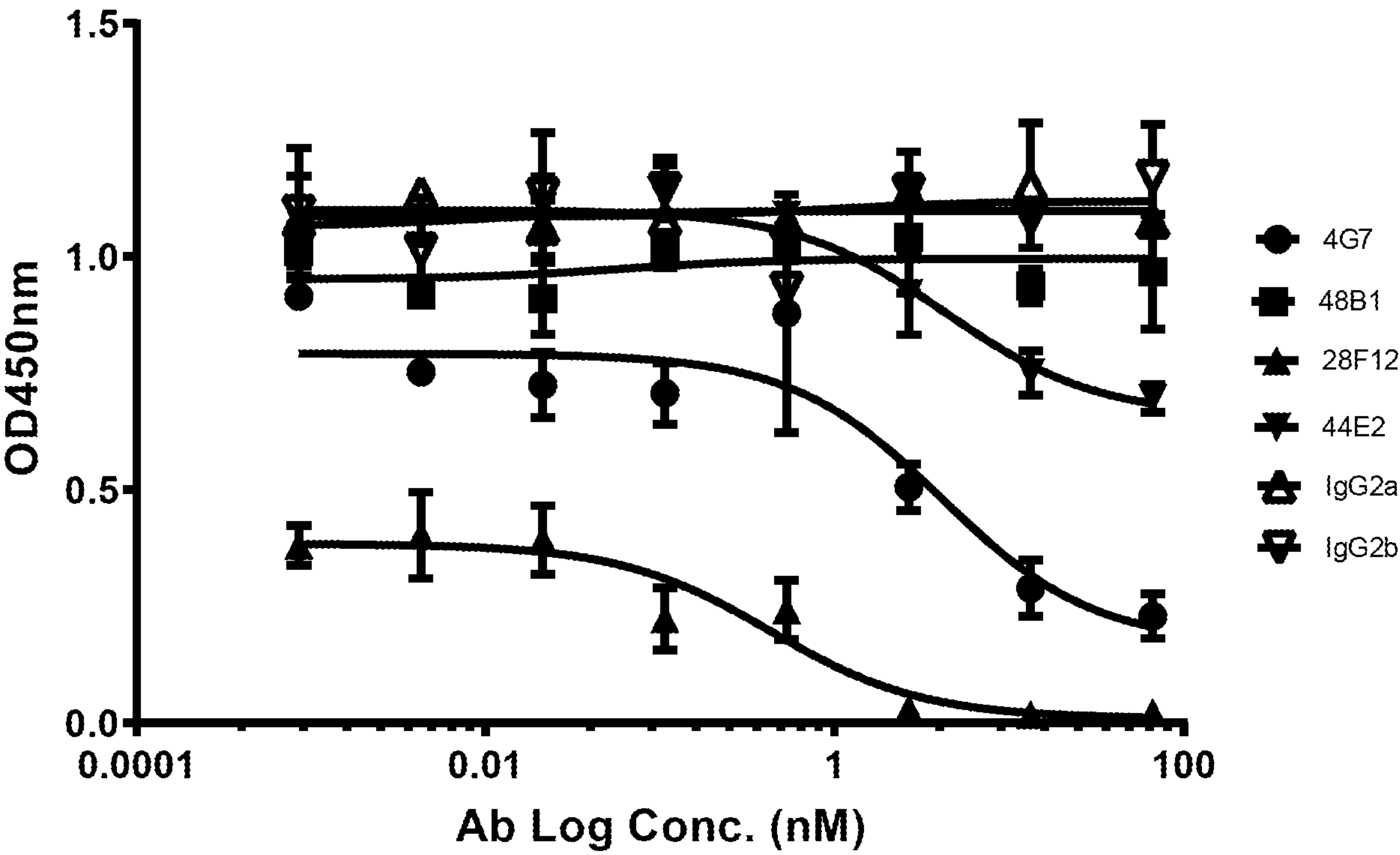


Figure 4

Induction of STAT-3 phosphorylation by IL-31

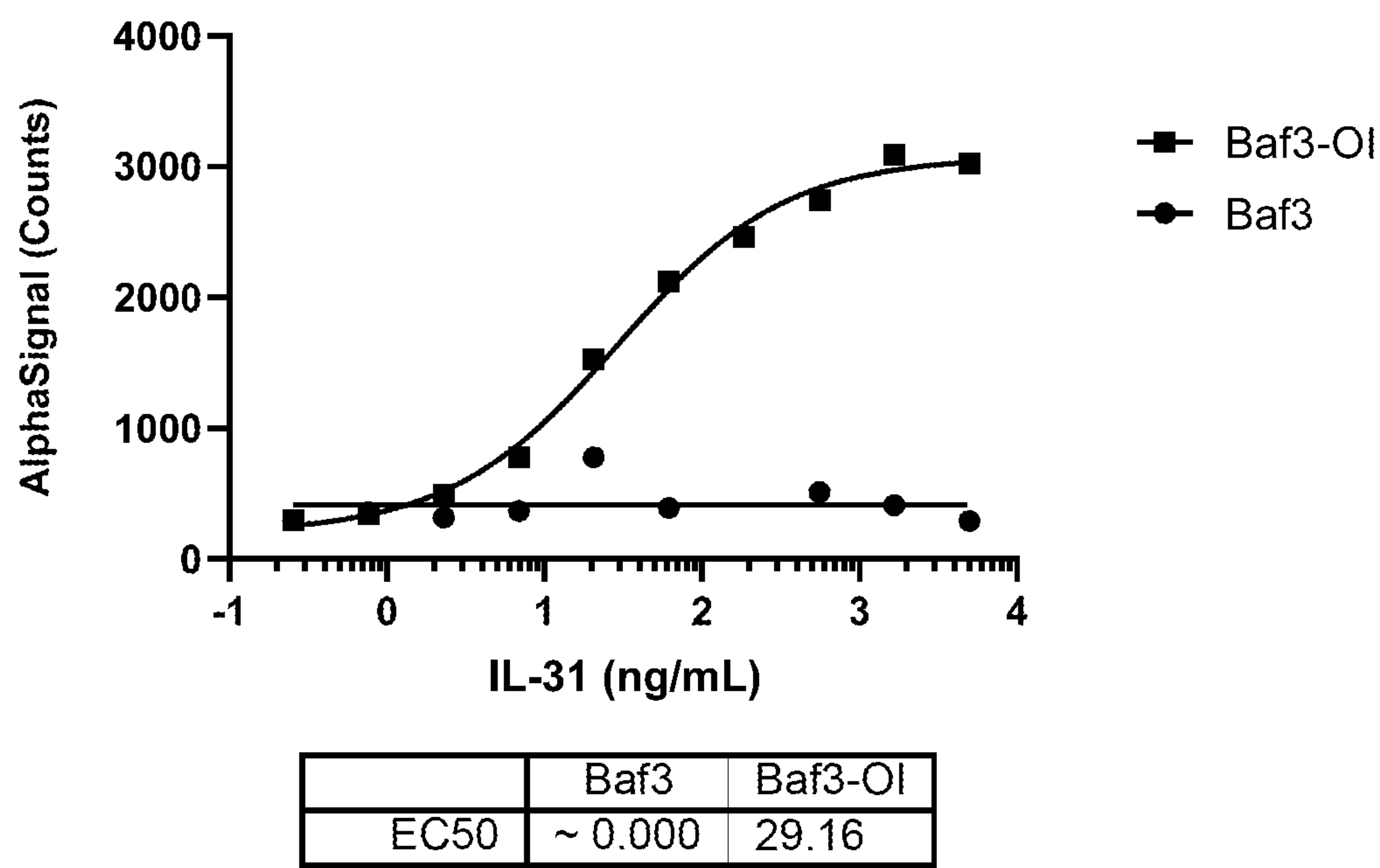


Figure 5

Inhibition of cIL-31 mediated STAT-3 phosphorylation in Ba/F3-OI cells by the selected xIL-31R1a antibodies

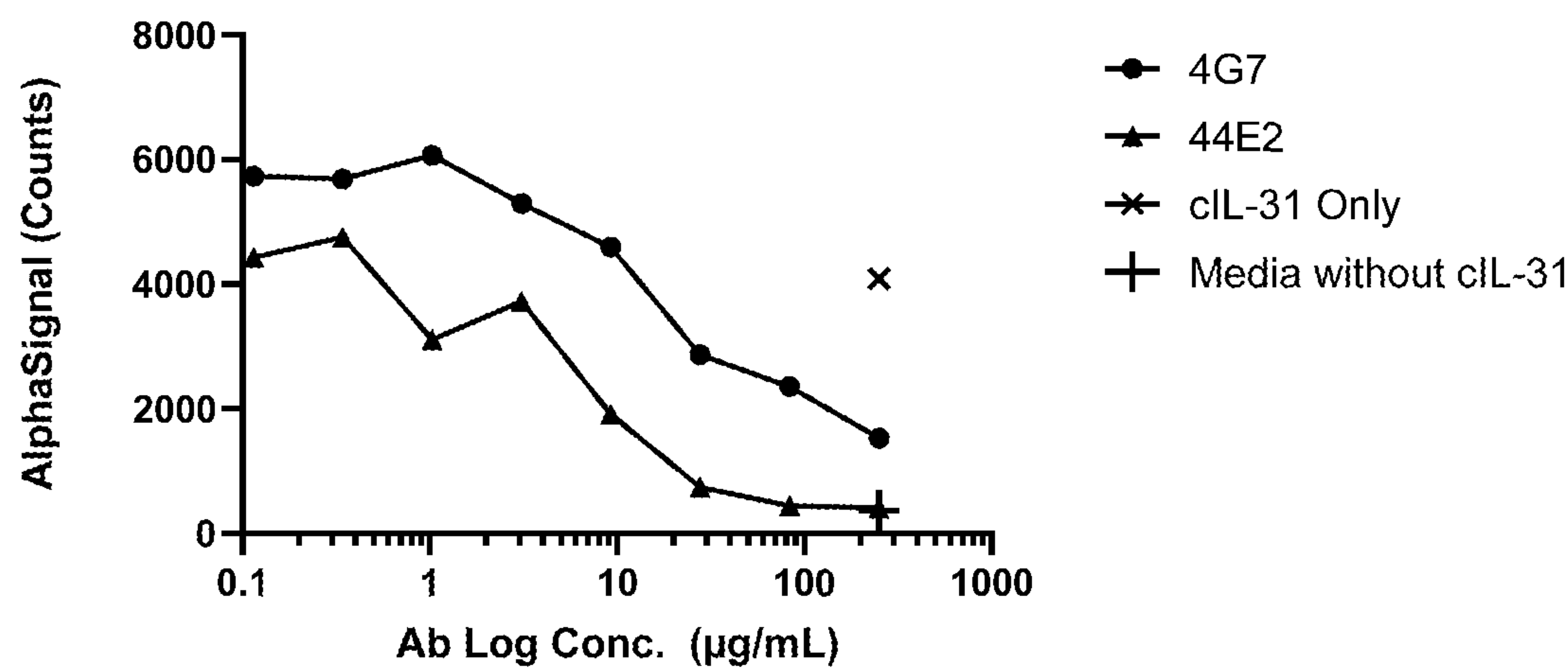


Fig 6A

Binding of caninized xIL-31R mAbs to cIL31-RA

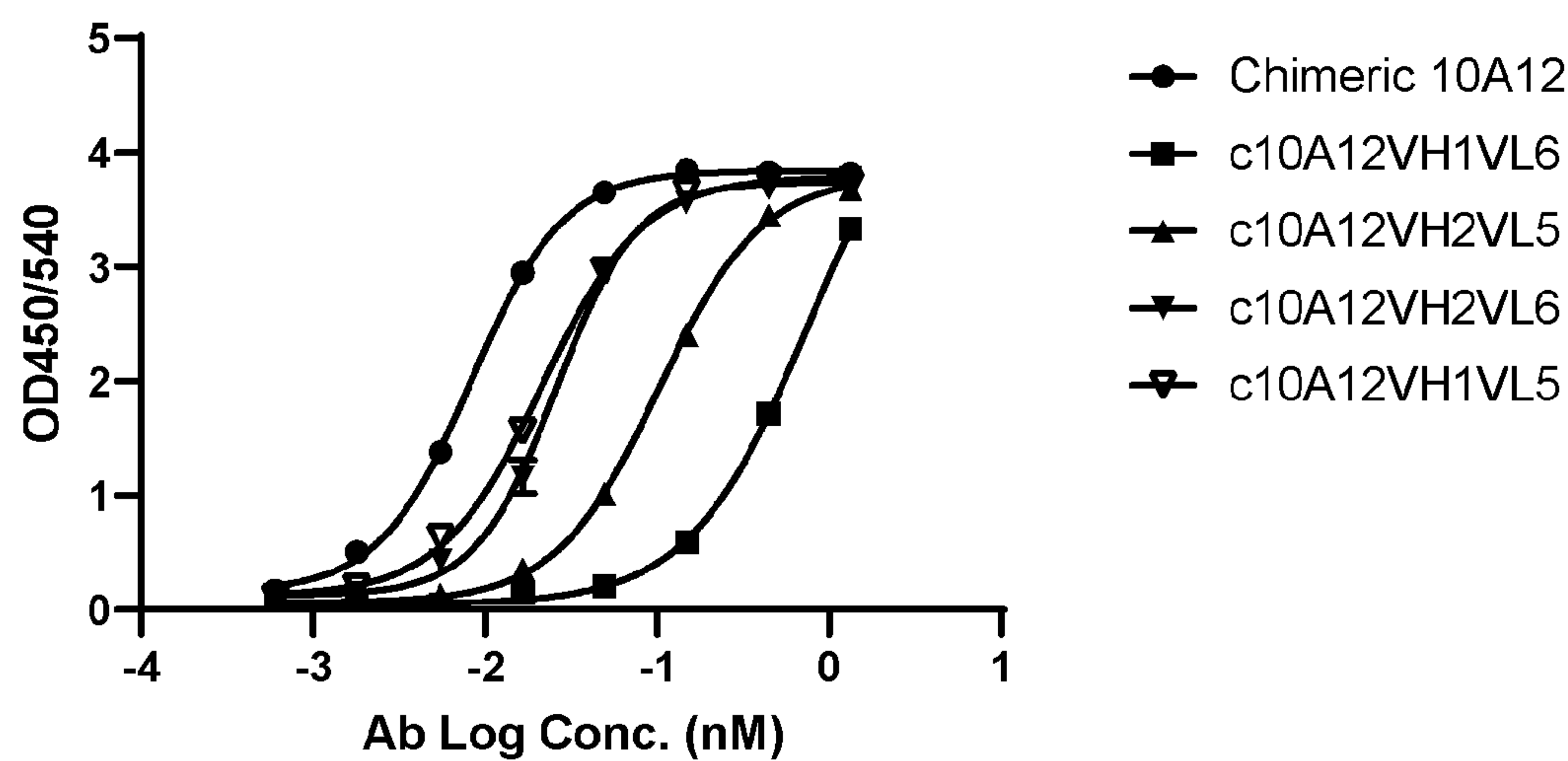


Fig 6B

Binding of caninized xIL-31R mAbs to cIL31-RA

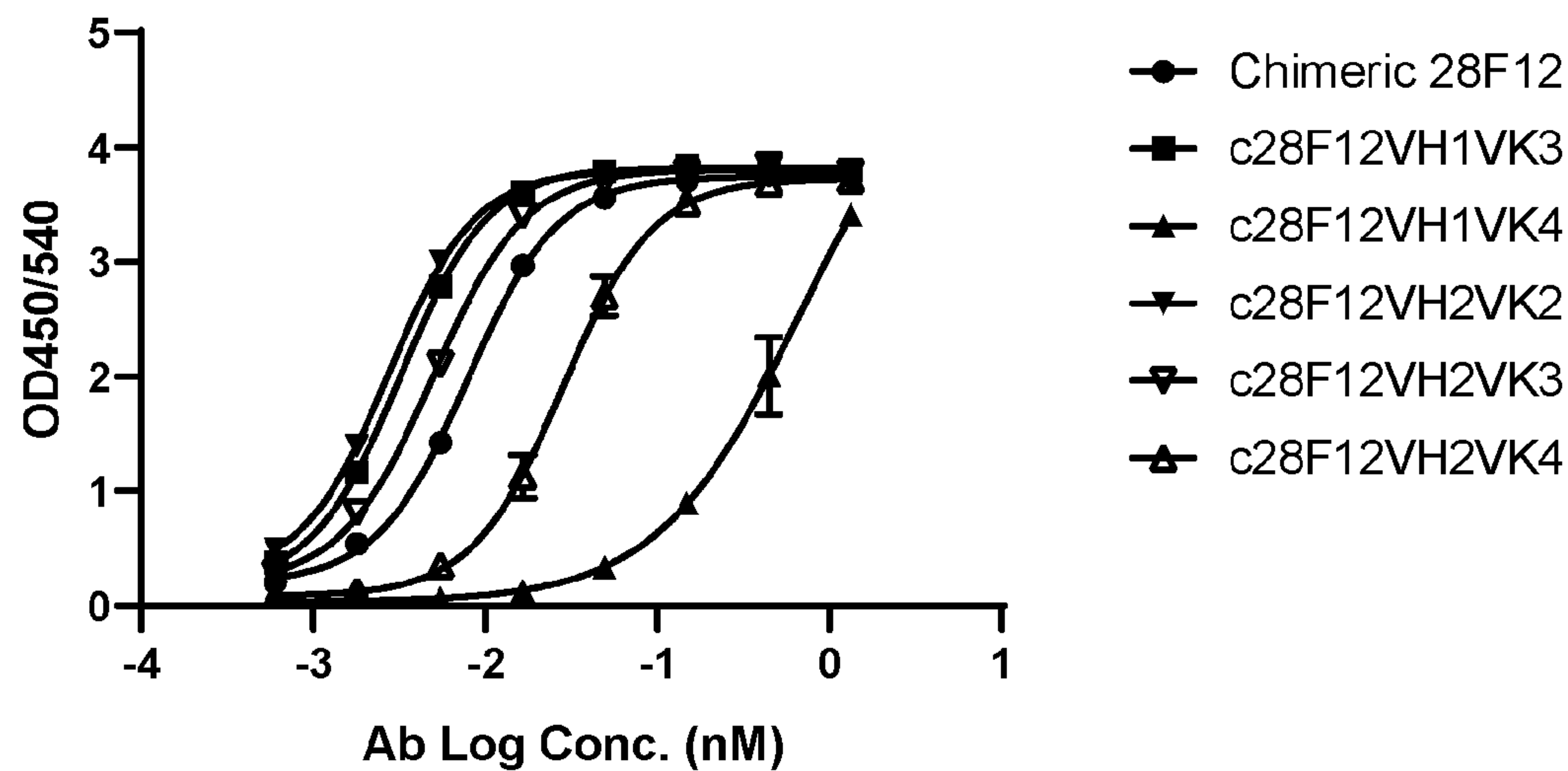


Fig 6C

Binding of caninized xIL-31R mAbs to cIL31-RA

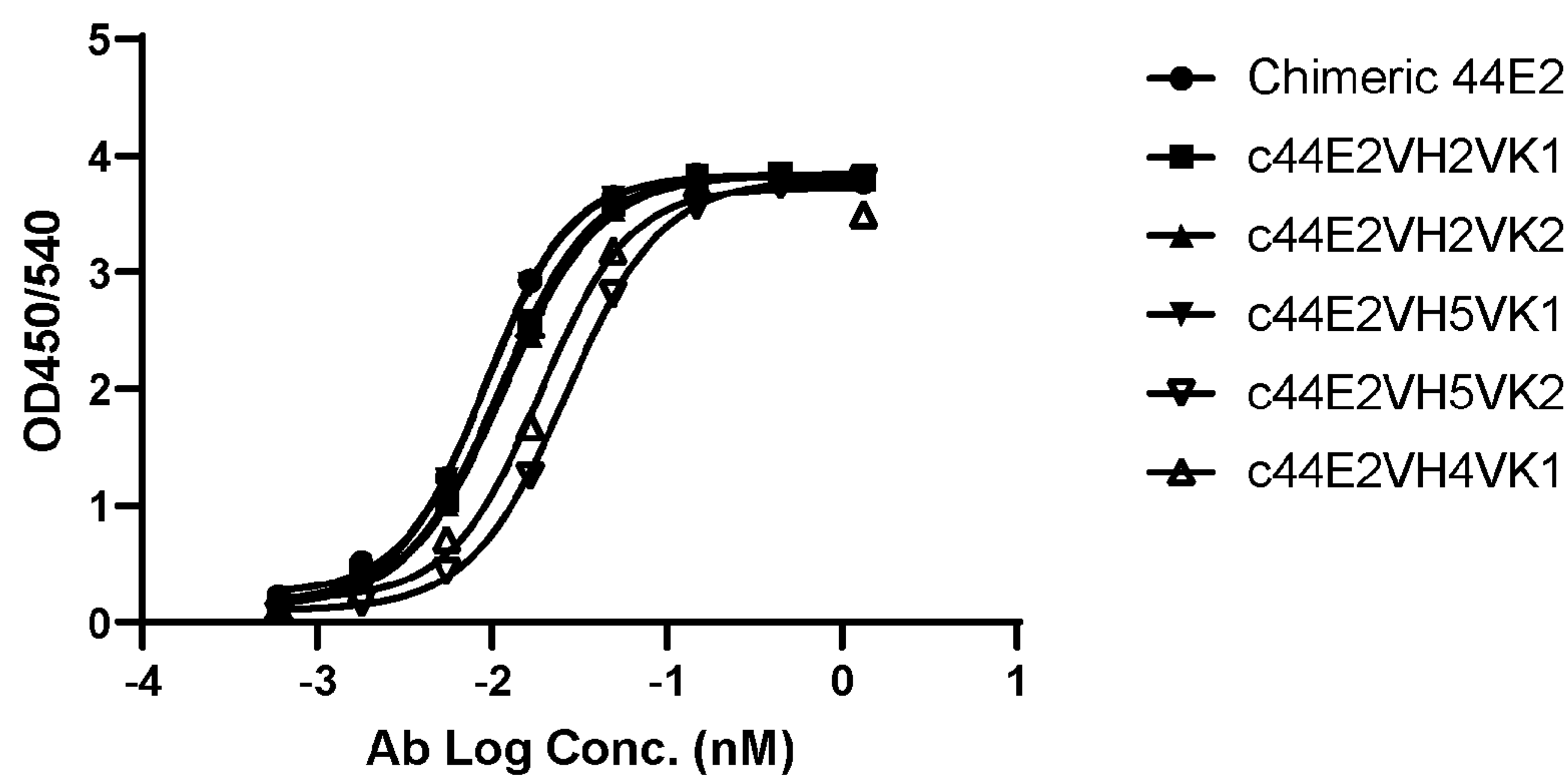


Fig 7A

**Inhibition of cIL-31 mediated STAT-3 phosphorylation
by caninized xIL-31RA mAbs to cIL-31RA**

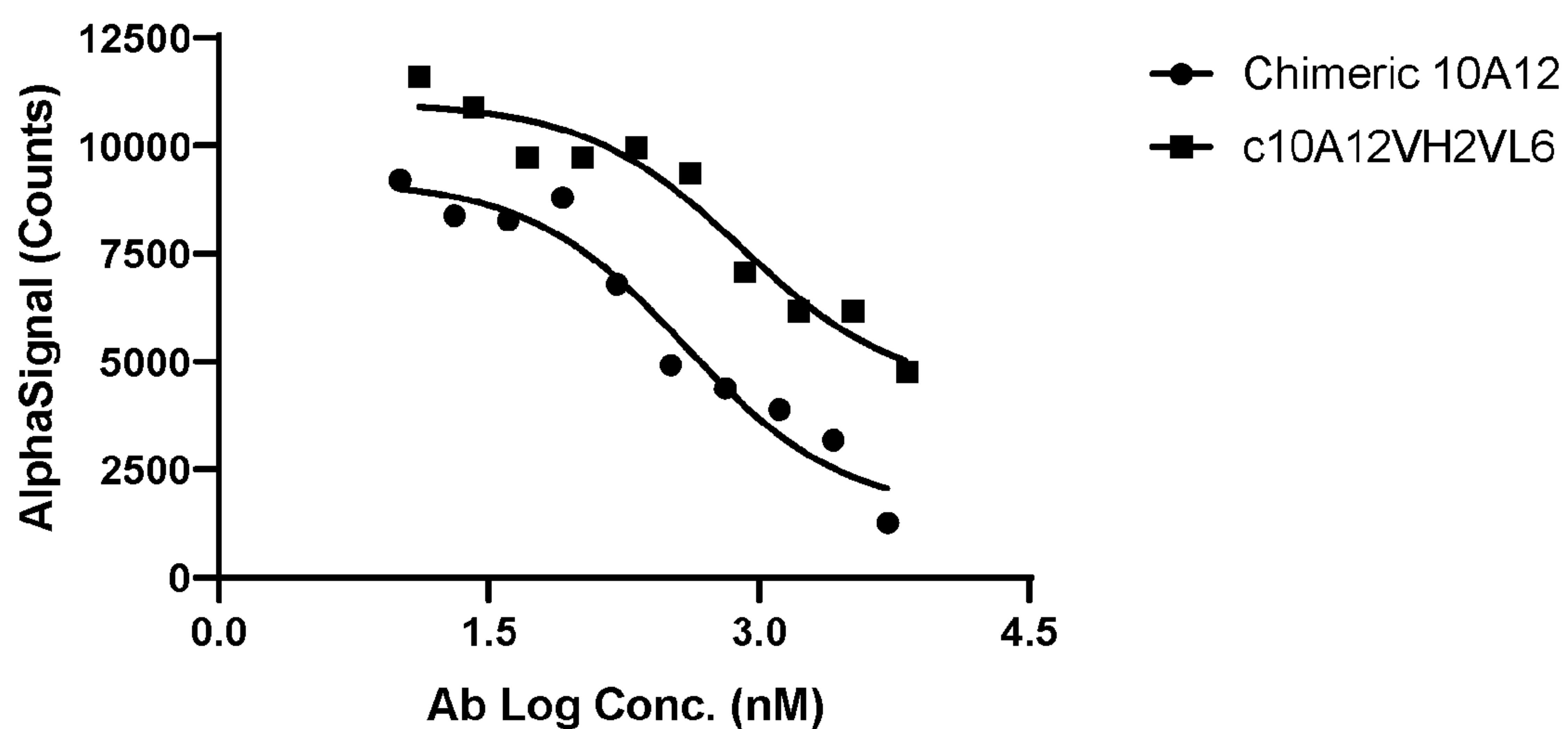


Fig 7B

**Inhibition of cIL-31 mediated STAT-3 phosphorylation
by caninized xIL-31RA mAbs to cIL-31RA**

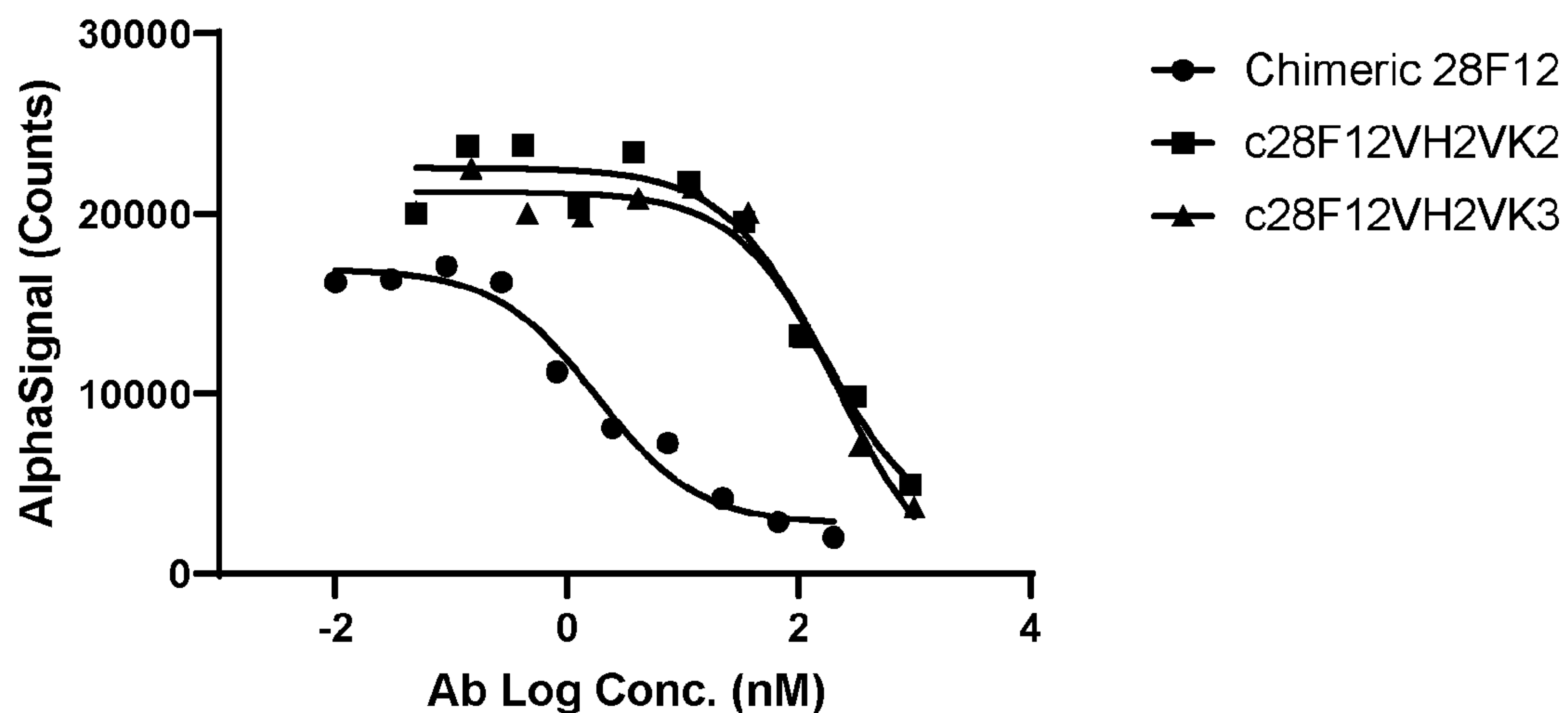


Fig 7C

Inhibition of cIL-31 mediated STAT-3 phosphorylation
by caninized xIL-31RA mAbs to cIL-31RA

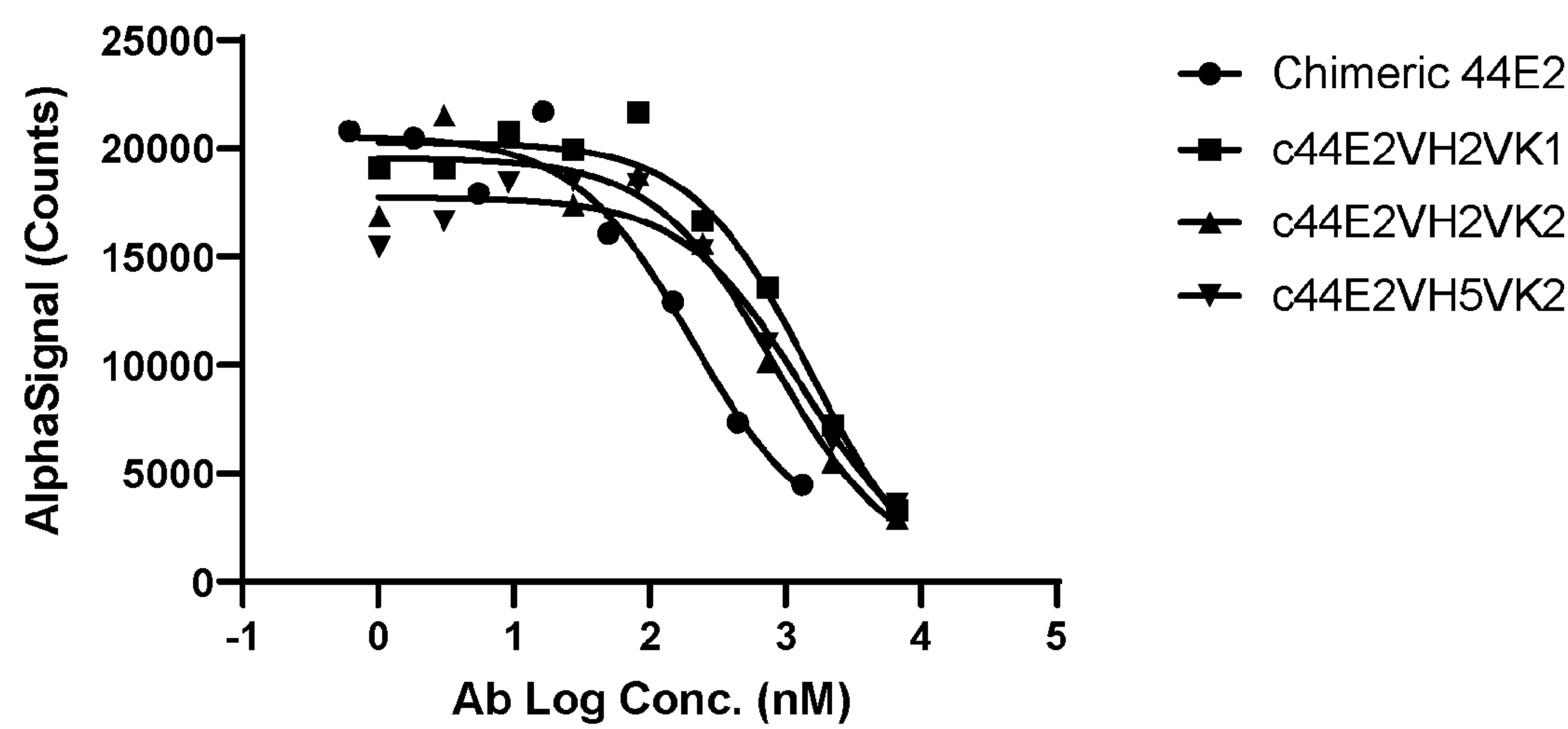


Fig. 8A

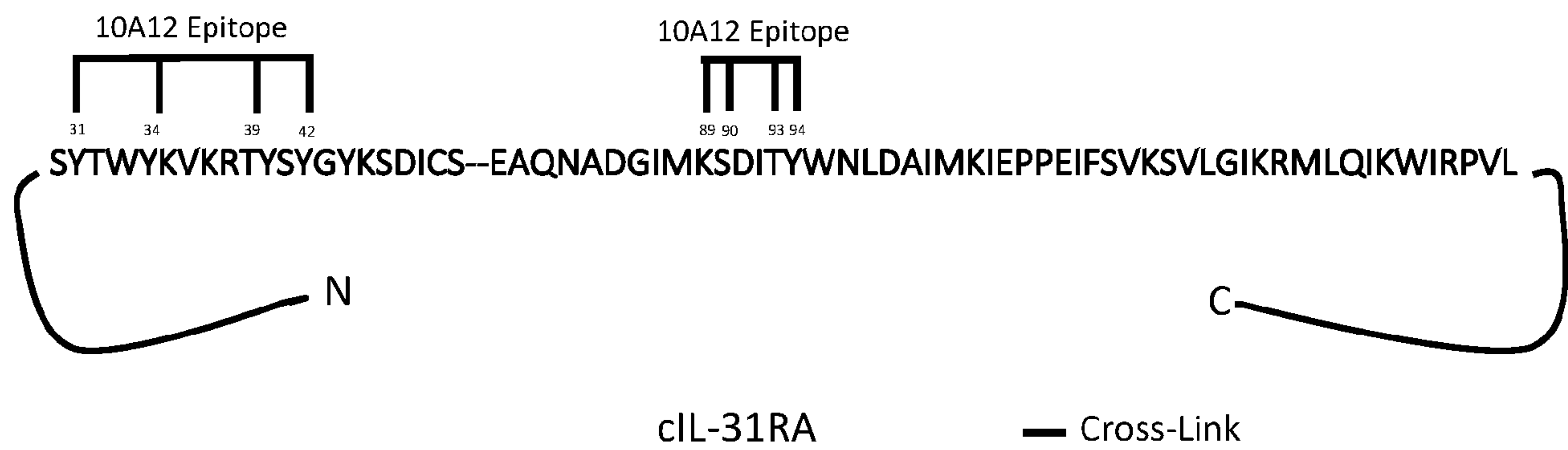


Fig. 8B

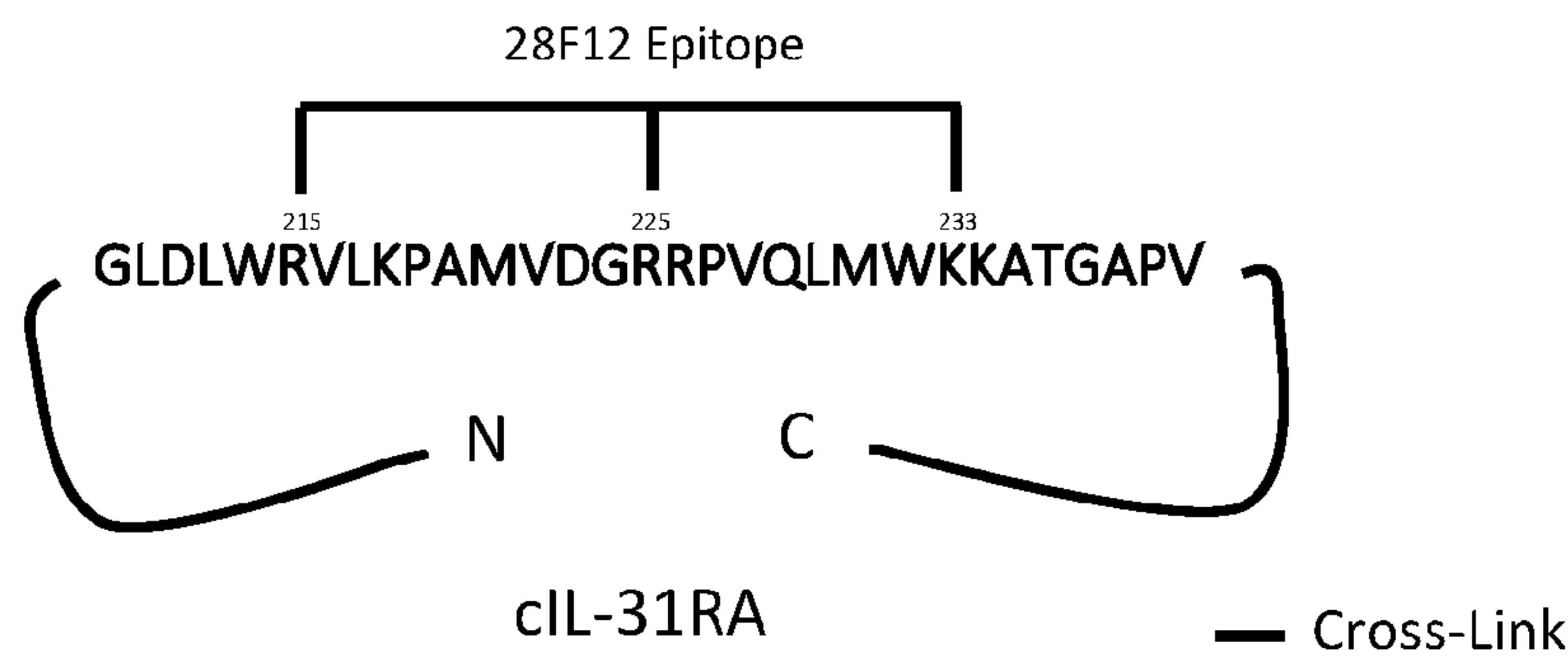
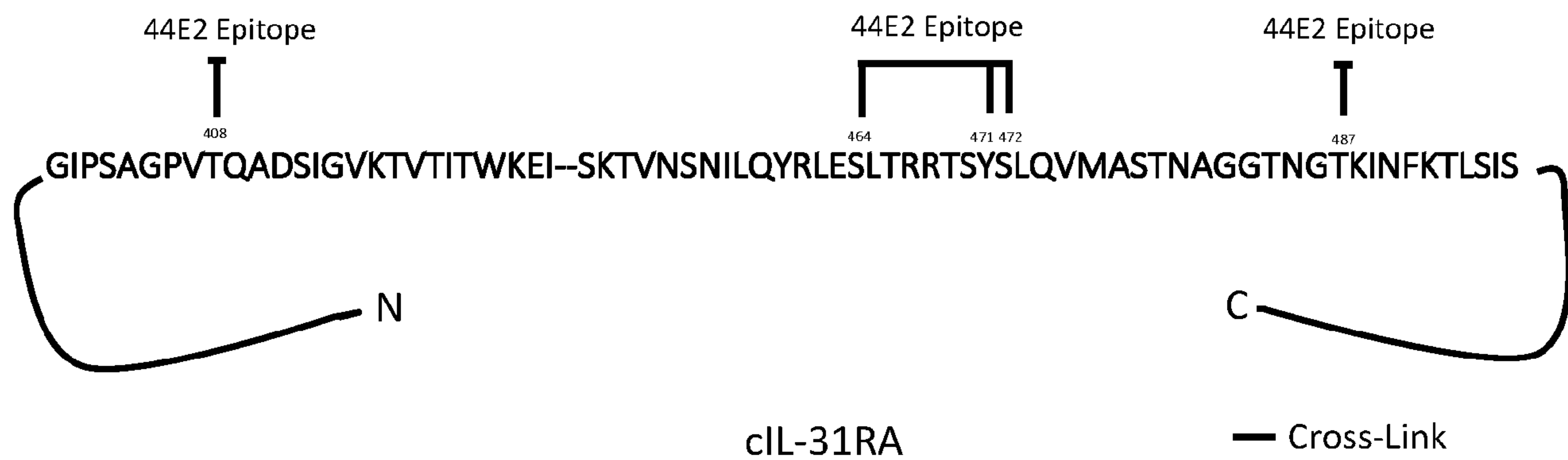


Fig. 8C



SEQUENCE LISTING

<110> INTERVET INC.
INTERVET INTERNATIONAL B.V.

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<130> 25071-WO-PCT

<140>

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<150> 63/235,258

<151> 2021-08-20

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<151> 2020-12-18

<150> 63/092,296

<151> 2020-10-15

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<160> 105

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agctgcagct tcctgcccc caccatcacc aaccccgaca actacaccat ccaggtggag	240
gcccagaacg ccgacggcat catgaagagc gacatcacct actggaacct ggacgccatc	300
atgaagatcg agcccccg gatcttcagc gtgaagagcg tgctgggcat caagagaatg	360
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ggcaccaccg aggaggaggc cccctacggc ctggacctgt ggagagtgt gaagcccgcc	660
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gccctgaacg agaagacctt ccagtgcac gaggccatgc aggcctgcct gaccaggac	960
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aactggacca tccagaagga cgagctgaag cccctgtggt gctacaacat cagcgtgtac	1140
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35 40 45

Cys Ser Thr Asp Asn Ser Thr Arg Gly Asn His Ala Ser Cys Ser Phe
50 55 60

Leu Pro Pro Thr Ile Thr Asn Pro Asp Asn Tyr Thr Ile Gln Val Glu
65 70 75 80

Ala Gln Asn Ala Asp Gly Ile Met Lys Ser Asp Ile Thr Tyr Trp Asn
85 90 95

Leu Asp Ala Ile Met Lys Ile Glu Pro Pro Glu Ile Phe Ser Val Lys
100 105 110

Ser Val Leu Gly Ile Lys Arg Met Leu Gln Ile Lys Trp Ile Arg Pro
115 120 125

Val Leu Ala Pro His Ser Ser Thr Leu Lys Tyr Thr Leu Arg Phe Arg
130 135 140

Thr Ile Asn Ser Ala Tyr Trp Met Glu Val Asn Phe Thr Lys Glu Asp
145 150 155 160

Ile Asp Arg Asp Glu Thr Tyr Asn Leu Thr Glu Leu Gln Ala Phe Thr
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Glu Tyr Val Met Thr Leu Arg Cys Ala Pro Ala Glu Ser Met Phe Trp
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Ser Gly Trp Ser Gln Glu Lys Val Gly Thr Thr Glu Glu Glu Ala Pro
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Tyr Gly Leu Asp Leu Trp Arg Val Leu Lys Pro Ala Met Val Asp Gly
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Arg Arg Pro Val Gln Leu Met Trp Lys Lys Ala Thr Gly Ala Pro Val
225 230 235 240

Leu Glu Lys Ala Leu Gly Tyr Asn Ile Trp Tyr Phe Pro Glu Asn Asn
245 250 255

Thr Asn Leu Thr Glu Thr Val Asn Thr Thr Asn Gln Thr His Glu Leu
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Tyr Leu Gly Gly Lys Thr Tyr Trp Val Tyr Val Val Ser Tyr Asn Ser
275 280 285

Leu Gly Glu Ser Pro Val Ala Thr Leu Arg Ile Pro Ala Leu Asn Glu
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Lys Thr Phe Gln Cys Ile Glu Ala Met Gln Ala Cys Leu Thr Gln Asp
305 310 315 320

Gln Leu Val Val Glu Trp Gln Ser Ser Ala Pro Glu Val Asp Thr Trp
325 330 335

Met Val Glu Trp Phe Pro Asp Val Asp Ser Glu Pro Ser Ser Phe Ser
340 345 350

Trp Glu Ser Val Ser Gln Ala Arg Asn Trp Thr Ile Gln Lys Asp Glu
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Leu Lys Pro Leu Trp Cys Tyr Asn Ile Ser Val Tyr Pro Val Leu Arg
370 375 380

Asp Arg Val Gly Gln Pro Tyr Ser Thr Gln Ala Tyr Val Gln Glu Gly
385 390 395 400

Ile Pro Ser Ala Gly Pro Val Thr Gln Ala Asp Ser Ile Gly Val Lys
405 410 415

Thr Val Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Lys Arg Asn Gly
420 425 430

Phe Ile Lys Asn Tyr Thr Ile Phe Tyr Gln Ala Glu Asp Gly Lys Glu
435 440 445

Phe Ser Lys Thr Val Asn Ser Asn Ile Leu Gln Tyr Arg Leu Glu Ser
450 455 460

Leu Thr Arg Arg Thr Ser Tyr Ser Leu Gln Val Met Ala Ser Thr Asn
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<400> 8

Met Gln Ser Asn Ser Tyr Pro Pro Thr
1 5

<210> 9

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Arg Ala Ser Ser Arg Ser Thr
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Gly

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His Gly Thr Ile Ala Ala Met Asp Tyr
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Glu Arg Asn Asn Gly Asp Ile Gly Asp Ser Tyr Val Ser
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His Thr Met Gly Tyr Phe Asp Tyr
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Lys Tyr Trp Met Thr
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Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
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Val Thr Val Ser Ser
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20 25 30

Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Asn Val
35 40 45

Ile Tyr Ala Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asn
65 70 75 80

Leu Gln Met Asp Asp Glu Ala Asp Tyr Phe Cys Gln Ser Tyr Asp Ser
85 90 95

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Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Arg Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
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Gly Arg His Gly Thr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Val Met
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Val Thr Val Ser Ser
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Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Asn Val
35 40 45

Ile Tyr Val Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asp
65 70 75 80

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20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg His Gly Thr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Val Met
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Val Thr Val Ser
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20 25 30

Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Asn Val
35 40 45

Ile Tyr Ala Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asn
65 70 75 80

Leu Gln Met Asp Asp Glu Ala Asp Tyr Phe Cys Gln Ser Tyr Asp Ser
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Asn Ile Asp Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
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20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg His Gly Thr Ile Ala Ala Met Asp Tyr Trp Gly Gln Gly Val
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Met Val Thr Val Ser Ser
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<213> *Rattus norvegicus*

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20 25 30

Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Ile Val
35 40 45

Ile Tyr Ala Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asn
65 70 75 80

Leu Gln Met Asp Asp Glu Ala Asp Tyr Phe Cys Gln Ser Tyr Asp Ser
85 90 95

Asn Ile Asp Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

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Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Phe Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Ser Ile Leu Ser
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg His Gly Thr Ile Ala Ala Met Asp Tyr Trp Gly Gln Gly Val
100 105 110

Met Val Thr Val Ser Ser
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Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Asn Val
35 40 45

Ile Tyr Ala Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asn
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20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
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Ala Arg His Thr Met Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Val Met
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Val Thr Val Ser Ser
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20 25 30

Tyr Val Ser Trp Tyr Gln Gln His Leu Gly Arg Pro Pro Ile Asn Val
35 40 45

Ile Tyr Ala Asp Asp Gln Arg Pro Ser Glu Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Thr Asn
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20 25 30

Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Asn Ser Val Leu Lys
50 55 60

Ser Arg Leu Ser Ile Ser Arg Asp Thr Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Glu Asp Thr Ala Ile Tyr Phe Cys Thr
85 90 95

Arg Arg Leu Ser Gly Tyr Asn Tyr Val Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 62
<211> 106
<212> PRT
<213> Rattus norvegicus

<400> 62
Asp Ile Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Leu Asn Cys Lys Ala Ser Gln Asn Ile Tyr Lys His
20 25 30

Leu Ala Trp Cys Gln Gln Lys Leu Gly Glu Pro Pro Asn Leu Leu Ile
35 40 45

Ser Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Tyr Tyr Ser Gly Asp Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 63
<211> 119
<212> PRT
<213> Rattus norvegicus

<400> 63
Glu Val Gln Leu Gln Gln Tyr Gly Ala Glu Leu Gly Lys Pro Gly Thr
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Val Ser Gly Tyr Asn Ile Arg Ser Thr
20 25 30

Phe Met His Trp Val Asn Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Val Asn Gly Asn Thr Ile Tyr Ser Glu Lys Phe
50 55 60

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

Met Gln Leu Ser Gln Leu Lys Ser Asp Asp Thr Ala Ile Tyr Phe Cys
85 90 95

Ala Met Phe Asn Tyr Ala Gly His Ser Gly Asp Tyr Trp Gly Gln Gly
100 105 110

Val Met Val Thr Val Ser Ser
115

<210> 64

<211> 107

<212> PRT

<213> Rattus norvegicus

<400> 64

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Val Ser Leu Gly
1 5 10 15

Asp Thr Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Gly Ile Tyr
20 25 30

Val Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Arg Arg Met Ile
35 40 45

Tyr Arg Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Val Ala Asp Tyr His Cys Leu Gln Tyr Asp Glu Tyr Pro Tyr
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 65
<211> 122
<212> PRT
<213> Rattus norvegicus

<400> 65
Glu Val Gln Leu Val Glu Ser Asp Gly Gly Leu Ala Gln Pro Gly Arg
1 5 10 15

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

Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Gly Pro Leu Thr Asp Trp Ala Pro Asn Trp Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 66
<211> 107
<212> PRT
<213> Rattus norvegicus

<400> 66

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Thr Val Thr Ile Gln Cys Gln Thr Ser Glu Asp Ile Tyr Ser Gly
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Phe Leu Ile
35 40 45

Tyr Gly Ala Ser Arg Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Ser Ser Met Gln Thr
65 70 75 80

Glu Asp Glu Gly Val Tyr Phe Cys Gln Gln Gly Leu Lys Tyr Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 67

<211> 121

<212> PRT

<213> Rattus norvegicus

<400> 67

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

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

Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Asn Thr Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Gly Pro Thr Thr Val Val Gly Gly Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 68

<211> 107

<212> PRT

<213> Rattus norvegicus

<400> 68

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Met Ser Ile Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Val Leu Ile
35 40 45

Tyr Arg Ala Ser Ser Arg Ser Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 69
<211> 121
<212> PRT
<213> Rattus norvegicus

<400> 69
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

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

Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Asn Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Gly Pro Thr Thr Val Val Gly Gly Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 70
<211> 107
<212> PRT
<213> Rattus norvegicus

<400> 70
Asp Ile Val Met Thr Gln Ser Pro Thr Ser Met Ser Ile Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Arg Pro Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 71

<211> 122

<212> PRT

<213> Rattus norvegicus

<400> 71

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

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

Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Asn Thr Gly Gly Ser Thr Phe Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Gly Pro Asp Tyr Gly Gly His Leu Asn Trp Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 72

<211> 107

<212> PRT

<213> Rattus norvegicus

<400> 72

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Met Ser Ile Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Cys Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 73

<211> 122

<212> PRT

<213> Rattus norvegicus

<400> 73

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

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

Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Asn Thr Gly Gly Ser Ser Tyr Tyr Ser Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Glu Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Gly Pro Asp Tyr Gly Gly His Leu Asn Trp Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 74

<211> 107

<212> PRT

<213> Rattus norvegicus

<400> 74

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Met Ser Ile Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

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

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 75

<211> 122

<212> PRT

<213> Rattus norvegicus

<400> 75

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

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

Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Asn Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Gly Pro Asp Tyr Gly Gly His Leu Asn Trp Phe Val Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 76

<211> 107

<212> PRT

<213> Rattus norvegicus

<400> 76

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Met Ser Ile Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 77

<211> 215

<212> PRT

<213> Canis lupus familiaris

<400> 77

Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr
1 5 10 15

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Leu
20 25 30

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
35 40 45

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Asn Gly
50 55 60

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
65 70 75 80

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
85 90 95

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
100 105 110

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
115 120 125

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

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
145 150 155 160

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
165 170 175

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
180 185 190

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
195 200 205

Leu Ser His Ser Pro Gly Lys
210 215

<210> 78
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> source
<223> /note="Modified canine"

<400> 78
Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr
1 5 10 15

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu
20 25 30

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
35 40 45

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly
50 55 60

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
65 70 75 80

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
85 90 95

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
100 105 110

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
115 120 125

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

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
145 150 155 160

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
165 170 175

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
180 185 190

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
195 200 205

Leu Ser His Ser Pro Gly
210

<210> 79
<211> 17
<212> PRT
<213> Canis lupus familiaris

<400> 79
Phe Asn Glu Cys Arg Cys Thr Asp Thr Pro Pro Cys Pro Val Pro Glu
1 5 10 15

Pro

<210> 80
<211> 22
<212> PRT
<213> Canis lupus familiaris

<400> 80
Pro Lys Arg Glu Asn Gly Arg Val Pro Arg Pro Pro Asp Cys Pro Lys
1 5 10 15

Cys Pro Ala Pro Glu Met
20

<210> 81

<211> 20
<212> PRT
<213> Canis lupus familiaris

<400> 81
Ala Lys Glu Cys Glu Cys Lys Cys Asn Cys Asn Asn Cys Pro Cys Pro
1 5 10 15

Gly Cys Gly Leu
20

<210> 82
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> source
<223> /note="Modified canine"

<400> 82
Pro Lys Glu Ser Thr Cys Lys Cys Ile Pro Pro Cys Pro Val Pro Glu
1 5 10 15

Ser

<210> 83
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 83
Gln Pro Val Leu Thr Gln Pro Pro Ser Leu Ser Ala Ser Leu Gly Thr
1 5 10 15

Thr Ala Arg Leu Thr Cys Glu Arg Ser Ser Gly Asp Ile Gly Asp Ser
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Arg Asp Leu
35 40 45

Leu Tyr Val Asp Asp Gln Arg Pro Ser Gly Val Ser Lys Ser Phe Ser
50 55 60

Gly Ser Lys Asp Thr Ser Ala Asn Ala Gly Leu Leu Leu Ile Ser Gly
65 70 75 80

Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
85 90 95

Asn Ile Asp Gly Pro Val Phe Gly Gly Gly Thr His Leu Thr Val Leu
100 105 110

Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
115 120 125

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

Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
145 150 155 160

Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
180 185 190

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

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser

210

215

<210> 84

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> source

<223> /note="Caninized rat"

<400> 84

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Lys His Gly Thr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val Phe Pro Leu
115 120 125

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

Leu Val Ser Gly Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro Ser Ser Arg
180 185 190

Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro Ala Ser Lys
195 200 205

Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly Arg Val Pro
210 215 220

Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met Leu Gly Gly
225 230 235 240

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

Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu Asp Pro Glu
260 265 270

Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys Gln Met Gln
275 280 285

Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu Lys Gly Lys
305 310 315 320

Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser Pro Ile Glu
325 330 335

Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro Ser Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr Val Ser Leu
355 360 365

Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp Val Glu Trp
370 375 380

Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg Thr Thr Pro
385 390 395 400

Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Ser
405 410 415

Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile Cys Ala Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser His
435 440 445

Ser Pro Gly Lys
450

<210> 85

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 85

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

20

25

30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Val
 35 40 45

Ala Ser Ile Ser Thr Gly Gly Gly Asn Thr Tyr Tyr Arg Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Ala Arg His Gly Thr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val Phe Pro Leu
 115 120 125

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

Leu Val Ser Gly Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160

Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val Leu Gln Ser
 165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro Ser Ser Arg
 180 185 190

Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro Ala Ser Lys
 195 200 205

Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly Arg Val Pro
 210 215 220

Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met Leu Gly Gly
225 230 235 240

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

Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu Asp Pro Glu
260 265 270

Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys Gln Met Gln
275 280 285

Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu Lys Gly Lys
305 310 315 320

Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser Pro Ile Glu
325 330 335

Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro Ser Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr Val Ser Leu
355 360 365

Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp Val Glu Trp
370 375 380

Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg Thr Thr Pro
385 390 395 400

Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Ser
405 410 415

Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile Cys Ala Val

420

425

430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser His
 435 440 445

Ser Pro Gly Lys
 450

<210> 86

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
 polypeptide"

<400> 86

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

Arg Val Thr Ile Ser Cys Glu Arg Ser Ser Gly Asp Ile Gly Asp Ser
 20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Ser Leu Leu
 35 40 45

Ile Tyr Val Asp Asp Gln Arg Pro Ser Gly Val Pro Glu Arg Phe Ser
 50 55 60

Gly Ser Lys Ser Gly Ser Ser Asn Ser Ala Thr Leu Thr Ile Thr Gly
 65 70 75 80

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
 85 90 95

Asn Ile Asp Gly Pro Val Phe Gly Gly Gly Thr His Leu Thr Val Leu
 100 105 110

Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
115 120 125

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

Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
145 150 155 160

Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
180 185 190

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

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
210 215

<210> 87

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 87

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

Thr Ala Arg Leu Thr Cys Glu Arg Ser Ser Gly Asp Ile Gly Asp Ser
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Arg Asp Val
35 40 45

Ile Tyr Val Asp Asp Gln Arg Pro Ser Glu Val Ser Lys Ser Phe Ser
50 55 60

Gly Ser Lys Asp Thr Ser Ala Asn Ala Gly Leu Leu Leu Ile Ser Gly
65 70 75 80

Leu Gln Pro Glu Asp Glu Ala Asp Tyr Phe Cys Gln Ser Tyr Asp Ser
85 90 95

Asn Ile Asp Gly Pro Val Phe Gly Gly Gly Thr His Leu Thr Val Leu
100 105 110

Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
115 120 125

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

Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
145 150 155 160

Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
180 185 190

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

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
210 215

<210> 88

<211> 457

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 88

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

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

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Val
35 40 45

Ala Thr Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Lys Gly Pro Leu Thr Asp Trp Ala Pro Asn Trp Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr
130 135 140

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

Val Ser Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ser Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr
180 185 190

Val Pro Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala
195 200 205

His Pro Ala Ser Lys Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu
210 215 220

Asn Gly Arg Val Pro Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro
225 230 235 240

Glu Met Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Ala Leu Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp
275 280 285

Gly Lys Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe
290 295 300

Ala Gly Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp
305 310 315 320

Trp Leu Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu
325 330 335

Pro Ser Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His
340 345 350

Gln Pro Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys
355 360 365

Asn Thr Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp
370 375 380

Ile Asp Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys
385 390 395 400

Tyr Arg Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu
405 410 415

Tyr Ser Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr
420 425 430

Phe Ile Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Glu Ser Leu Ser His Ser Pro Gly Lys
450 455

<210> 89

<211> 457

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 89

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Val
35 40 45

Ala Thr Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

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

Ala Leu Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp
275 280 285

Gly Lys Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe
290 295 300

Ala Gly Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp
305 310 315 320

Trp Leu Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu
325 330 335

Pro Ser Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His
340 345 350

Gln Pro Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys
355 360 365

Asn Thr Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp
370 375 380

Ile Asp Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys
385 390 395 400

Tyr Arg Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu
405 410 415

Tyr Ser Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr
420 425 430

Phe Ile Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Glu Ser Leu Ser His Ser Pro Gly Lys
450 455

<210> 90

<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 90
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Thr Ala Ser Ile Ser Cys Gln Thr Ser Glu Asp Ile Tyr Ser Gly
20 25 30

Leu Ala Trp Phe Arg Gln Lys Pro Gly Gln Ser Pro Gln Arg Leu Ile
35 40 45

Tyr Gly Ala Ser Arg Leu Glu Asp Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Thr Val Glu Ala
65 70 75 80

Asp Asp Thr Gly Val Tyr Tyr Cys Gln Gln Gly Leu Lys Tyr Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln
100 105 110

Pro Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly
115 120 125

Ser Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile
130 135 140

Asn Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser
180 185 190

Cys Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe
195 200 205

Gln Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 91

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 91

Glu Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Leu Ser Gln Glu
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Gln Thr Ser Glu Asp Ile Tyr Ser Gly
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Arg Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Ser Phe Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Gly Leu Lys Tyr Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln
100 105 110

Pro Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly
115 120 125

Ser Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile
130 135 140

Asn Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser
180 185 190

Cys Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe
195 200 205

Gln Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 92

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 92

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

Glu Lys Val Thr Ile Thr Cys Gln Thr Ser Glu Asp Ile Tyr Ser Gly
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Arg Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Ser Phe Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Gly Leu Lys Tyr Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln
100 105 110

Pro Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly
115 120 125

Ser Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile
130 135 140

Asn Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser
180 185 190

Cys Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe
195 200 205

Gln Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 93
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 93
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Thr Ala Ser Ile Ser Cys Gln Thr Ser Glu Asp Ile Tyr Ser Gly
20 25 30

Leu Ala Trp Phe Arg Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Arg Leu Glu Asp Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Thr Val Glu Ala
65 70 75 80

Asp Asp Thr Gly Val Tyr Phe Cys Gln Gln Gly Leu Lys Tyr Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln
100 105 110

Pro Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly
115 120 125

Ser Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile
130 135 140

Asn Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser
180 185 190

Cys Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe
195 200 205

Gln Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 94

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 94

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Phe Thr Phe Ser Ser Asn
20 25 30

Gly Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Asn Ser Val Leu Lys
50 55 60

Ser Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Lys Arg Leu Ser Gly Tyr Asn Tyr Val Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr Val Ala
130 135 140

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

Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro
180 185 190

Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro
195 200 205

Ala Ser Lys Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly
210 215 220

Arg Val Pro Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met
225 230 235 240

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

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu
260 265 270

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
275 280 285

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly
290 295 300

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
305 310 315 320

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
325 330 335

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
340 345 350

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
355 360 365

Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp
370 375 380

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
385 390 395 400

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
405 410 415

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
420 425 430

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
435 440 445

Leu Ser His Ser Pro Gly Lys
450 455

<210> 95

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 95

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

Thr Leu Ser Leu Thr Cys Val Val Ser Gly Gly Ser Val Thr Ser Asn
20 25 30

Gly Val Ser Trp Ile Arg Gln Arg Pro Gly Arg Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Asn Ser Val Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Ala Asp Thr Ala Lys Asn Gln Phe Ser Leu
65 70 75 80

Gln Leu Ser Ser Met Thr Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Arg Leu Ser Gly Tyr Asn Tyr Val Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr Val Ala
130 135 140

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

Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro

180

185

190

Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro
 195 200 205

Ala Ser Lys Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly
 210 215 220

Arg Val Pro Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met
 225 230 235 240

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

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu
 260 265 270

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
 275 280 285

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly
 290 295 300

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
 305 310 315 320

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
 325 330 335

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
 340 345 350

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
 355 360 365

Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp
 370 375 380

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
385 390 395 400

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
405 410 415

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
420 425 430

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
435 440 445

Leu Ser His Ser Pro Gly Lys
450 455

<210> 96

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 96

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Asn
20 25 30

Gly Val Ser Trp Ile Arg Gln Arg Pro Gly Arg Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Asn Ser Val Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Ala Asp Thr Ala Lys Asn Gln Phe Ser Leu
65 70 75 80

Gln Leu Ser Ser Met Thr Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Arg Leu Ser Gly Tyr Asn Tyr Val Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr Val Ala
130 135 140

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

Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro
180 185 190

Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro
195 200 205

Ala Ser Lys Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly
210 215 220

Arg Val Pro Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met
225 230 235 240

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

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu
260 265 270

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
275 280 285

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly
290 295 300

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
305 310 315 320

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
325 330 335

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
340 345 350

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
355 360 365

Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp
370 375 380

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
385 390 395 400

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
405 410 415

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
420 425 430

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
435 440 445

Leu Ser His Ser Pro Gly Lys
450 455

<210> 97

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 97

Glu Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Leu Ser Gln Glu
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Tyr Lys His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Ser Phe Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Gly Asp Thr
85 90 95

Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln Pro
100 105 110

Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly Ser
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile Asn
130 135 140

Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr

165

170

175

Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser Cys
 180 185 190

Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe Gln
 195 200 205

Arg Ser Glu Cys Gln Arg Val Asp
 210 215

<210> 98

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
 polypeptide"

<400> 98

Glu Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Leu Ser Gln Glu
 1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Tyr Lys His
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Ser Phe Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Tyr Tyr Ser Gly Asp Thr
 85 90 95

Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln Pro
100 105 110

Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly Ser
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile Asn
130 135 140

Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
165 170 175

Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser Cys
180 185 190

Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe Gln
195 200 205

Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 99

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 99

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

Glu Ser Val Ser Ile Asn Cys Lys Ala Ser Gln Asn Ile Tyr Lys His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Glu Arg Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Leu Gln Ala
65 70 75 80

Glu Asp Val Gly Asp Tyr Tyr Cys Gln Gln Tyr Tyr Ser Gly Asp Thr
85 90 95

Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg Asn Asp Ala Gln Pro
100 105 110

Ala Val Tyr Leu Phe Gln Pro Ser Pro Asp Gln Leu His Thr Gly Ser
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr Pro Lys Asp Ile Asn
130 135 140

Val Lys Trp Lys Val Asp Gly Val Ile Gln Asp Thr Gly Ile Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
165 170 175

Leu Thr Met Ser Ser Thr Glu Tyr Leu Ser His Glu Leu Tyr Ser Cys
180 185 190

Glu Ile Thr His Lys Ser Leu Pro Ser Thr Leu Ile Lys Ser Phe Gln
195 200 205

Arg Ser Glu Cys Gln Arg Val Asp
210 215

<210> 100

<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 100
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Phe Ser Leu Thr Ser Asn
20 25 30

Gly Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gln Trp Ile
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Asn Ser Val Leu Lys
50 55 60

Ser Arg Leu Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Arg Leu Ser Gly Tyr Asn Tyr Val Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Thr Ala Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Cys Gly Ser Thr Ser Gly Ser Thr Val Ala
130 135 140

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

Trp Asn Ser Gly Ser Leu Thr Ser Gly Val His Thr Phe Pro Ser Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Met Val Thr Val Pro
180 185 190

Ser Ser Arg Trp Pro Ser Glu Thr Phe Thr Cys Asn Val Ala His Pro
195 200 205

Ala Ser Lys Thr Lys Val Asp Lys Pro Val Pro Lys Arg Glu Asn Gly
210 215 220

Arg Val Pro Arg Pro Pro Asp Cys Pro Lys Cys Pro Ala Pro Glu Met
225 230 235 240

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

Leu Leu Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Leu
260 265 270

Asp Pro Glu Asp Pro Glu Val Gln Ile Ser Trp Phe Val Asp Gly Lys
275 280 285

Gln Met Gln Thr Ala Lys Thr Gln Pro Arg Glu Glu Gln Phe Ala Gly
290 295 300

Thr Tyr Arg Val Val Ser Val Leu Pro Ile Gly His Gln Asp Trp Leu
305 310 315 320

Lys Gly Lys Gln Phe Thr Cys Lys Val Asn Asn Lys Ala Leu Pro Ser
325 330 335

Pro Ile Glu Arg Thr Ile Ser Lys Ala Arg Gly Gln Ala His Gln Pro
340 345 350

Ser Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Leu Ser Lys Asn Thr
355 360 365

Val Ser Leu Thr Cys Leu Ile Lys Asp Phe Phe Pro Pro Asp Ile Asp
370 375 380

Val Glu Trp Gln Ser Asn Gly Gln Gln Glu Pro Glu Ser Lys Tyr Arg
385 390 395 400

Thr Thr Pro Pro Gln Leu Asp Glu Asp Gly Ser Tyr Phe Leu Tyr Ser
405 410 415

Lys Leu Ser Val Asp Lys Ser Arg Trp Gln Arg Gly Asp Thr Phe Ile
420 425 430

Cys Ala Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
435 440 445

Leu Ser His Ser Pro Gly Lys
450 455

<210> 101

<211> 31

<212> PRT

<213> Canis lupus familiaris

<400> 101

Gly Leu Asp Leu Trp Arg Val Leu Lys Pro Ala Met Val Asp Gly Arg
1 5 10 15

Arg Pro Val Gln Leu Met Trp Lys Lys Ala Thr Gly Ala Pro Val
20 25 30

<210> 102

<211> 26

<212> PRT

<213> Canis lupus familiaris

<400> 102

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1 5 10 15

Lys Thr Val Thr Ile Thr Trp Lys Glu Ile
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<210> 103

<211> 48

<212> PRT

<213> Canis lupus familiaris

<400> 103

Ser Lys Thr Val Asn Ser Asn Ile Leu Gln Tyr Arg Leu Glu Ser Leu
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Thr Arg Arg Thr Ser Tyr Ser Leu Gln Val Met Ala Ser Thr Asn Ala
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Gly Gly Thr Asn Gly Thr Lys Ile Asn Phe Lys Thr Leu Ser Ile Ser
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<210> 104

<211> 21

<212> PRT

<213> Canis lupus familiaris

<400> 104

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1 5 10 15

Ser Asp Ile Cys Ser
20

<210> 105

<211> 51

<212> PRT

<213> Canis lupus familiaris

<400> 105

Glu Ala Gln Asn Ala Asp Gly Ile Met Lys Ser Asp Ile Thr Tyr Trp
1 5 10 15

Asn Leu Asp Ala Ile Met Lys Ile Glu Pro Pro Glu Ile Phe Ser Val
20 25 30

Lys Ser Val Leu Gly Ile Lys Arg Met Leu Gln Ile Lys Trp Ile Arg
35 40 45

Pro Val Leu
50