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(54) Title: ANTI-IL-17RA IMMUNOGLOBULIN SINGLE HEAVY VARIABLE DOMAIN ANTIBODIES

(57) Abstract: Binding molecules that bind specifically to IL-17RA. The binding molecules are useful in the treatment of disease,for example psoriasis.

ANTI-IL-17RA IMMUNOGLOBULIN SINGLE HEAVY VARIABLE DOMAIN ANTIBODIES

Field of the Invention

The invention relates to IL-17RA binding molecules, and the use of such binding molecule in the treatment of disease.

Introduction

Psoriasis is a chronic relapsing and remitting inflammatory skin disease affecting 2-3% of the world's population (~125m sufferers) that causes significant morbidity and decreased quality of life, largely due to clinical flare-ups and disfiguring lesions in visible areas of the skin, systemic manifestations and drug-related side effects. The common form of the disease, termed 'plaque psoriasis vulgaris', is observed in more than 80% of patients and is characterized by erythematous scaly plaques (typically on elbows, knees, scalp and buttocks) which can vary in size from minimal to the involvement of the entire skin surface.

Depending on the degree of body surface area (BSA) involvement, psoriasis can be categorised into mild (<3% BSA involvement), moderate (3-10% BSA) and severe (>10% BSA) disease. Topical agents such as corticosteroids, vitamin D derivatives, coal tar and topical retinoids are the cornerstone of the initial management of psoriasis and are an important part of the treatment ladder applied to patients across the spectrum of disease severity. Patients diagnosed with mild-to-moderate disease are typically prescribed topical agents as monotherapy. Patients with severe disease are typically prescribed topical agents as an adjunct to phototherapy or systemic (small molecule) therapies such as methotrexate, cyclosporine or oral retinoids etc. The treatment regime for moderate-to-severe psoriasis also includes antibody-based therapies.

In recent years the importance of the Th17 pathway has become well validated in psoriasis and several monoclonal antibodies (mAbs) targeting components of this pathway (including IL17RA) have shown the significant importance of modulating this pathway and influencing psoriasis. IL-17RA is one of a family of related receptors (named IL-17RA, to IL-17RE) which multimerise to form signalling complexes. Each receptor complex exhibits differential binding to one of a range of related ligands (IL-

17A, IL-17B, IL-17C, IL-17D, IL-17E or IL-17F). In their active form, all of the ligands are covalent homodimers (except IL-17A and IL-17F which are also known to heterodimerise). It is thought that IL-17A, IL-17F and IL-17A/IL-17F all signal through the same receptor subunits, IL-17RA and IL-17RC, which together form a heteromeric complex. Nonetheless, IL-17A and IL-17F have distinct biological effects. Studies comparing *Il17a*$^{-/-}$ mice with *Il17f*$^{-/-}$ mice indicate that IL-17A plays a central role in driving autoimmunity (in particular the pathology associated with psoriasis) and that it does so through primarily through signaling via IL-17RA. The role of IL-17A/F heterodimers is still to be fully elucidated. While psoriasis may have a systemic component in some patients, the disease is primarily one of the skin. IL-17 secreted by Th17 cells acts on epidermal keratinocytes, via IL-17R complexes present on these cells, to initiate a feedback loop of keratinocyte hyper-proliferation and on-going inflammation, thereby generating the psoriatic plaque. It is believed that the primary element of pathological activity is locally in the skin, and therefore inhibition of the IL-17/IL-17R interaction is the best validated target for topical therapy. This is in contrast to other validated Th17 targets, such as IL-23, where a significant phase of activity is in regional lymph nodes.

Current treatments for psoriasis include topical agents such as corticosteroids, vitamin D derivatives, coal tar and topical retinoids, these are the cornerstones of the initial management of psoriasis (Nast *et al.*, Arch Dermatol Res (2007) 299:111–138) and, depending on disease severity, are typically prescribed as monotherapy.

Patients with severe disease are typically prescribed topical agents as an adjunct to phototherapy or systemic (small molecule) therapies such as methotrexate, cyclosporine or oral retinoids (Nast *et al.,* Arch Dermatol Res (2007) 299:111–138). Phototherapy can be effective but is inconvenient and associated with a significant risk of skin cancer. Small molecule systemic therapies are associated with increased cardiovascular risk; renal dysfunction, leucopenia and thrombocytopenia. For example, methotrexate may cause a neutropenia and liver damage and is contraindicated for males and females of reproductive age without due precaution. Cyclosporine is a potent immunosuppressant, which has potential adverse effects on the kidneys and blood pressure. Acitretin is an oral retinoid that has a range of side effects, and is also contraindicated for females of reproductive age without due precaution (Nast *et al.* Arch Dermatol Res (2007) 299:111–138).

The treatment regimen for moderate-to-severe psoriasis also includes antibody-based therapies. Approved treatments include adalimumab (Humira®), a humanized monoclonal antibody with activity against TNF-alpha(α), the TNF-α inhibitor etanercept (Enbrel®), the TNF-α inhibitor infliximab (Remicade®) and most recently ustekinumab (Stelara®), a human mAb that targets the common p40 subunit of IL12 and IL23, thereby blocking the signalling of both cytokines.

Systemic biologics have transformed treatment of moderate-to-severe psoriasis but, as with any immunosuppressive regimen, chronic use can have significant side-effects such as increased risk of infections or malignancies. Thus, there is a need for new highly effective and safe therapy options for both topical and systemic use.

Several other monoclonal antibodies agents in development have been shown to markedly reduce disease severity in patients with moderate-to-severe plaque psoriasis. These agents include ixekizumab (Eli Lilly) and secukinumab (Novartis), both of which target IL-17A, and brodalumab (Amgen) that binds to and inhibits signalling of IL-17RA and therefore would be expected to block IL-17 family members that utilize this receptor, including IL-17A, IL-17F, IL-17A/F and possibly IL-17E.

The clinical results for the IL17-R inhibitor brodalumab indicate the importance of IL17-RA in psoriasis pathophysiology. In independent clinical studies up to and including significant Phase II trials, it has been reported markedly to reduce disease severity in patients with moderate-to-severe plaque psoriasis, and is said to demonstrate a favorable safety and tolerability profile, robust clinical activity, significant improvements in PASI and other scores for psoriasis severity, and a substantial positive impact on patient quality of life (Papp KA *et al.* N Engl J Med. 2012;366(13):1181–1189; Papp KA *et al.* J Invest Dermatol. 2012;132(10):2466–2469; Gordon KB *et al.* Br J Dermatol. 2014;170(3):705–715)

Similarly, inhibition of IL-17A (the major cytokine signaling through IL-17RA) by several antibody antagonists in clinical development have been shown to be highly effective for the treatment of patients with moderate-severe psoriasis. In particular, secukinumab (currently in substantial phase III clinical studies) has been shown to down-regulate cytokines, chemokines and proteins associated with inflammatory responses in lesional skin.

The therapeutic products currently on the market for the treatment of psoriasis offer varying degrees of symptomatic relief and reduced relapse rates but none are currently considered curative and therefore require chronic administration. While many pre-existing topical agents can be effective for short periods of time, due to treatment-limiting toxicity most are restricted to short term use. This means that patients need routine monitoring for side effects and regular cycling onto new treatment protocols. Phototherapy can be effective but is inconvenient and associated with a significant risk of skin cancer and many conventional (small molecule) systemic therapies are associated with increased cardiovascular risk; renal dysfunction, leucopenia and thrombocytopenia. Systemic biologics have transformed treatment of moderate-to-severe psoriasis but, as with any immunosuppressive regime, chronic use can have significant side-effects such as increased risk of infections or malignancies.

None of the current therapeutic interventions are curative, and therefore all require chronic use. Therapeutic regimens have to take account of this by adopting strategies to reduce toxicity, including rotational or sequential therapies, drug holidays, and combination therapy. Importantly, for some drugs there is an absolute lifetime limit on the exposure that any one patient can safely receive.

Thus, there is a need for new highly effective and safe therapy options for both topical and systemic use. In particular, there is therefore a clear unmet need for new topical drugs with the efficacy of a biological in patients with severe disease, where a long-term maintenance therapy could keep symptoms under control following systemic mAb use and therefore improve the safety profile for chronic use. Similarly, those patients who are not treated systemically because their disease is considered sufficiently severe, would greatly benefit from the topical, in particular dermal, application of a drug with biological efficacy.

Antibodies have proven themselves to be extremely effective therapeutic agents for treating a large number of different disease indications. In particular, there has been a clear trend towards development of fully human antibodies for therapeutic use over the various alternatives. Due to their size and other physical properties, however, it is currently the case that monoclonal antibodies have to be administered either intravenously (iv) or subcutaneously (sc) and therefore have a high systemic exposure. Thus, although the antibodies can be highly effective, their route of delivery can often be suboptimal, resulting either in antibody binding to target antigen at non-disease locations (potentially compromising the healthy function of normal, non-disease tissue)

or resulting in suboptimal PK/PD characteristics. Either outcome may result in a loss of efficacy and/or a compromised safety profile by virtue of the suboptimal route of administration.

Due to their small size and other favourable biophysical characteristics, antibody fragments are potentially attractive candidates for alternative routes of administration. In particular, V_H fragments are the smallest, most robust portion of an immunoglobulin molecule that retain target specificity and potency. It would therefore be advantageous to deliver V_H domain therapeutics topically on the skin, so that they penetrate to therapeutically beneficial locations within the skin to treat disease locally. Any V_H that might enter the bloodstream will be cleared rapidly and therefore have little or no systemic exposure, thereby minimising potential mechanism-related systemic toxicity.

The invention is thus aimed at providing a safe and effective therapy of conditions associated with the Th17 pathway, in particular for topical treatment of psoriasis.

Summary of the invention

The invention relates to isolated IL-17RA binding molecules, related uses and methods, including their use in medical treatment.

In a first aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (V_H) comprising a CDR3 sequence comprising SEQ ID NO. 3 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3.

In a second aspect, the invention relates to a binding molecule, comprising at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain comprising at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 3 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3. In a third aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1267 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1267.

In a fourth aspect, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising an antigen binding site comprising a CDR3

sequence having SEQ ID NO. 1267 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1267.

In a fifth aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1767.

In a another aspect, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1767.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2131 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2131.

In a fourth aspect, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising an antigen binding site comprising a CDR3 sequence having SEQ ID NO. 2131 or a sequence with at least 60%, at least 70%, at least 90%, or at least 95% homology to SEQ ID NO. 2131.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2559 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2559.

In another aspect, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 2559 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2559.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H comprising a CDR3 sequence comprising SEQ ID NO. 2575 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2575.

In another aspect, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising at least one antigen binding site comprising

a CDR3 sequence having SEQ ID NO. 2575 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2575.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2579 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In another, the invention relates to a binding molecule comprising at least one immunoglobulin single domain antibody directed against human IL-17RA wherein said domain is a human V_H domain comprising at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 2579 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2579.

In another aspect, the invention relates to a binding molecule comprising an immunoglobulin single domain antibody directed against human IL-17RA wherein the binding molecule has an IC50 for inhibition of IL-6 production of about 0.2 to about 500 nM when tested as described in the examples, i.e. by measuring the ability of IL-17R-binding molecule to inhibit IL-17R induced IL-6 release from the cell line HT1080.

In another aspect, the invention relates to a binding molecule comprising an immunoglobulin single domain antibody directed against human IL-17RA wherein said binding molecule has a KD (M) value in the range of from 6 x 10-11 to 3 x 10-7, preferably in the range of from 1 x 10^{-9} to 6 x 10^{-11}, preferably when assessed by BIAcore®.

In another aspect, the invention relates to a pharmaceutical composition comprising a binding molecule as described above and a pharmaceutical carrier.

In another aspect, the invention relates to a method for treating a disease selected from autoimmune diseases, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection comprising administering to a patient in need thereof a binding molecule or pharmaceutical composition of the invention.

In another aspect, the invention relates to a binding molecule or a pharmaceutical composition of the invention for use in the treatment of a disease selected from an autoimmune disease, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.

In another aspect, the invention relates to the use of a binding molecule or a pharmaceutical composition of the invention in the manufacture of a medicament for the treatment of a disease selected from an autoimmune disease, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.

In another aspect, the invention relates to an *in vivo* or *in vitro* method for reducing human IL-17RA activity comprising contacting human IL-17RA with a binding molecule as described above.

In another aspect, the invention relates to a method for determining the presence of human IL-17RA in a test sample by an immunoassay comprising contacting said sample with a binding molecule as described above and at least one detectable label.

In another aspect, the invention relates to an isolated nucleic acid molecule comprising a nucleotide sequence encoding a binding molecule of the invention.

In another aspect, the invention relates to an isolated nucleic acid construct comprising a nucleic acid as described above.

In another aspect, the invention relates to an isolated host cell comprising a nucleic acid or a construct as described above.

In another aspect, the invention relates to a method for producing a binding molecule as described above comprising expressing a nucleic acid encoding said binding molecule in a host cell and isolating the binding molecule from the host cell culture.

In another aspect, the invention relates to kit comprising a binding molecule or a pharmaceutical composition of the invention as described above

Drawings

Figure 1. Family 1 sequences. This figure shows the full length V_H sequence for clones in family 1. Framework (FR) and complementarity-determining regions (CDR) are labelled and shown in table form for ease of reference. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 2. Family 2 sequences. This figure shows the full length V_H sequence for clones in family 2. Framework (FR) and complementarity-determining regions (CDR) are labelled and shown in table form for ease of reference. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 3. Family 3 sequences. This figure shows the full length V_H sequence for clones in family 3 and shown in table form for ease of reference. Framework (FR) and complementarity-determining regions (CDR) are labelled. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 4. Family 4 sequences. This figure shows the full length V_H sequence for clones in family 4 and shown in table form for ease of reference. Framework (FR) and complementarity-determining regions (CDR) are labelled. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 5. Family 5 sequences. This figure shows the full length V_H sequence for clones in family 5 and shown in table form for ease of reference. Framework (FR) and complementarity-determining regions (CDR) are labelled. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 6. Family 6 sequences. This figure shows the full length V_H sequence for clones in family 6. Framework (FR) and complementarity-determining regions (CDR) are labelled. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 7. Family 7 sequences. This figure shows the full length V_H sequence for clones in family 7. Framework (FR) and complementarity-determining regions (CDR) are labelled. CDR1, CDR2 and CDR3 are highlighted in bold.

Figure 8 shows serum ELISA data, confirming immunogen-induced heavy chain antibody response.

Figure 9 shows *in vitro* selection Mouse ELISA data: (A) V_H isolated from peripreps binding to IL-17RA, (B) V_H isolated from phage preparations binding to IL-17RA and (C) V_H isolated from phage preparations binding to human IgG1.

Figure 10 shows the results of biochemical assays: IL-17RA ligand inhibition assays.

A: the x-axis shows the concentration of V_H (M), the y-axis shows the OD_{450} nm, for V_H 49G11 (●) the IC_{50} (nM) was 900 and for V_H 2.1 (■) the IC_{50} (nM) was 4.

B: the x-axis shows V_H concentration M $(\log)_{10}$, the y-axis shows the OD_{450} nm, for V_H 4.55 (●) the IC_{50} (nM) was 6928; for V_H 3.1 (■) the IC_{50} (nM) was 11; for V_H 3.20 (▲), the IC_{50} (nM) was 22; for V_H 49G11 (▼), the IC_{50} (nM) was 885.

Figure 11 shows the results of cell-based assays for IL-17RA V_H clones.

A: the x-axis shows V_H concentration M $(\log)_{10}$, the y-axis shows the OD_{450} nm; V_H SEV49G11 (●) had a weak IC_{50} (nM), V_H 2.1 (■) had an IC_{50} (nM) of 363, V_H 62A4 (▲)
(QVQLVESGGGLVQPGRSLTLSCTASGFTFHDYAMHWVRQPPGGGLEWVAGVSWN GNNVGYADSVKGRFTISRDNAKKSLYLQMNSLRSEDTALYYCAKGGMGSGSHPDSF STWGQGTMVTVSS, SEQ ID No. 2604) had a weak IC_{50} (nM), V_H SEV136H4L (▽) had an IC_{50} (nM) of 5; no IC_{50} (nM) was recorded for V_H 846A5 (⭘).

B: the x-axis shows V_H concentration M $(\log)_{10}$, the y-axis shows the OD_{450} nm; MAB177 (●) had an IC_{50} (nM) of 65, V_H 2.2 (■) had an IC_{50} (nM) of 165, V_H 1.1 (▲) had an IC_{50} (nM) of 39, V_H 1.2 (▼) had an IC_{50} (nM) of 141, no IC_{50} (nM) was recorded for LH86A5 (⭘).

Figure 12 shows the BIAcore™ traces for IL-17R V_H (A) Clone 2.1, (B) Clone 2.2, (C) clone 1.1 and (D) clone 1.2

Figure 13 shows clone 2.1 V_H family optimisation, the full sequence of clone 2.1 is shown as the top line in bold (SEQ ID NO: 1268). Figure also discloses SEQ ID NOS

1640, 1632, 1664, 1644, 1636, 1668, 1764, 1720, 1724, 1376, 1760, 1692, 1708, 1688, 1728, 1684, 1676, 1672, 1744, 1748, 1648, 1696, 1716, 1712, 1704, 1660, 1752, 1652, 1656, 1736, 1680, 1700, 1756, 1740, and 1732, respectively, in order of appearance.

Figure 14 shows specificity ELISAs for clones 1.2, 1.1, 2.1, 62A4 and 86A5.

Figure 15 shows epitope competition for IL-17RA V_H clones V_H 1.1 and 2.2, which bind to different epitopes on IL-17RA.

Figure 16 shows HPLC SEC for IL-17 RA for clones (A) 2.1, (B) 1.2 and (C) 1.1.

Detailed description

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, pathology, oncology, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook *et al.* Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Enzymatic reactions and purification techniques are performed according to the manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The IL-17 family of cytokines includes six members, IL-17/IL-17A, IL-17B, IL-17C, IL-17D, IL-17E/IL-25, and IL-17F, which are produced by multiple cell types. Members of this family have a highly conserved C-terminus containing a cysteine-knot fold

structure. Most IL-17 proteins are secreted as disulfide-linked dimers, with the exception of IL-17B, which is secreted as a non-covalent homodimer.

Signaling by IL-17 family cytokines is mediated by members of the IL-17 receptor family (IL-17R), IL-17 R/IL-17 RA, IL-17 B R/IL-17 RB, IL-17 RC, IL-17 RD, and IL-17 RE. Activation of these receptors triggers intracellular pathways that induce the production of pro-inflammatory cytokines and anti-microbial peptides. IL-17A, IL-17F, and IL-17A/F are produced primarily by activated T cells and signal through an oligomerized receptor complex consisting of IL-17 RA and IL-17 RC. Ligand binding to this complex leads to recruitment of the intracellular adaptor proteins, Act1 and TRAF-6, and downstream activation of the transcription factors, NF kappa B, AP-1, and C/EBP. IL-17E activates similar signaling pathways through a receptor complex formed by IL-17 RA and IL-17 B R/IL-17RB. Signaling by IL-17E induces Th2-type immune responses and may be involved in promoting the pathogenesis of asthma. Less is known about the signaling pathways activated by other IL-17 family cytokines. Recent studies suggest that IL-17C is produced primarily by epithelial cells and binds to a receptor complex consisting of IL-17 RA and IL-17 RE. Autocrine signaling by IL-17C in epithelial cells stimulates the production of anti-microbial peptides and pro-inflammatory cytokines, but like IL-17A, overexpression of IL-17C may contribute to the development of autoimmune diseases. Similar to IL-17E, IL-17B binds to IL-17 B R/IL-17 RB, but the major target cells and effects of IL-17B signaling have not been reported. In addition, the receptor for IL-17D and the ligand for IL-17 RD are currently unknown.

The invention provides isolated IL-17RA binding molecules that bind human IL-17RA, pharmaceutical compositions comprising such binding molecules, as well as isolated nucleic acids encoding such binding molecules, recombinant expression vectors and isolated host cells for making such binding proteins. Also provided by the invention are methods of using the binding molecules disclosed herein to detect human IL-17RA, to inhibit human IL-17RA either *in vitro* or *in vivo*, and methods of treating disease. One aspect of the invention provides isolated human anti-human IL-17RA binding molecules, specifically those comprising, or consisting of, single domain antibodies that bind to human IL-17RA with high affinity, a slow off rate and high neutralizing capacity. In one embodiment, the binding molecule is a heavy chain only antibody.

In preferred embodiments, the binding molecules of the invention bind specifically to human IL-17RA and do not cross react with, or do not show substantial binding to,

other members of the human IL-17R receptor family. This limited cross-reactivity with IL-17R homologues exhibited by the binding members of the invention offers advantages for their therapeutic and/or diagnostic use as side effects by undesirable cross reactivity are reduced. This also offers advantages in dosing for therapeutic applications.

Binding molecules of the invention are isolated from their natural environment.

An IL-17RA binding molecule of the invention is directed against, that is capable of binding to human IL-17RA (Protein accession NO. Q96F46 Uniprot, SEQ ID NO. 2601) showing the full-length precursor IL-17RA including the signal peptide) and/or cynomolgus monkey IL-17R.

SEQ ID NO. 2603

MGAARSPPSAVPGPLLGLLLLLLGVLAPGGASLRLLDHRALVCSQPGLNCTVKNSTCLDD
SWIHPRNLTPSSPKDLQIQLHFAHTQQGDLFPVAHIEWTLQTDASILYLEGAELSVLQLN
TNERLCVRFEFLSKLRHHHRRWRFTFSHFVVDPDQEYEVTVHHLPKPIPDGDPNHQSKNF
LVPDCEHARMKVTTPCMSSGSLWDPNITVETLEAHQLRVSFTLWNESTHYQILLTSFPHM
ENHSCFEHMHHIPAPRPEEFHQRSNVTLTLRNLKGCCRHQVQIQPFFSSCLNDCLRHSAT
VSCPEMPDTPEPIPDYMPLWVYWFITGISILLVGSVILLIVCMTWRLAGPGSEKYSDDTK
YTDGLPAADLIPPPLKPRKVWIIYSADHPLYVDVVLKFAQFLLTACGTEVALDLLEEQAI
SEAGVMTWVGRQKQEMVESNSKIIVLCSRGTRAKWQALLGRGAPVRLRCDHGKPVGDLFT
AAMNMILPDFKRPACFGTYVVCYFSEVSCDGDVPDLFGAAPRYPLMDRFEEVYFRIQDLE
MFQPGRMHRVGELSGDNYLRSPGGRQLRAALDRFRDWQVRCPDWFECENLYSADDQDAPS
LDEEVFEEPLLPPGTGIVKRAPLVREPGSQACLAIDPLVGEEGGAAVAKLEPHLQPRGQP
APQPLHTLVLAAEEGALVAAVEPGPLADGAAVRLALAGEGEACPLLGSPGAGRNSVLFLP
VDPEDSPLGSSTPMASPDLLPEDVREHLEGLMLSLFEQSLSCQAQGGCSRPAMVLTDPHT
PYEEEQRQSVQSDQGYISRSSPQPPEGLTEMEEEEEEEQDPGKPALPLSPEDLESLRSLQ
RQLLFRQLQKNSGWDTMGSESEGPSA

The terms "IL-17R binding molecule", “IL-17R binding protein”, “anti-IL-17R single domain antibody” or “anti-IL-17R antibody” all refer to a molecule capable of binding to/directed to the IL-17RA antigen. Thus, unless otherwise stated, the term human IL-17R refers to human IL-17RA. The binding reaction may be shown by standard methods (qualitative assays) including, for example, a binding assay, competition assay or a bioassay for determining the inhibition of IL-17R binding to its receptor or any kind of binding assays, with reference to a negative control test in which an antibody of unrelated specificity. The term "IL-17R binding molecule" includes an IL-17R binding protein or peptide.

The invention relates to isolated binding molecules capable of binding to human IL-17RA comprising a heavy chain variable immunoglobulin domain (V_H) comprising a

CDR3 sequence as shown in any of figures 1 to 7 with reference to tables 1 to 7 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. In one embodiment, the binding molecule comprises a set of CDR1, 2 and 3 sequences selected from the sets of CDR1, 2 and 3 sequences as shown in any of figures 1 to 7 with reference to tables 1 to 7. In one embodiment, the binding molecule comprises a V_H with a set of CDR1, 2 and 3 sequences selected from the sets of CDR1, 2 and 3 sequences as shown in any of figures 1 to 7 with reference to tables 1 to 7. In one embodiment, the binding molecule comprises a heavy chain only antibody.

In another aspect, the invention relates to an isolated binding molecule comprising at least one immunoglobulin single domain antibody directed against/capable of binding to IL-17RA wherein said domain is a V_H domain and wherein said IL-17RA binding molecule comprises at least one antigen binding site.

In one embodiment, the binding molecule may comprise at least one single domain antibody directed against IL-17RA wherein said domain is a V_H domain comprising a CDR3 as shown in any of figures 1 to 7 with reference to tables 1 to 7 or a sequence with at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% homology to said CDR3 or said V_H.

In one embodiment, said at least one single variable heavy chain domain antibody comprises a set of CDR1, 2 and 3 sequences or a V_H a set of CDR1, 2 and 3 sequences wherein the CDR sequences are selected from the sets of CDR1, 2 and 3 sequences as shown in any of figures 1 to 7 with reference to tables 1 to 7. In another embodiment, the binding molecules comprises or consists of a V_H domain as shown for a clone selected from clones 1.1 to 1.316, 2.1 to 2.125, 3.1 to 3.91, 4.1 to 4.107, 5.1 to 5.4, 6.1 or 7.1.

In one embodiment of the aspects above, said homology is at least 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 82%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

"Homology" generally refers to the percentage of amino acid residues in the candidate sequence that are identical with the residues of the polypeptide with which it is compared (sequence identity), after aligning the sequences and in some embodiments after introducing gaps, if necessary, to achieve the maximum percent homology, and

not considering any conservative substitutions as part of the sequence identity. Neither N- or C-terminal extensions, tags or insertions shall be construed as reducing identity or homology. Methods and computer programs for the alignment are well known.

The term "antibody", broadly refers to any immunoglobulin (Ig) molecule, or antigen binding portion thereof, comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivation thereof, which retains the essential epitope binding features of an Ig molecule. Such mutant, variant, or derivative antibody formats are known in the art.
In a full-length antibody, each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, C_H1, C_H2 and C_H3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.
Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG 1, IgG2, IgG 3, IgG4, IgAl and IgA2) or subclass.

In certain embodiments, the binding molecules of the invention comprise or consist of at least one single domain antibody wherein said domain is a V_H immunoglobulin domain. Thus, the binding molecules of the invention comprise or consist of at least one immunoglobulin single variable heavy chain domain antibody (sVD, sdAb or ISV) that has a V_H domain, but is devoid of a V_L domain. Single domain antibodies have been described in the art; they are antibodies whose complementary determining regions are part of a single domain polypeptide, for example a V_H polypeptide.

As described further herein, the binding molecule may comprise two or more V_H domains. Such binding molecules may be monospecific or multispecific.

Binding molecules that comprise a single domain antibody wherein said domain is a V_H domain are also termed Humabody® V_H.

Thus, in some embodiments the binding molecule does not comprise a light chain. In some embodiments the binding molecule does not comprise heavy chain domains C_H2 and C_H3. In some embodiments the binding molecule does not comprise a hinge region and heavy chain domains C_H2 and C_H3. In some embodiments the binding molecule does not comprise heavy chain domains C_H1, C_H2, and CH3. In some embodiments the binding molecule does not comprise heavy chain domain C_H1, a hinge region heavy chain domain C_H2 and heavy chain domain C_H3. In preferred embodiments the binding molecule does not comprise a light chain, a heavy chain domain C_H1, a hinge region heavy chain domain C_H2 and heavy chain domain C_H3.

Each V_H domain comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. For example, the V_H domain may comprise C or N terminal extensions. In one embodiment, the V_H domain comprises C terminal extensions of from 1 to 10, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids. In one embodiment, the V_H domain comprises C terminal extensions of from 1 to 12, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids of the C_H1 domain. In one embodiment, said extension comprises at least 1 alanine residue, for example a single alanine residue, a pair of alanine residues or a triplet of alanine residues. Such extended V_H domains are within the scope of the invention. Also within the scope of the invention are V_H domains that comprise additional C or N terminal residues, for example linker residues introduced from the expression vector used or His tags, e.g. hexa-His (HHHHHH, SEQ ID NO: 2605).

Preferably, the one or more V_H domain is a human V_H domain. As used herein, a human V_H domain includes a V_H domain that is derived from or based on a human V_H domain amino acid or nucleic acid sequence. Thus, the term includes variable heavy chain regions derived from human germline immunoglobulin sequences. As used herein, the term human V_H domain includes V_H domains that are isolated from transgenic mice expressing human immunoglobulin V genes, in particular in response to an immunisation with an antigen of interest. The human V_H domains of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced *in vitro*, e.g. by random or site-specific mutagenesis, or introduced by somatic mutation *in vivo*). The term “human V_H domain” therefore also includes modified human V_H sequences.

Thus, the invention provides a binding molecule comprising at least one immunoglobulin single domain antibody capable of binding/directed against IL-17RA wherein said domain is a human V_H domain and wherein said IL-17A binding molecule comprises at least one antigen binding site. The single domain antibody is specifically directed against/capable of binding human IL-17RA.

As used herein, the term V_H or "variable domain" refers to immunoglobulin variable domains defined by Kabat *et al.*, Sequences of Immunological Interest, 5th ed., U.S. Dept. Health & Human Services, Washington, D.C. (1991). The numbering and positioning of CDR amino acid residues within the variable domains is in accordance with the well-known Kabat numbering convention.

More particularly, the invention provides a V_H immunoglobulin domain that can bind to human IL-17RA with an affinity, a Kon-rate, a Koff rate, KD and/or KA as further described herein.

The binding molecules of the invention comprise amino acid sequences and preferred sequences and/or parts thereof, such as CDRs, as defined herein.

The term "CDR" refers to the complementarity-determining region within antibody variable sequences. There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat as used herein. The terms "Kabat numbering", "Kabat definitions" and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (i.e., hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat *et al.* (1971) Ann. NY Acad. Sci. 190:382-391 and Kabat, *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

As described in more detail in the experimental part, the inventors isolated parent molecules (resulting in 7 families of clones: clone 1.1 is the parent clone for family 1 as shown in Fig. 1, clone 2.1 is the parent clone for family 2 as shown in Fig. 2, clone 3.1

is the parent clone for family 3 as shown in Fig. 3, clone 4.1 is the parent clone for family 4 as shown in Fig. 4, clone 5.1 is the parent clone for family 5 as shown in Fig. 5, clone 6.1 is the parent clone for family 6 as shown in Fig. 6 and clone 7.1 is the parent clone for family 7 as shown in Fig. 7); each having a set of CDR sequences (CDR1, 2 and 3) as shown in Figures 1, 2, 3, 4, 5, 6 and 7. Through a process of optimization, a panel of clones with CDR3 sequences derived from the parent CDR3 sequences was generated for each of family 1, 2, 3, 4, 5, 6 and 7. Optimised V_H domain sequences show improved affinities to IL-17RA and improved potencies in the IL-17RA cell-based assay compared to the parent molecule as shown in the examples.

In one aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 1 or family 1-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody capable of binding/directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said V_H domain comprises a family 1 or family 1-like sequence. These include the V_H sequence of the parent clone (clone 1.1) or a part thereof, for example a CDR3 sequence and V_H sequences of clones or parts thereof that are derived from the parent clone 1.1 through a process of optimization, for example sequences as shown as shown in Figure 1. CDR sequences and full length sequences of clones in family 1 are numbered according to table 1 as shown below.

Clone name	**CDR1** SEQ ID NO.	**CDR2** SEQ ID NO.	**CDR3** SEQ ID NO.	**VH FULL LENGTH** SEQ ID NO.
1.1	SEQ ID NO. 1	SEQ ID NO. 2	SEQ ID NO. 3	SEQ ID NO. 4
1.2	SEQ ID NO. 5	SEQ ID NO. 6	SEQ ID NO. 7	SEQ ID NO. 8
1.3	SEQ ID NO. 9	SEQ ID NO. 10	SEQ ID NO. 11	SEQ ID NO. 12
1.4	SEQ ID NO. 13	SEQ ID NO. 14	SEQ ID NO. 15	SEQ ID NO. 16
1.5	SEQ ID NO. 17	SEQ ID NO. 18	SEQ ID NO. 19	SEQ ID NO. 20
1.6	SEQ ID NO. 21	SEQ ID NO. 22	SEQ ID NO. 23	SEQ ID NO. 24
1.7	SEQ ID NO. 25	SEQ ID NO. 26	SEQ ID NO. 27	SEQ ID NO. 28
1.8	SEQ ID NO. 29	SEQ ID NO. 30	SEQ ID NO. 31	SEQ ID NO. 32
1.9	SEQ ID NO. 33	SEQ ID NO. 34	SEQ ID NO. 35	SEQ ID NO. 36

1.10	SEQ ID NO. 37	SEQ ID NO. 38	SEQ ID NO. 39	SEQ ID NO. 40
1.11	SEQ ID NO. 41	SEQ ID NO. 42	SEQ ID NO. 43	SEQ ID NO. 44
1.12	SEQ ID NO. 45	SEQ ID NO. 46	SEQ ID NO. 47	SEQ ID NO. 48
1.13	SEQ ID NO. 49	SEQ ID NO. 50	SEQ ID NO. 51	SEQ ID NO. 52
1.14	SEQ ID NO. 53	SEQ ID NO. 54	SEQ ID NO. 55	SEQ ID NO. 56
1.15	SEQ ID NO. 57	SEQ ID NO. 58	SEQ ID NO. 59	SEQ ID NO. 60
1.16	SEQ ID NO. 61	SEQ ID NO. 62	SEQ ID NO. 63	SEQ ID NO. 64
1.17	SEQ ID NO. 65	SEQ ID NO. 66	SEQ ID NO. 67	SEQ ID NO. 68
1.18	SEQ ID NO. 69	SEQ ID NO. 70	SEQ ID NO. 71	SEQ ID NO. 72
1.19	SEQ ID NO. 73	SEQ ID NO. 74	SEQ ID NO. 75	SEQ ID NO. 76
1.20	SEQ ID NO. 77	SEQ ID NO. 78	SEQ ID NO. 79	SEQ ID NO. 80
1.21	SEQ ID NO. 81	SEQ ID NO. 82	SEQ ID NO. 83	SEQ ID NO. 84
1.22	SEQ ID NO. 85	SEQ ID NO. 86	SEQ ID NO. 87	SEQ ID NO. 88
1.23	SEQ ID NO. 89	SEQ ID NO. 90	SEQ ID NO. 91	SEQ ID NO. 92
1.24	SEQ ID NO. 93	SEQ ID NO. 94	SEQ ID NO. 95	SEQ ID NO. 96
1.25	SEQ ID NO. 97	SEQ ID NO. 98	SEQ ID NO. 99	SEQ ID NO. 100
1.26	SEQ ID NO. 101	SEQ ID NO. 102	SEQ ID NO. 103	SEQ ID NO. 104
1.27	SEQ ID NO. 105	SEQ ID NO. 106	SEQ ID NO. 107	SEQ ID NO. 108
1.28	SEQ ID NO. 109	SEQ ID NO. 110	SEQ ID NO. 111	SEQ ID NO. 112
1.29	SEQ ID NO. 113	SEQ ID NO. 114	SEQ ID NO. 115	SEQ ID NO. 116
1.30	SEQ ID NO. 117	SEQ ID NO. 118	SEQ ID NO. 119	SEQ ID NO. 120
1.31	SEQ ID NO. 121	SEQ ID NO. 122	SEQ ID NO. 123	SEQ ID NO. 124
1.32	SEQ ID NO. 125	SEQ ID NO. 126	SEQ ID NO. 127	SEQ ID NO. 128
1.33	SEQ ID NO. 129	SEQ ID NO. 130	SEQ ID NO. 131	SEQ ID NO. 132
1.34	SEQ ID NO. 133	SEQ ID NO. 134	SEQ ID NO. 135	SEQ ID NO. 136
1.35	SEQ ID NO. 137	SEQ ID NO. 138	SEQ ID NO. 139	SEQ ID NO. 140
1.36	SEQ ID NO. 141	SEQ ID NO. 142	SEQ ID NO. 143	SEQ ID NO. 144
1.37	SEQ ID NO. 145	SEQ ID NO. 146	SEQ ID NO. 147	SEQ ID NO. 148
1.38	SEQ ID NO. 149	SEQ ID NO. 150	SEQ ID NO. 151	SEQ ID NO. 152
1.39	SEQ ID NO. 153	SEQ ID NO. 154	SEQ ID NO. 155	SEQ ID NO. 156
1.40	SEQ ID NO. 157	SEQ ID NO. 158	SEQ ID NO. 159	SEQ ID NO. 160
1.41	SEQ ID NO. 161	SEQ ID NO. 162	SEQ ID NO. 163	SEQ ID NO. 164
1.42	SEQ ID NO. 165	SEQ ID NO. 166	SEQ ID NO. 167	SEQ ID NO. 168

1.43	SEQ ID NO. 169	SEQ ID NO. 170	SEQ ID NO. 171	SEQ ID NO. 172
1.44	SEQ ID NO. 173	SEQ ID NO. 174	SEQ ID NO. 175	SEQ ID NO. 176
1.45	SEQ ID NO. 177	SEQ ID NO. 178	SEQ ID NO. 179	SEQ ID NO. 180
1.46	SEQ ID NO. 181	SEQ ID NO. 182	SEQ ID NO. 183	SEQ ID NO. 184
1.47	SEQ ID NO. 185	SEQ ID NO. 186	SEQ ID NO. 187	SEQ ID NO. 188
1.48	SEQ ID NO. 189	SEQ ID NO. 190	SEQ ID NO. 191	SEQ ID NO. 192
1.49	SEQ ID NO. 193	SEQ ID NO. 194	SEQ ID NO. 195	SEQ ID NO. 196
1.50	SEQ ID NO. 197	SEQ ID NO. 198	SEQ ID NO. 199	SEQ ID NO. 200
1.51	SEQ ID NO. 201	SEQ ID NO. 202	SEQ ID NO. 203	SEQ ID NO. 204
1.52	SEQ ID NO. 205	SEQ ID NO. 206	SEQ ID NO. 207	SEQ ID NO. 208
1.53	SEQ ID NO. 209	SEQ ID NO. 210	SEQ ID NO. 211	SEQ ID NO. 212
1.54	SEQ ID NO. 213	SEQ ID NO. 214	SEQ ID NO. 215	SEQ ID NO. 216
1.55	SEQ ID NO. 217	SEQ ID NO. 218	SEQ ID NO. 219	SEQ ID NO. 220
1.56	SEQ ID NO. 221	SEQ ID NO. 222	SEQ ID NO. 223	SEQ ID NO. 224
1.57	SEQ ID NO. 225	SEQ ID NO. 226	SEQ ID NO. 227	SEQ ID NO. 228
1.58	SEQ ID NO. 229	SEQ ID NO. 230	SEQ ID NO. 231	SEQ ID NO. 232
1.59	SEQ ID NO. 233	SEQ ID NO. 234	SEQ ID NO. 235	SEQ ID NO. 236
1.60	SEQ ID NO. 237	SEQ ID NO. 238	SEQ ID NO. 239	SEQ ID NO. 240
1.61	SEQ ID NO. 241	SEQ ID NO. 242	SEQ ID NO. 243	SEQ ID NO. 244
1.62	SEQ ID NO. 245	SEQ ID NO. 246	SEQ ID NO. 247	SEQ ID NO. 248
1.63	SEQ ID NO. 249	SEQ ID NO. 250	SEQ ID NO. 251	SEQ ID NO. 252
1.64	SEQ ID NO. 253	SEQ ID NO. 254	SEQ ID NO. 255	SEQ ID NO. 256
1.65	SEQ ID NO. 257	SEQ ID NO. 258	SEQ ID NO. 259	SEQ ID NO. 260
1.66	SEQ ID NO. 261	SEQ ID NO. 262	SEQ ID NO. 263	SEQ ID NO. 264
1.67	SEQ ID NO. 265	SEQ ID NO. 266	SEQ ID NO. 267	SEQ ID NO. 268
1.68	SEQ ID NO. 269	SEQ ID NO. 270	SEQ ID NO. 271	SEQ ID NO. 272
1.69	SEQ ID NO. 273	SEQ ID NO. 274	SEQ ID NO. 275	SEQ ID NO. 276
1.70	SEQ ID NO. 277	SEQ ID NO. 278	SEQ ID NO. 279	SEQ ID NO. 280
1.71	SEQ ID NO. 281	SEQ ID NO. 282	SEQ ID NO. 283	SEQ ID NO. 284
1.72	SEQ ID NO. 285	SEQ ID NO. 286	SEQ ID NO. 287	SEQ ID NO. 288
1.73	SEQ ID NO. 289	SEQ ID NO. 290	SEQ ID NO. 291	SEQ ID NO. 292
1.74	SEQ ID NO. 293	SEQ ID NO. 294	SEQ ID NO. 295	SEQ ID NO. 296
1.75	SEQ ID NO. 297	SEQ ID NO. 298	SEQ ID NO. 299	SEQ ID NO. 300

1.76	SEQ ID NO. 301	SEQ ID NO. 302	SEQ ID NO. 303	SEQ ID NO. 304
1.77	SEQ ID NO. 305	SEQ ID NO. 306	SEQ ID NO. 307	SEQ ID NO. 308
1.78	SEQ ID NO. 309	SEQ ID NO. 310	SEQ ID NO. 311	SEQ ID NO. 312
1.79	SEQ ID NO. 313	SEQ ID NO. 314	SEQ ID NO. 315	SEQ ID NO. 316
1.80	SEQ ID NO. 317	SEQ ID NO. 318	SEQ ID NO. 319	SEQ ID NO. 320
1.81	SEQ ID NO. 321	SEQ ID NO. 322	SEQ ID NO. 323	SEQ ID NO. 324
1.82	SEQ ID NO. 325	SEQ ID NO. 326	SEQ ID NO. 327	SEQ ID NO. 328
1.83	SEQ ID NO. 329	SEQ ID NO. 330	SEQ ID NO. 331	SEQ ID NO. 332
1.84	SEQ ID NO. 333	SEQ ID NO. 334	SEQ ID NO. 335	SEQ ID NO. 336
1.85	SEQ ID NO. 337	SEQ ID NO. 338	SEQ ID NO. 339	SEQ ID NO. 340
1.86	SEQ ID NO. 341	SEQ ID NO. 342	SEQ ID NO. 343	SEQ ID NO. 344
1.87	SEQ ID NO. 345	SEQ ID NO. 346	SEQ ID NO. 347	SEQ ID NO. 348
1.88	SEQ ID NO. 349	SEQ ID NO. 350	SEQ ID NO. 351	SEQ ID NO. 352
1.89	SEQ ID NO. 353	SEQ ID NO. 354	SEQ ID NO. 355	SEQ ID NO. 356
1.90	SEQ ID NO. 357	SEQ ID NO. 358	SEQ ID NO. 359	SEQ ID NO. 360
1.91	SEQ ID NO. 361	SEQ ID NO. 362	SEQ ID NO. 363	SEQ ID NO. 364
1.92	SEQ ID NO. 365	SEQ ID NO. 366	SEQ ID NO. 367	SEQ ID NO. 368
1.93	SEQ ID NO. 369	SEQ ID NO. 370	SEQ ID NO. 371	SEQ ID NO. 372
1.94	SEQ ID NO. 373	SEQ ID NO. 374	SEQ ID NO. 375	SEQ ID NO. 376
1.95	SEQ ID NO. 377	SEQ ID NO. 378	SEQ ID NO. 379	SEQ ID NO. 380
1.96	SEQ ID NO. 381	SEQ ID NO. 382	SEQ ID NO. 383	SEQ ID NO. 384
1.97	SEQ ID NO. 385	SEQ ID NO. 386	SEQ ID NO. 387	SEQ ID NO. 388
1.98	SEQ ID NO. 389	SEQ ID NO. 390	SEQ ID NO. 391	SEQ ID NO. 392
1.99	SEQ ID NO. 393	SEQ ID NO. 394	SEQ ID NO. 395	SEQ ID NO. 396
1.100	SEQ ID NO. 397	SEQ ID NO. 398	SEQ ID NO. 399	SEQ ID NO. 400
1.101	SEQ ID NO. 401	SEQ ID NO. 402	SEQ ID NO. 403	SEQ ID NO. 404
1.102	SEQ ID NO. 405	SEQ ID NO. 406	SEQ ID NO. 407	SEQ ID NO. 408
1.103	SEQ ID NO. 409	SEQ ID NO. 410	SEQ ID NO. 411	SEQ ID NO. 412
1.104	SEQ ID NO. 413	SEQ ID NO. 414	SEQ ID NO. 415	SEQ ID NO. 416
1.105	SEQ ID NO. 417	SEQ ID NO. 418	SEQ ID NO. 419	SEQ ID NO. 420
1.106	SEQ ID NO. 421	SEQ ID NO. 422	SEQ ID NO. 423	SEQ ID NO. 424
1.107	SEQ ID NO. 425	SEQ ID NO. 426	SEQ ID NO. 427	SEQ ID NO. 428
1.108	SEQ ID NO. 429	SEQ ID NO. 430	SEQ ID NO. 431	SEQ ID NO. 432

1.109	SEQ ID NO. 433	SEQ ID NO. 434	SEQ ID NO. 435	SEQ ID NO. 436
1.110	SEQ ID NO. 437	SEQ ID NO. 438	SEQ ID NO. 439	SEQ ID NO. 440
1.111	SEQ ID NO. 441	SEQ ID NO. 442	SEQ ID NO. 443	SEQ ID NO. 444
1.112	SEQ ID NO. 445	SEQ ID NO. 446	SEQ ID NO. 447	SEQ ID NO. 448
1.113	SEQ ID NO. 449	SEQ ID NO. 450	SEQ ID NO. 451	SEQ ID NO. 452
1.114	SEQ ID NO. 453	SEQ ID NO. 454	SEQ ID NO. 455	SEQ ID NO. 456
1.115	SEQ ID NO. 457	SEQ ID NO. 458	SEQ ID NO. 459	SEQ ID NO. 460
1.116	SEQ ID NO. 461	SEQ ID NO. 462	SEQ ID NO. 463	SEQ ID NO. 464
1.117	SEQ ID NO. 465	SEQ ID NO. 466	SEQ ID NO. 467	SEQ ID NO. 468
1.118	SEQ ID NO. 469	SEQ ID NO. 470	SEQ ID NO. 471	SEQ ID NO. 472
1.119	SEQ ID NO. 473	SEQ ID NO. 474	SEQ ID NO. 475	SEQ ID NO. 476
1.120	SEQ ID NO. 477	SEQ ID NO. 478	SEQ ID NO. 479	SEQ ID NO. 480
1.121	SEQ ID NO. 481	SEQ ID NO. 482	SEQ ID NO. 483	SEQ ID NO. 484
1.122	SEQ ID NO. 485	SEQ ID NO. 486	SEQ ID NO. 487	SEQ ID NO. 488
1.123	SEQ ID NO. 489	SEQ ID NO. 490	SEQ ID NO. 491	SEQ ID NO. 492
1.124	SEQ ID NO. 493	SEQ ID NO. 494	SEQ ID NO. 495	SEQ ID NO. 496
1.125	SEQ ID NO. 497	SEQ ID NO. 498	SEQ ID NO. 499	SEQ ID NO. 500
1.126	SEQ ID NO. 501	SEQ ID NO. 502	SEQ ID NO. 503	SEQ ID NO. 504
1.127	SEQ ID NO. 505	SEQ ID NO. 506	SEQ ID NO. 507	SEQ ID NO. 508
1.128	SEQ ID NO. 509	SEQ ID NO. 510	SEQ ID NO. 511	SEQ ID NO. 512
1.129	SEQ ID NO. 513	SEQ ID NO. 514	SEQ ID NO. 515	SEQ ID NO. 516
1.130	SEQ ID NO. 517	SEQ ID NO. 518	SEQ ID NO. 519	SEQ ID NO. 520
1.131	SEQ ID NO. 521	SEQ ID NO. 522	SEQ ID NO. 523	SEQ ID NO. 524
1.132	SEQ ID NO. 525	SEQ ID NO. 526	SEQ ID NO. 527	SEQ ID NO. 528
1.133	SEQ ID NO. 529	SEQ ID NO. 530	SEQ ID NO. 531	SEQ ID NO. 532
1.134	SEQ ID NO. 533	SEQ ID NO. 534	SEQ ID NO. 535	SEQ ID NO. 536
1.135	SEQ ID NO. 537	SEQ ID NO. 538	SEQ ID NO. 539	SEQ ID NO. 540
1.136	SEQ ID NO. 541	SEQ ID NO. 542	SEQ ID NO. 543	SEQ ID NO. 544
1.137	SEQ ID NO. 545	SEQ ID NO. 546	SEQ ID NO. 547	SEQ ID NO. 548
1.138	SEQ ID NO. 549	SEQ ID NO. 550	SEQ ID NO. 551	SEQ ID NO. 552
1.139	SEQ ID NO. 553	SEQ ID NO. 554	SEQ ID NO. 555	SEQ ID NO. 556
1.140	SEQ ID NO. 557	SEQ ID NO. 558	SEQ ID NO. 559	SEQ ID NO. 560
1.141	SEQ ID NO. 561	SEQ ID NO. 562	SEQ ID NO. 563	SEQ ID NO. 564

1.142	SEQ ID NO. 565	SEQ ID NO. 566	SEQ ID NO. 567	SEQ ID NO. 568
1.143	SEQ ID NO. 569	SEQ ID NO. 570	SEQ ID NO. 571	SEQ ID NO. 572
1.144	SEQ ID NO. 573	SEQ ID NO. 574	SEQ ID NO. 575	SEQ ID NO. 576
1.145	SEQ ID NO. 577	SEQ ID NO. 578	SEQ ID NO. 579	SEQ ID NO. 580
1.146	SEQ ID NO. 581	SEQ ID NO. 582	SEQ ID NO. 583	SEQ ID NO. 584
1.147	SEQ ID NO. 585	SEQ ID NO. 586	SEQ ID NO. 587	SEQ ID NO. 588
1.148	SEQ ID NO. 589	SEQ ID NO. 590	SEQ ID NO. 591	SEQ ID NO. 592
1.149	SEQ ID NO. 593	SEQ ID NO. 594	SEQ ID NO. 595	SEQ ID NO. 596
1.150	SEQ ID NO. 597	SEQ ID NO. 598	SEQ ID NO. 599	SEQ ID NO. 600
1.151	SEQ ID NO. 601	SEQ ID NO. 602	SEQ ID NO. 603	SEQ ID NO. 604
1.152	SEQ ID NO. 605	SEQ ID NO. 606	SEQ ID NO. 607	SEQ ID NO. 608
1.153	SEQ ID NO. 609	SEQ ID NO. 610	SEQ ID NO. 611	SEQ ID NO. 612
1.154	SEQ ID NO. 613	SEQ ID NO. 614	SEQ ID NO. 615	SEQ ID NO. 616
1.155	SEQ ID NO. 617	SEQ ID NO. 618	SEQ ID NO. 619	SEQ ID NO. 620
1.156	SEQ ID NO. 621	SEQ ID NO. 622	SEQ ID NO. 623	SEQ ID NO. 624
1.157	SEQ ID NO. 625	SEQ ID NO. 626	SEQ ID NO. 627	SEQ ID NO. 628
1.158	SEQ ID NO. 629	SEQ ID NO. 630	SEQ ID NO. 631	SEQ ID NO. 632
1.159	SEQ ID NO. 633	SEQ ID NO. 634	SEQ ID NO. 635	SEQ ID NO. 636
1.160	SEQ ID NO. 637	SEQ ID NO. 638	SEQ ID NO. 639	SEQ ID NO. 640
1.161	SEQ ID NO. 641	SEQ ID NO. 642	SEQ ID NO. 643	SEQ ID NO. 644
1.162	SEQ ID NO. 645	SEQ ID NO. 646	SEQ ID NO. 647	SEQ ID NO. 648
1.163	SEQ ID NO. 649	SEQ ID NO. 650	SEQ ID NO. 651	SEQ ID NO. 652
1.164	SEQ ID NO. 653	SEQ ID NO. 654	SEQ ID NO. 655	SEQ ID NO. 656
1.165	SEQ ID NO. 657	SEQ ID NO. 658	SEQ ID NO. 659	SEQ ID NO. 660
1.166	SEQ ID NO. 661	SEQ ID NO. 662	SEQ ID NO. 663	SEQ ID NO. 664
1.167	SEQ ID NO. 665	SEQ ID NO. 666	SEQ ID NO. 667	SEQ ID NO. 668
1.168	SEQ ID NO. 669	SEQ ID NO. 670	SEQ ID NO. 671	SEQ ID NO. 672
1.169	SEQ ID NO. 673	SEQ ID NO. 674	SEQ ID NO. 675	SEQ ID NO. 676
1.170	SEQ ID NO. 677	SEQ ID NO. 678	SEQ ID NO. 679	SEQ ID NO. 680
1.171	SEQ ID NO. 681	SEQ ID NO. 682	SEQ ID NO. 683	SEQ ID NO. 684
1.172	SEQ ID NO. 685	SEQ ID NO. 686	SEQ ID NO. 687	SEQ ID NO. 688
1.173	SEQ ID NO. 689	SEQ ID NO. 690	SEQ ID NO. 691	SEQ ID NO. 692
1.174	SEQ ID NO. 693	SEQ ID NO. 694	SEQ ID NO. 695	SEQ ID NO. 696

1.175	SEQ ID NO. 697	SEQ ID NO. 698	SEQ ID NO. 699	SEQ ID NO. 700
1.176	SEQ ID NO. 701	SEQ ID NO. 702	SEQ ID NO. 703	SEQ ID NO. 704
1.177	SEQ ID NO. 705	SEQ ID NO. 706	SEQ ID NO. 707	SEQ ID NO. 708
1.178	SEQ ID NO. 709	SEQ ID NO. 710	SEQ ID NO. 711	SEQ ID NO. 712
1.179	SEQ ID NO. 713	SEQ ID NO. 714	SEQ ID NO. 715	SEQ ID NO. 716
1.180	SEQ ID NO. 717	SEQ ID NO. 718	SEQ ID NO. 719	SEQ ID NO. 720
1.181	SEQ ID NO. 721	SEQ ID NO. 722	SEQ ID NO. 723	SEQ ID NO. 724
1.182	SEQ ID NO. 725	SEQ ID NO. 726	SEQ ID NO. 727	SEQ ID NO. 728
1.183	SEQ ID NO. 729	SEQ ID NO. 730	SEQ ID NO. 731	SEQ ID NO. 732
1.184	SEQ ID NO. 733	SEQ ID NO. 734	SEQ ID NO. 735	SEQ ID NO. 736
1.185	SEQ ID NO. 737	SEQ ID NO. 738	SEQ ID NO. 739	SEQ ID NO. 740
1.186	SEQ ID NO. 741	SEQ ID NO. 742	SEQ ID NO. 743	SEQ ID NO. 744
1.187	SEQ ID NO. 745	SEQ ID NO. 746	SEQ ID NO. 747	SEQ ID NO. 748
1.188	SEQ ID NO. 749	SEQ ID NO. 750	SEQ ID NO. 751	SEQ ID NO. 752
1.189	SEQ ID NO. 753	SEQ ID NO. 754	SEQ ID NO. 755	SEQ ID NO. 756
1.190	SEQ ID NO. 757	SEQ ID NO. 758	SEQ ID NO. 759	SEQ ID NO. 760
1.191	SEQ ID NO. 761	SEQ ID NO. 762	SEQ ID NO. 763	SEQ ID NO. 764
1.192	SEQ ID NO. 765	SEQ ID NO. 766	SEQ ID NO. 767	SEQ ID NO. 768
1.193	SEQ ID NO. 769	SEQ ID NO. 770	SEQ ID NO. 771	SEQ ID NO. 772
1.194	SEQ ID NO. 773	SEQ ID NO. 774	SEQ ID NO. 775	SEQ ID NO. 776
1.195	SEQ ID NO. 777	SEQ ID NO. 778	SEQ ID NO. 779	SEQ ID NO. 780
1.196	SEQ ID NO. 781	SEQ ID NO. 782	SEQ ID NO. 783	SEQ ID NO. 784
1.197	SEQ ID NO. 785	SEQ ID NO. 786	SEQ ID NO. 787	SEQ ID NO. 788
1.198	SEQ ID NO. 789	SEQ ID NO. 790	SEQ ID NO. 791	SEQ ID NO. 792
1.199	SEQ ID NO. 793	SEQ ID NO. 794	SEQ ID NO. 795	SEQ ID NO. 796
1.200	SEQ ID NO. 797	SEQ ID NO. 798	SEQ ID NO. 799	SEQ ID NO. 800
1.201	SEQ ID NO. 801	SEQ ID NO. 802	SEQ ID NO. 803	SEQ ID NO. 804
1.202	SEQ ID NO. 805	SEQ ID NO. 806	SEQ ID NO. 807	SEQ ID NO. 808
1.203	SEQ ID NO. 809	SEQ ID NO. 810	SEQ ID NO. 811	SEQ ID NO. 812
1.204	SEQ ID NO. 813	SEQ ID NO. 814	SEQ ID NO. 815	SEQ ID NO. 816
1.205	SEQ ID NO. 817	SEQ ID NO. 818	SEQ ID NO. 819	SEQ ID NO. 820
1.206	SEQ ID NO. 821	SEQ ID NO. 822	SEQ ID NO. 823	SEQ ID NO. 824
1.207	SEQ ID NO. 825	SEQ ID NO. 826	SEQ ID NO. 827	SEQ ID NO. 828

1.208	SEQ ID NO. 829	SEQ ID NO. 830	SEQ ID NO. 831	SEQ ID NO. 832
1.209	SEQ ID NO. 833	SEQ ID NO. 834	SEQ ID NO. 835	SEQ ID NO. 836
1.210	SEQ ID NO. 837	SEQ ID NO. 838	SEQ ID NO. 839	SEQ ID NO. 840
1.211	SEQ ID NO. 841	SEQ ID NO. 842	SEQ ID NO. 843	SEQ ID NO. 844
1.212	SEQ ID NO. 845	SEQ ID NO. 846	SEQ ID NO. 847	SEQ ID NO. 848
1.213	SEQ ID NO. 849	SEQ ID NO. 850	SEQ ID NO. 851	SEQ ID NO. 852
1.214	SEQ ID NO. 853	SEQ ID NO. 854	SEQ ID NO. 855	SEQ ID NO. 856
1.215	SEQ ID NO. 857	SEQ ID NO. 858	SEQ ID NO. 859	SEQ ID NO. 860
1.216	SEQ ID NO. 861	SEQ ID NO. 862	SEQ ID NO. 863	SEQ ID NO. 864
1.217	SEQ ID NO. 865	SEQ ID NO. 866	SEQ ID NO. 867	SEQ ID NO. 868
1.218	SEQ ID NO. 869	SEQ ID NO. 870	SEQ ID NO. 871	SEQ ID NO. 872
1.219	SEQ ID NO. 873	SEQ ID NO. 874	SEQ ID NO. 875	SEQ ID NO. 876
1.220	SEQ ID NO. 877	SEQ ID NO. 878	SEQ ID NO. 879	SEQ ID NO. 880
1.221	SEQ ID NO. 881	SEQ ID NO. 882	SEQ ID NO. 883	SEQ ID NO. 884
1.222	SEQ ID NO. 885	SEQ ID NO. 886	SEQ ID NO. 887	SEQ ID NO. 888
1.223	SEQ ID NO. 889	SEQ ID NO. 890	SEQ ID NO. 891	SEQ ID NO. 892
1.224	SEQ ID NO. 893	SEQ ID NO. 894	SEQ ID NO. 895	SEQ ID NO. 896
1.225	SEQ ID NO. 897	SEQ ID NO. 898	SEQ ID NO. 899	SEQ ID NO. 900
1.226	SEQ ID NO. 901	SEQ ID NO. 902	SEQ ID NO. 903	SEQ ID NO. 904
1.227	SEQ ID NO. 905	SEQ ID NO. 906	SEQ ID NO. 907	SEQ ID NO. 908
1.228	SEQ ID NO. 909	SEQ ID NO. 910	SEQ ID NO. 911	SEQ ID NO. 912
1.229	SEQ ID NO. 913	SEQ ID NO. 914	SEQ ID NO. 915	SEQ ID NO. 916
1.230	SEQ ID NO. 917	SEQ ID NO. 918	SEQ ID NO. 919	SEQ ID NO. 920
1.231	SEQ ID NO. 921	SEQ ID NO. 922	SEQ ID NO. 923	SEQ ID NO. 924
1.232	SEQ ID NO. 925	SEQ ID NO. 926	SEQ ID NO. 927	SEQ ID NO. 928
1.233	SEQ ID NO. 929	SEQ ID NO. 930	SEQ ID NO. 931	SEQ ID NO. 932
1.234	SEQ ID NO. 933	SEQ ID NO. 934	SEQ ID NO. 935	SEQ ID NO. 936
1.235	SEQ ID NO. 937	SEQ ID NO. 938	SEQ ID NO. 939	SEQ ID NO. 940
1.236	SEQ ID NO. 941	SEQ ID NO. 942	SEQ ID NO. 943	SEQ ID NO. 944
1.237	SEQ ID NO. 945	SEQ ID NO. 946	SEQ ID NO. 947	SEQ ID NO. 948
1.238	SEQ ID NO. 949	SEQ ID NO. 950	SEQ ID NO. 951	SEQ ID NO. 952
1.239	SEQ ID NO. 953	SEQ ID NO. 954	SEQ ID NO. 955	SEQ ID NO. 956
1.240	SEQ ID NO. 957	SEQ ID NO. 958	SEQ ID NO. 959	SEQ ID NO. 960

1.241	SEQ ID NO. 961	SEQ ID NO. 962	SEQ ID NO. 963	SEQ ID NO. 964
1.242	SEQ ID NO. 965	SEQ ID NO. 966	SEQ ID NO. 967	SEQ ID NO. 968
1.243	SEQ ID NO. 969	SEQ ID NO. 970	SEQ ID NO. 971	SEQ ID NO. 972
1.244	SEQ ID NO. 973	SEQ ID NO. 974	SEQ ID NO. 975	SEQ ID NO. 976
1.245	SEQ ID NO. 977	SEQ ID NO. 978	SEQ ID NO. 979	SEQ ID NO. 980
1.246	SEQ ID NO. 981	SEQ ID NO. 982	SEQ ID NO. 983	SEQ ID NO. 984
1.247	SEQ ID NO. 985	SEQ ID NO. 986	SEQ ID NO. 987	SEQ ID NO. 988
1.248	SEQ ID NO. 989	SEQ ID NO. 990	SEQ ID NO. 991	SEQ ID NO. 992
1.249	SEQ ID NO. 993	SEQ ID NO. 994	SEQ ID NO. 995	SEQ ID NO. 996
1.250	SEQ ID NO. 997	SEQ ID NO. 998	SEQ ID NO. 999	SEQ ID NO. 1000
1.251	SEQ ID NO. 1001	SEQ ID NO. 1002	SEQ ID NO. 1003	SEQ ID NO. 1004
1.252	SEQ ID NO. 1005	SEQ ID NO. 1006	SEQ ID NO. 1007	SEQ ID NO. 1008
1.253	SEQ ID NO. 1009	SEQ ID NO. 1010	SEQ ID NO. 1011	SEQ ID NO. 1012
1.254	SEQ ID NO. 1013	SEQ ID NO. 1014	SEQ ID NO. 1015	SEQ ID NO. 1016
1.255	SEQ ID NO. 1017	SEQ ID NO. 1018	SEQ ID NO. 1019	SEQ ID NO. 1020
1.256	SEQ ID NO. 1021	SEQ ID NO. 1022	SEQ ID NO. 1023	SEQ ID NO. 1024
1.257	SEQ ID NO. 1025	SEQ ID NO. 1026	SEQ ID NO. 1027	SEQ ID NO. 1028
1.258	SEQ ID NO. 1029	SEQ ID NO. 1030	SEQ ID NO. 1031	SEQ ID NO. 1032
1.259	SEQ ID NO. 1033	SEQ ID NO. 1034	SEQ ID NO. 1035	SEQ ID NO. 1036
1.260	SEQ ID NO. 1037	SEQ ID NO. 1038	SEQ ID NO. 1039	SEQ ID NO. 1040
1.261	SEQ ID NO. 1041	SEQ ID NO. 1042	SEQ ID NO. 1043	SEQ ID NO. 1044
1.262	SEQ ID NO. 1045	SEQ ID NO. 1046	SEQ ID NO. 1047	SEQ ID NO. 1048
1.263	SEQ ID NO. 1049	SEQ ID NO. 1050	SEQ ID NO. 1051	SEQ ID NO. 1052
1.264	SEQ ID NO. 1053	SEQ ID NO. 1054	SEQ ID NO. 1055	SEQ ID NO. 1056
1.265	SEQ ID NO. 1057	SEQ ID NO. 1058	SEQ ID NO. 1059	SEQ ID NO. 1060
1.266	SEQ ID NO. 1061	SEQ ID NO. 1062	SEQ ID NO. 1063	SEQ ID NO. 1064
1.267	SEQ ID NO. 1065	SEQ ID NO. 1066	SEQ ID NO. 1067	SEQ ID NO. 1068
1.268	SEQ ID NO. 1069	SEQ ID NO. 1070	SEQ ID NO. 1071	SEQ ID NO. 1072
1.269	SEQ ID NO. 1073	SEQ ID NO. 1074	SEQ ID NO. 1075	SEQ ID NO. 1076
1.270	SEQ ID NO. 1077	SEQ ID NO. 1078	SEQ ID NO. 1079	SEQ ID NO. 1080
1.271	SEQ ID NO. 1081	SEQ ID NO. 1082	SEQ ID NO. 1083	SEQ ID NO. 1084
1.272	SEQ ID NO. 1085	SEQ ID NO. 1086	SEQ ID NO. 1087	SEQ ID NO. 1088
1.273	SEQ ID NO. 1089	SEQ ID NO. 1090	SEQ ID NO. 1091	SEQ ID NO. 1092

1.274	SEQ ID NO. 1093	SEQ ID NO. 1094	SEQ ID NO. 1095	SEQ ID NO. 1096
1.275	SEQ ID NO. 1097	SEQ ID NO. 1098	SEQ ID NO. 1099	SEQ ID NO. 1100
1.276	SEQ ID NO. 1101	SEQ ID NO. 1102	SEQ ID NO. 1103	SEQ ID NO. 1104
1.277	SEQ ID NO. 1105	SEQ ID NO. 1106	SEQ ID NO. 1107	SEQ ID NO. 1108
1.278	SEQ ID NO. 1109	SEQ ID NO. 1110	SEQ ID NO. 1111	SEQ ID NO. 1112
1.279	SEQ ID NO. 1113	SEQ ID NO. 1114	SEQ ID NO. 1115	SEQ ID NO. 1116
1.280	SEQ ID NO. 1117	SEQ ID NO. 1118	SEQ ID NO. 1119	SEQ ID NO. 1120
1.281	SEQ ID NO. 1121	SEQ ID NO. 1122	SEQ ID NO. 1123	SEQ ID NO. 1124
1.282	SEQ ID NO. 1125	SEQ ID NO. 1126	SEQ ID NO. 1127	SEQ ID NO. 1128
1.283	SEQ ID NO. 1129	SEQ ID NO. 1130	SEQ ID NO. 1131	SEQ ID NO. 1132
1.284	SEQ ID NO. 1133	SEQ ID NO. 1134	SEQ ID NO. 1135	SEQ ID NO. 1136
1.285	SEQ ID NO. 1137	SEQ ID NO. 1138	SEQ ID NO. 1139	SEQ ID NO. 1140
1.286	SEQ ID NO. 1141	SEQ ID NO. 1142	SEQ ID NO. 1143	SEQ ID NO. 1144
1.287	SEQ ID NO. 1145	SEQ ID NO. 1146	SEQ ID NO. 1147	SEQ ID NO. 1148
1.288	SEQ ID NO. 1149	SEQ ID NO. 1150	SEQ ID NO. 1151	SEQ ID NO. 1152
1.289	SEQ ID NO. 1153	SEQ ID NO. 1154	SEQ ID NO. 1155	SEQ ID NO. 1156
1.290	SEQ ID NO. 1157	SEQ ID NO. 1158	SEQ ID NO. 1159	SEQ ID NO. 1160
1.291	SEQ ID NO. 1161	SEQ ID NO. 1162	SEQ ID NO. 1163	SEQ ID NO. 1164
1.292	SEQ ID NO. 1165	SEQ ID NO. 1166	SEQ ID NO. 1167	SEQ ID NO. 1168
1.293	SEQ ID NO. 1169	SEQ ID NO. 1170	SEQ ID NO. 1171	SEQ ID NO. 1172
1.294	SEQ ID NO. 1173	SEQ ID NO. 1174	SEQ ID NO. 1175	SEQ ID NO. 1176
1.295	SEQ ID NO. 1177	SEQ ID NO. 1178	SEQ ID NO. 1179	SEQ ID NO. 1180
1.296	SEQ ID NO. 1181	SEQ ID NO. 1182	SEQ ID NO. 1183	SEQ ID NO. 1184
1.297	SEQ ID NO. 1185	SEQ ID NO. 1186	SEQ ID NO. 1187	SEQ ID NO. 1188
1.298	SEQ ID NO. 1189	SEQ ID NO. 1190	SEQ ID NO. 1191	SEQ ID NO. 1192
1.299	SEQ ID NO. 1193	SEQ ID NO. 1194	SEQ ID NO. 1195	SEQ ID NO. 1196
1.300	SEQ ID NO. 1197	SEQ ID NO. 1198	SEQ ID NO. 1199	SEQ ID NO. 1200
1.301	SEQ ID NO. 1201	SEQ ID NO. 1202	SEQ ID NO. 1203	SEQ ID NO. 1204
1.302	SEQ ID NO. 1205	SEQ ID NO. 1206	SEQ ID NO. 1207	SEQ ID NO. 1208
1.303	SEQ ID NO. 1209	SEQ ID NO. 1210	SEQ ID NO. 1211	SEQ ID NO. 1212
1.304	SEQ ID NO. 1213	SEQ ID NO. 1214	SEQ ID NO. 1215	SEQ ID NO. 1216
1.305	SEQ ID NO. 1217	SEQ ID NO. 1218	SEQ ID NO. 1219	SEQ ID NO. 1220
1.306	SEQ ID NO. 1221	SEQ ID NO. 1222	SEQ ID NO. 1223	SEQ ID NO. 1224

1.307	SEQ ID NO. 1225	SEQ ID NO. 1226	SEQ ID NO. 1227	SEQ ID NO. 1228
1.308	SEQ ID NO. 1229	SEQ ID NO. 1230	SEQ ID NO. 1231	SEQ ID NO. 1232
1.309	SEQ ID NO. 1233	SEQ ID NO. 1234	SEQ ID NO. 1235	SEQ ID NO. 1236
1.310	SEQ ID NO. 1237	SEQ ID NO. 1238	SEQ ID NO. 1239	SEQ ID NO. 1240
1.311	SEQ ID NO. 1241	SEQ ID NO. 1242	SEQ ID NO. 1243	SEQ ID NO. 1244
1.312	SEQ ID NO. 1245	SEQ ID NO. 1246	SEQ ID NO. 1247	SEQ ID NO. 1248
1.313	SEQ ID NO. 1249	SEQ ID NO. 1250	SEQ ID NO. 1251	SEQ ID NO. 1252
1.314	SEQ ID NO. 1253	SEQ ID NO. 1254	SEQ ID NO. 1255	SEQ ID NO. 1256
1.315	SEQ ID NO. 1257	SEQ ID NO. 1258	SEQ ID NO. 1259	SEQ ID NO. 1260
1.316	SEQ ID NO. 1261	SEQ ID NO. 1262	SEQ ID NO. 1263	SEQ ID NO. 1264

Table 1. This shows SEQ ID NOs. of family 1 CDR sequences and of family 1 full-length V_H sequences that are within the scope of the invention. Corresponding sequences are shown in Figure 1.

In one aspect of the invention, the family 1 or family 1-like binding molecule comprises a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 3 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3.

In one embodiment, the family 1 or family 1-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain and wherein said V_H domain comprises at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 3 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3.

In one embodiment, homology is at least 90% homology to SEQ ID NO. 3.

In one embodiment, the CDR3 sequence is selected from one of the CDR3 sequences as shown in table 1 with reference to Fig 1. Thus, the CDR3 sequence is selected from SEQ ID Nos. 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 51, 55, 59, 63, 67, 71, 75, 79, 83, 87, 91, 95, 99, 103, 107, 111, 115, 119, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171,175, 179, 183, 187, 191, 195, 199, 203, 207, 211, 215, 219, 223, 227, 231, 235, 239, 243,247, 251, 255, 259, 263, 267, 271, 275, 279, 283, 287, 291, 295, 299, 30, 307, 311, 315, 319, 323, 327, 331, 335, 339, 343, 347, 351, 355, 363,

367, 371, 375, 379, 383, 387, 391, 395, 399, 403, 407, 411, 415, 419, 423, 427, 431, 435, 439, 443, 447, 451, 455, 459, 463, 467, 471, 475, 479, 483, 487, 491, 495, 499, 503. 507, 511, 515, 519, 523, 527, 531, 535, 539, 543, 547, 551, 555, 563, 567, 571, 575, 579, 583, 587, 591, 595, 599, 603, 607, 611, 615, 619, 623, 627, 631, 635, 639, 643, 647, 651, 655, 659, 663, 667, 675, 679, 683, 687, 691, 695, 699, 703, 707, 711, 715, 723, 727, 731, 735, 739, 743, 747, 751, 755, 759, 763, 767, 771, 775, 779, 783, 787, 791, 795, 799, 803, 807, 811, 815, 819, 823, 827, 831, 835, 839, 843, 847, 851, 855, 859, 871, 875, 879, 883, 887, 891, 895, 899, 903, 907, 911, 915, 919, 923, 927, 931, 935, 939, 943, 947, 951, 955, 959, 963, 967, 971, 975, 979, 983, 987, 991, 995, 999, 1003, 1007, 1011, 1015, 1019, 1023, 1027, 1031, 1035, 1039, 1043, 1047, 1051, 1055, 1059, 1063, 1067, 1071, 1075, 1079, 1083, 1087, 1091, 1095, 1099, 1103, 1107, 1111, 1115, 1119, 1123, 1127, 1131, 1135, 1139, 1143, 1147, 1151, 1155, 1159, 1163, 1167, 1171, 1175, 1179, 1183, 1187, 1191, 1195, 1199, 1203, 1207, 1211, 1215, 1219, 1223, 1227, 1231, 1235, 1239, 1243, 1247, 1251, 1259 or 1263.

In one embodiment, the family 1 or family 1-like binding molecule comprises at least one antigen binding site comprising CDR1, CDR2 and CDR3, said CDR1 region comprising or consisting of amino acid sequence SEQ ID NO. 1 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 region comprising or consisting of the amino acid sequence SEQ ID NO. 2 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 region comprising or consisting of the amino acid sequence SEQ ID NO. 3 or a sequence with at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. For example, the CDR sequence may be a CDR sequence selected from those shown in Figure 1.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 1 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence as shown in SEQ ID NO: 2 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 3 or a sequence with at least 60%, 65%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In one embodiment, CDR1 comprises or consists of one of the CDR1 amino acid sequence listed above in table 1 with reference to Fig. 1, CDR2 comprises or consists of one of the CDR2 amino acid sequence listed above in table 1 with reference to Fig. 1 and CDR3 comprises or consists of one of the CDR3 amino acid sequence listed above in table 1 with reference to Fig. 1. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 1.1 to 1.316 in Figure 1. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 1.1 to 1.6 in Figure 1. In one embodiment, the binding molecule comprises a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 1.1 to 1.316 in Figure 1. In one embodiment, the binding molecule has a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 1.1 to 1.6 in Figure 1.

Thus, in one embodiment, CDR1 is SEQ ID NO. 1, CDR2 is SEQ ID NO. 2 and CDR3 is SEQ ID NO. 3. In another embodiment, CDR1 is SEQ ID NO. 5, CDR2 is SEQ ID NO. 6 and CDR3 is SEQ ID NO. 7. In another embodiment, CDR1 is SEQ ID NO. 9, CDR2 is SEQ ID NO. 10 and CDR3 is SEQ ID NO. 11. In another embodiment, CDR1 is SEQ ID NO. 13, CDR2 is SEQ ID NO. 14 and CDR3 is SEQ ID NO. 15. In another embodiment, CDR1 is SEQ ID NO. 17, CDR2 is SEQ ID NO. 18 and CDR3 is SEQ ID NO. 19. In another embodiment, CDR1 is SEQ ID NO. 21, CDR2 is SEQ ID NO. 22 and CDR3 is SEQ ID NO. 23.

In one embodiment, the family 1 or family 1-like sequence has a V_H domain that comprises or consists of SEQ ID NO. 4 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. CDR sequences of such sequences are shown in Figure 1. For example, the V_H domain comprises or consists of one of the V_H amino acid sequences listed above for clones 1.1 to 1.316 in table 1 with reference to Fig. 1. Thus, the V_H sequence comprises or consists of a sequence selected from SEQ ID NOs. 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, 360, 364, 368, 372, 376, 380, 384, 388, 392, 396, 400, 404, 408, 412, 416, 420, 424,

428, 432, 436, 440, 444, 448, 452, 456, 460, 464, 468, 472, 476, 480, 484, 488, 492, 496, 500, 504, 508, 512, 516, 520, 524, 528, 532, 536, 540, 544, 548, 552, 556, 560, 564, 568, 572, 576, 580, 584, 588, 592, 596, 600, 604, 608, 612, 616, 620, 624, 628, 632, 636, 640, 644, 648, 652, 656, 660, 664, 668, 672, 676, 680, 684, 688, 692, 696, 700, 704, 708, 712, 716, 720, 724, 728, 732, 736, 740, 744, 748, 752, 756, 760, 764, 768, 772, 776, 780, 784. 788, 792, 796, 800, 804, 808, 812, 816, 820, 824, 828, 832, 836, 840, 844, 848, 852, 856, 860, 864, 868, 872, 876, 880, 884, 888, 892 896, 900, 904, 908, 912, 916, 920, 924, 928, 932, 936, 940, 944, 948, 952, 956, 960, 964, 968, 972, 976, 980, 984, 988, 992, 996, 1000, 1004, 1008, 1012, 1016, 1020, 1024, 1028, 1032, 1036, 1040, 1044, 1048, 1052, 1056, 1060, 1064, 1068, 1072, 1076, 108,0 1084, 1088, 1092, 1096, 1100, 1104, 1108, 1112, 1116 1120, 1124, 1128, 1132, 1136, 1140, 1144, 1148, 1152, 1156, 1160, 1164, 1168, 1172, 1176, 1180, 1184, 1188, 1192, 1196, 1200, 1204, 1208, 1212, 1216, 1220, 1224, 1228, 1232, 1236, 1240, 1244, 1248, 1252, 1256, 1260 or 1264. In another embodiment, the V_H sequence is selected from one of the sequences in the forgoing but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences. In one embodiment, the V_H domain comprises or consists of SEQ ID NO. 4 or a sequence which comprises one or more amino acid substitutions, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions.

In one embodiment, said V_H domain comprises or consists of a sequence selected from SEQ ID NOs. 4, 8, 12, 16, 20 or 24 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In another aspect, the invention relates to a binding molecule comprising or consisting of a V_H domain as shown in SEQ ID NO. 4 or a variant thereof comprising amino acid substitutions compared to SEQ ID NO. 4 as follows residue 1 is E, residue 30 is A, residue 55 is A, residue 58 is K, I, residue 59 is G, residue 63 is T, residue 100 is S, residue 101 is S, residue 104 is Y and/or residue 106 is S.

The family 1 or family 1-like binding molecules preferably have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

The term "KD" refers to the "equilibrium dissociation constant" and refers to the value obtained in a titration measurement at equilibrium, or by dividing the dissociation rate constant (Koff) by the association rate constant (Kon). “KA” refers to the affinity constant. The association rate constant, the dissociation rate constant and the equilibrium dissociation constant are used to represent the binding affinity of an antibody to an antigen. Methods for determining association and dissociation rate constants are well known in the art. Using fluorescence-based techniques offers high sensitivity and the ability to examine samples in physiological buffers at equilibrium. Other experimental approaches and instruments such as a BIAcore® (biomolecular interaction analysis) assay can be used.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 2 or family 2-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said IL-17RA binding molecule comprises a family 2 or family 2-like sequence. These include the parent sequence and sequences of clones that are derived from the parent clone (clone 2.2) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones or parts thereof that are derived from the parent clone 2.1 through a process of optimization, for example as shown in Figure 2. CDR sequences and full length sequences of clones in family 2 are numbered according to table 2 as shown below.

Clone name	**CDR1** Seq ID No	**CDR2** Seq ID No	**CDR3** Seq ID No	**VH Full length sequence** Seq ID No
2.1	SEQ ID NO. 1265	SEQ ID NO. 1266	SEQ ID NO. 1267	SEQ ID NO. 1268
2.2	SEQ ID NO. 1269	SEQ ID NO. 1270	SEQ ID NO. 1271	SEQ ID NO. 1272
2.3	SEQ ID NO. 1273	SEQ ID NO. 1274	SEQ ID NO. 1275	SEQ ID NO. 1276
2.4	SEQ ID NO. 1277	SEQ ID NO. 1278	SEQ ID NO. 1279	SEQ ID NO. 1280
2.5	SEQ ID NO. 1281	SEQ ID NO. 1282	SEQ ID NO. 1283	SEQ ID NO. 1284
2.6	SEQ ID NO. 1285	SEQ ID NO. 1286	SEQ ID NO. 1287	SEQ ID NO. 1288
2.7	SEQ ID NO. 1289	SEQ ID NO. 1290	SEQ ID NO. 1291	SEQ ID NO. 1292
2.8	SEQ ID NO. 1293	SEQ ID NO. 1294	SEQ ID NO. 1295	SEQ ID NO. 1296
2.9	SEQ ID NO. 1297	SEQ ID NO. 1298	SEQ ID NO. 1299	SEQ ID NO. 1300
2.10	SEQ ID NO. 1301	SEQ ID NO. 1302	SEQ ID NO. 1303	SEQ ID NO. 1304
2.11	SEQ ID NO. 1305	SEQ ID NO. 1306	SEQ ID NO. 1307	SEQ ID NO. 1308
2.12	SEQ ID NO. 1309	SEQ ID NO. 1310	SEQ ID NO. 1311	SEQ ID NO. 1312

2.13	SEQ ID NO. 1313	SEQ ID NO. 1314	SEQ ID NO. 1315	SEQ ID NO. 1316
2.14	SEQ ID NO. 1317	SEQ ID NO. 1318	SEQ ID NO. 1319	SEQ ID NO. 1320
2.15	SEQ ID NO. 1321	SEQ ID NO. 1322	SEQ ID NO. 1323	SEQ ID NO. 1324
2.16	SEQ ID NO. 1325	SEQ ID NO. 1326	SEQ ID NO. 1327	SEQ ID NO. 1328
2.17	SEQ ID NO. 1329	SEQ ID NO. 1330	SEQ ID NO. 1331	SEQ ID NO. 1332
2.18	SEQ ID NO. 1333	SEQ ID NO. 1334	SEQ ID NO. 1335	SEQ ID NO. 1336
2.19	SEQ ID NO. 1337	SEQ ID NO. 1338	SEQ ID NO. 1339	SEQ ID NO. 1340
2.20	SEQ ID NO. 1341	SEQ ID NO. 1342	SEQ ID NO. 1343	SEQ ID NO. 1344
2.21	SEQ ID NO. 1345	SEQ ID NO. 1346	SEQ ID NO. 1347	SEQ ID NO. 1348
2.22	SEQ ID NO. 1349	SEQ ID NO. 1350	SEQ ID NO. 1351	SEQ ID NO. 1352
2.23	SEQ ID NO. 1353	SEQ ID NO. 1354	SEQ ID NO. 1355	SEQ ID NO. 1356
2.24	SEQ ID NO. 1357	SEQ ID NO. 1358	SEQ ID NO. 1359	SEQ ID NO. 1360
2.25	SEQ ID NO. 1361	SEQ ID NO. 1362	SEQ ID NO. 1363	SEQ ID NO. 1364
2.26	SEQ ID NO. 1365	SEQ ID NO. 1366	SEQ ID NO. 1367	SEQ ID NO. 1368
2.27	SEQ ID NO. 1369	SEQ ID NO. 1370	SEQ ID NO. 1371	SEQ ID NO. 1372
2.28	SEQ ID NO. 1373	SEQ ID NO. 1374	SEQ ID NO. 1375	SEQ ID NO. 1376
2.29	SEQ ID NO. 1377	SEQ ID NO. 1378	SEQ ID NO. 1379	SEQ ID NO. 1380
2.30	SEQ ID NO. 1381	SEQ ID NO. 1382	SEQ ID NO. 1383	SEQ ID NO. 1384
2.31	SEQ ID NO. 1385	SEQ ID NO. 1386	SEQ ID NO. 1387	SEQ ID NO. 1388
2.32	SEQ ID NO. 1389	SEQ ID NO. 1390	SEQ ID NO. 1391	SEQ ID NO. 1392
2.33	SEQ ID NO. 1393	SEQ ID NO. 1394	SEQ ID NO. 1395	SEQ ID NO. 1396
2.34	SEQ ID NO. 1397	SEQ ID NO. 1398	SEQ ID NO. 1399	SEQ ID NO. 1400
2.35	SEQ ID NO. 1401	SEQ ID NO. 1402	SEQ ID NO. 1403	SEQ ID NO. 1404
2.36	SEQ ID NO. 1405	SEQ ID NO. 1406	SEQ ID NO. 1407	SEQ ID NO. 1408
2.37	SEQ ID NO. 1409	SEQ ID NO. 1410	SEQ ID NO. 1411	SEQ ID NO. 1412
2.38	SEQ ID NO. 1413	SEQ ID NO. 1414	SEQ ID NO. 1415	SEQ ID NO. 1416
2.39	SEQ ID NO. 1417	SEQ ID NO. 1418	SEQ ID NO. 1419	SEQ ID NO. 1420
2.40	SEQ ID NO. 1421	SEQ ID NO. 1422	SEQ ID NO. 1423	SEQ ID NO. 1424
2.41	SEQ ID NO. 1425	SEQ ID NO. 1426	SEQ ID NO. 1427	SEQ ID NO. 1428
2.42	SEQ ID NO. 1429	SEQ ID NO. 1430	SEQ ID NO. 1431	SEQ ID NO. 1432
2.43	SEQ ID NO. 1433	SEQ ID NO. 1434	SEQ ID NO. 1435	SEQ ID NO. 1436
2.44	SEQ ID NO. 1437	SEQ ID NO. 1438	SEQ ID NO. 1439	SEQ ID NO. 1440
2.45	SEQ ID NO. 1441	SEQ ID NO. 1442	SEQ ID NO. 1443	SEQ ID NO. 1444
2.46	SEQ ID NO. 1445	SEQ ID NO. 1446	SEQ ID NO. 1447	SEQ ID NO. 1448
2.47	SEQ ID NO. 1449	SEQ ID NO. 1450	SEQ ID NO. 1451	SEQ ID NO. 1452
2.48	SEQ ID NO. 1453	SEQ ID NO. 1454	SEQ ID NO. 1455	SEQ ID NO. 1456
2.49	SEQ ID NO. 1457	SEQ ID NO. 1458	SEQ ID NO. 1459	SEQ ID NO. 1460
2.50	SEQ ID NO. 1461	SEQ ID NO. 1462	SEQ ID NO. 1463	SEQ ID NO. 1464
2.51	SEQ ID NO. 1465	SEQ ID NO. 1466	SEQ ID NO. 1467	SEQ ID NO. 1468
2.52	SEQ ID NO. 1469	SEQ ID NO. 1470	SEQ ID NO. 1471	SEQ ID NO. 1472
2.53	SEQ ID NO. 1473	SEQ ID NO. 1474	SEQ ID NO. 1475	SEQ ID NO. 1476
2.54	SEQ ID NO. 1477	SEQ ID NO. 1478	SEQ ID NO. 1479	SEQ ID NO. 1480
2.55	SEQ ID NO. 1481	SEQ ID NO. 1482	SEQ ID NO. 1483	SEQ ID NO. 1484
2.56	SEQ ID NO. 1485	SEQ ID NO. 1486	SEQ ID NO. 1487	SEQ ID NO. 1488

2.57	SEQ ID NO. 1489	SEQ ID NO. 1490	SEQ ID NO. 1491	SEQ ID NO. 1492
2.58	SEQ ID NO. 1493	SEQ ID NO. 1494	SEQ ID NO. 1495	SEQ ID NO. 1496
2.59	SEQ ID NO. 1497	SEQ ID NO. 1498	SEQ ID NO. 1499	SEQ ID NO. 1500
2.60	SEQ ID NO. 1501	SEQ ID NO. 1502	SEQ ID NO. 1503	SEQ ID NO. 1504
2.61	SEQ ID NO. 1505	SEQ ID NO. 1506	SEQ ID NO. 1507	SEQ ID NO. 1508
2.62	SEQ ID NO. 1509	SEQ ID NO. 1510	SEQ ID NO. 1511	SEQ ID NO. 1512
2.63	SEQ ID NO. 1513	SEQ ID NO. 1514	SEQ ID NO. 1515	SEQ ID NO. 1516
2.64	SEQ ID NO. 1517	SEQ ID NO. 1518	SEQ ID NO. 1519	SEQ ID NO. 1520
2.65	SEQ ID NO. 1521	SEQ ID NO. 1522	SEQ ID NO. 1523	SEQ ID NO. 1524
2.66	SEQ ID NO. 1525	SEQ ID NO. 1526	SEQ ID NO. 1527	SEQ ID NO. 1528
2.67	SEQ ID NO. 1529	SEQ ID NO. 1530	SEQ ID NO. 1531	SEQ ID NO. 1532
2.68	SEQ ID NO. 1533	SEQ ID NO. 1534	SEQ ID NO. 1535	SEQ ID NO. 1536
2.69	SEQ ID NO. 1537	SEQ ID NO. 1538	SEQ ID NO. 1539	SEQ ID NO. 1540
2.70	SEQ ID NO. 1541	SEQ ID NO. 1542	SEQ ID NO. 1543	SEQ ID NO. 1544
2.71	SEQ ID NO. 1545	SEQ ID NO. 1546	SEQ ID NO. 1547	SEQ ID NO. 1548
2.72	SEQ ID NO. 1549	SEQ ID NO. 1550	SEQ ID NO. 1551	SEQ ID NO. 1552
2.73	SEQ ID NO. 1553	SEQ ID NO. 1554	SEQ ID NO. 1555	SEQ ID NO. 1556
2.74	SEQ ID NO. 1557	SEQ ID NO. 1558	SEQ ID NO. 1559	SEQ ID NO. 1560
2.75	SEQ ID NO. 1561	SEQ ID NO. 1562	SEQ ID NO. 1563	SEQ ID NO. 1564
2.76	SEQ ID NO. 1565	SEQ ID NO. 1566	SEQ ID NO. 1567	SEQ ID NO. 1568
2.77	SEQ ID NO. 1569	SEQ ID NO. 1570	SEQ ID NO. 1571	SEQ ID NO. 1572
2.78	SEQ ID NO. 1573	SEQ ID NO. 1574	SEQ ID NO. 1575	SEQ ID NO. 1576
2.79	SEQ ID NO. 1577	SEQ ID NO. 1578	SEQ ID NO. 1579	SEQ ID NO. 1580
2.80	SEQ ID NO. 1581	SEQ ID NO. 1582	SEQ ID NO. 1583	SEQ ID NO. 1584
2.81	SEQ ID NO. 1585	SEQ ID NO. 1586	SEQ ID NO. 1587	SEQ ID NO. 1588
2.82	SEQ ID NO. 1589	SEQ ID NO. 1590	SEQ ID NO. 1591	SEQ ID NO. 1592
2.83	SEQ ID NO. 1593	SEQ ID NO. 1594	SEQ ID NO. 1595	SEQ ID NO. 1596
2.84	SEQ ID NO. 1597	SEQ ID NO. 1598	SEQ ID NO. 1599	SEQ ID NO. 1600
2.85	SEQ ID NO. 1601	SEQ ID NO. 1602	SEQ ID NO. 1603	SEQ ID NO. 1604
2.86	SEQ ID NO. 1605	SEQ ID NO. 1606	SEQ ID NO. 1607	SEQ ID NO. 1608
2.87	SEQ ID NO. 1609	SEQ ID NO. 1610	SEQ ID NO. 1611	SEQ ID NO. 1612
2.88	SEQ ID NO. 1613	SEQ ID NO. 1614	SEQ ID NO. 1615	SEQ ID NO. 1616
2.89	SEQ ID NO. 1617	SEQ ID NO. 1618	SEQ ID NO. 1619	SEQ ID NO. 1620
2.90	SEQ ID NO. 1621	SEQ ID NO. 1622	SEQ ID NO. 1623	SEQ ID NO. 1624
2.91	SEQ ID NO. 1625	SEQ ID NO. 1626	SEQ ID NO. 1627	SEQ ID NO. 1628
2.92	SEQ ID NO. 1629	SEQ ID NO. 1630	SEQ ID NO. 1631	SEQ ID NO. 1632
2.93	SEQ ID NO. 1633	SEQ ID NO. 1634	SEQ ID NO. 1635	SEQ ID NO. 1636
2.94	SEQ ID NO. 1637	SEQ ID NO. 1638	SEQ ID NO. 1639	SEQ ID NO. 1640
2.95	SEQ ID NO. 1641	SEQ ID NO. 1642	SEQ ID NO. 1643	SEQ ID NO. 1644
2.96	SEQ ID NO. 1645	SEQ ID NO. 1646	SEQ ID NO. 1647	SEQ ID NO. 1648
2.97	SEQ ID NO. 1649	SEQ ID NO. 1650	SEQ ID NO. 1651	SEQ ID NO. 1652
2.98	SEQ ID NO. 1653	SEQ ID NO. 1654	SEQ ID NO. 1655	SEQ ID NO. 1656
2.99	SEQ ID NO. 1657	SEQ ID NO. 1658	SEQ ID NO. 1659	SEQ ID NO. 1660
2.100	SEQ ID NO. 1661	SEQ ID NO. 1662	SEQ ID NO. 1663	SEQ ID NO. 1664

2.101	SEQ ID NO. 1665	SEQ ID NO. 1666	SEQ ID NO. 1667	SEQ ID NO. 1668
2.102	SEQ ID NO. 1669	SEQ ID NO. 1670	SEQ ID NO. 1671	SEQ ID NO. 1672
2.103	SEQ ID NO. 1673	SEQ ID NO. 1674	SEQ ID NO. 1675	SEQ ID NO. 1676
2.104	SEQ ID NO. 1677	SEQ ID NO. 1678	SEQ ID NO. 1679	SEQ ID NO. 1680
2.105	SEQ ID NO. 1681	SEQ ID NO. 1682	SEQ ID NO. 1683	SEQ ID NO. 1684
2.106	SEQ ID NO. 1685	SEQ ID NO. 1686	SEQ ID NO. 1687	SEQ ID NO. 1688
2.107	SEQ ID NO. 1689	SEQ ID NO. 1690	SEQ ID NO. 1691	SEQ ID NO. 1692
2.108	SEQ ID NO. 1693	SEQ ID NO. 1694	SEQ ID NO. 1695	SEQ ID NO. 1696
2.109	SEQ ID NO. 1697	SEQ ID NO. 1698	SEQ ID NO. 1699	SEQ ID NO. 1700
2.110	SEQ ID NO. 1701	SEQ ID NO. 1702	SEQ ID NO. 1703	SEQ ID NO. 1704
2.111	SEQ ID NO. 1705	SEQ ID NO. 1706	SEQ ID NO. 1707	SEQ ID NO. 1708
2.112	SEQ ID NO. 1709	SEQ ID NO. 1710	SEQ ID NO. 1711	SEQ ID NO. 1712
2.113	SEQ ID NO. 1713	SEQ ID NO. 1714	SEQ ID NO. 1715	SEQ ID NO. 1716
2.114	SEQ ID NO. 1717	SEQ ID NO. 1718	SEQ ID NO. 1719	SEQ ID NO. 1720
2.115	SEQ ID NO. 1721	SEQ ID NO. 1722	SEQ ID NO. 1723	SEQ ID NO. 1724
2.116	SEQ ID NO. 1725	SEQ ID NO. 1726	SEQ ID NO. 1727	SEQ ID NO. 1728
2.117	SEQ ID NO. 1729	SEQ ID NO. 1730	SEQ ID NO. 1731	SEQ ID NO. 1732
2.118	SEQ ID NO. 1733	SEQ ID NO. 1734	SEQ ID NO. 1735	SEQ ID NO. 1736
2.119	SEQ ID NO. 1737	SEQ ID NO. 1738	SEQ ID NO. 1739	SEQ ID NO. 1740
2.120	SEQ ID NO. 1741	SEQ ID NO. 1742	SEQ ID NO. 1743	SEQ ID NO. 1744
2.121	SEQ ID NO. 1745	SEQ ID NO. 1746	SEQ ID NO. 1747	SEQ ID NO. 1748
2.122	SEQ ID NO. 1749	SEQ ID NO. 1750	SEQ ID NO. 1751	SEQ ID NO. 1752
2.123	SEQ ID NO. 1753	SEQ ID NO. 1754	SEQ ID NO. 1755	SEQ ID NO. 1756
2.124	SEQ ID NO. 1757	SEQ ID NO. 1758	SEQ ID NO. 1759	SEQ ID NO. 1760
2.125	SEQ ID NO. 1761	SEQ ID NO. 1762	SEQ ID NO. 1763	SEQ ID NO. 1764

Table 2. This shows SEQ ID NOs of family 2 CDR sequences and of family 2 full-length V_H sequences that are within the scope of the invention. Corresponding sequences are shown in Figure 2.

In one aspect, the invention relates to a family 2 or family 2-like binding molecule comprises a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1237 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1237.

In one embodiment, the family 2 or family 2-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain and wherein said V_H comprises at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 1267 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. In one embodiment, sequence homology is at least 90%.

In one embodiment, the CDR3 sequence is selected from one of the CDR3 sequences as shown in table 2 with reference to Fig 2. Thus, the CDR3 region comprises or consists of a sequence selected from SEQ ID Nos. 1267, 1271, 1275, 1279, 1283, 1287, 1291, 1295, 1299, 1303, 1307, 1311, 1315, 1319, 1323, 1327, 1331, 1335, 1339, 1343, 1347, 1351, 1355, 1359, 1363, 1367, 1371, 13751379, 1383, 1387, 1391, 1395, 1399, 1403, 1407, 1411, 1415, 1419, 1423, 1427, 1431, 1435, 1439, 1443, 1447, 1451, 1455, 1459, 1463, 1467, 1471, 1475, 1479, 1483, 1487, 1491, 1495, 1499, 1503, 1507, 1511, 1515, 1519, 1523, 1527, 1531, 1535, 1539, 1543,, 1547, 1551, 1555, 1559, 1563, 1567, 1571, 1575, 1579, 1583, 1587, 1591, 1595, 1599, 1603, 1607, 1611, 1615, 1619, 1623, 1627, 1631, 1635, 1639, 1643, 1647, 1651, 1655, 1659, 1663, 1667, 1671, 1675, 1679, 1683, 1687, 1691, 1695, 1699, 1703, 1707, 1711, 1715, 1719, 1723, 1727, 1731, 1735, 1739, 1743, 1747, 1751, 1755, 1759 or 1763.

In one embodiment, the family 2 or family 2-like sequence comprises at least one antigen binding site comprising hypervariable regions CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 1265 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 1266 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 1267 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. For example, the CDR sequence may be a CDR sequence selected from those shown in Figure 2.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 1265 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 1266 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 1267 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In one embodiment, CDR1 comprises or consists of one of the CDR1 amino acid sequence listed above in table 2 with reference to Fig. 2, CDR2 comprises or consists of one of the CDR2 amino acid sequence listed above in table 2 with reference to Fig. 2 and CDR3 comprises or consists of one of the CDR3 amino acid sequence listed above in table 2 with reference to Fig. 2. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 2.1 to 2.125 in Figure 2. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 2.1 to 2.3 in Figure 2.

In one embodiment, the binding molecule comprises a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 2.1 to 2.125 in Figure 2. In one embodiment, the binding molecule has a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 2.1 to 2.3 in Figure 2.

Thus, in one embodiment, CDR1 is SEQ ID NO. 1269, CDR2 is SEQ ID NO. 1270 and CDR3 is SEQ ID NO. 1271. In another embodiment, CDR1 is SEQ ID NO. 1272, CDR2 is SEQ ID NO. 1273 and CDR3 is SEQ ID NO. 1274.

In one embodiment, the family 2 or family 2-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 1268 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. CDR sequences of such sequences are shown in Figure 2. For example, the V_H domain comprises or consists of one of the V_H amino acid sequences listed above for clones 2.1 to 2.125 in table 2 with reference to figure 2.

Thus, the V_H domain comprises or consists of a sequence selected from SEQ ID NOs. 1268, 1272, 1276, 1280, 1284, 1288, 1292, 1296, 1300, 1304, 1308, 1312, 1316, 1320 1324, 1328, 1332, 1336, 1340, 1344, 1348, 1352, 1356, 1360, 1364, 1368, 1372, 1376 1380, 1384, 1388, 1392, 1396, 1400, 1404, 1408, 1412, 1416, 1420, 1424, 1428, 1432, 1436, 1440, 1444, 1448, 1452, 1456, 1460, 1464, 1468, 1476, 1480, 1484, 1488, 1492, 1496, 1500, 1504, 1508, 1512, 1516, 1520, 1524, 1528, 1532, 1536, 1540, 1544, 1548, 1552, 1556, 1560, 1564, , 1568, 1572, 1576, 1580, 1584, 1588, 1592, 1596, 1600, 1604, 1608, 1612, 1616, 1620, 1624, 1628, 1632, 1636, 1640, 1644, 1648, 1652, 1656, 1660, 1664, 1668, 1672, 1676, 1680, 1684, 1688, 1692, 1696, 1700,1704, 1708, 1712, 1716
1720, 1724, 1728, 1732, 1736, 1740, 1744, 1748, 1752, 1756, 1760 or 1764.

In another embodiment, the V_H domain comprises a sequence selected from one of the sequences in the forgoing but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences. In one embodiment, the V_H domain comprises or consists of SEQ ID NO. 1268 or a sequence which comprises one or more amino acid substitutions, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. For example, V_H domain comprises or consists of a sequence selected from SEQ ID NO. 1268 or 1272.

In one embodiment, the family 2 or family 2-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 1268 or 1272, or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 96%, 97%, 98%, 99% homology thereto.

In another aspect, the invention relates to a binding molecule comprising or consisting of a V_H domain as shown in SEQ ID NO. 1268 or a variant thereof comprising amino acid substitutions compared to SEQ ID NO. 1268 as follows residue 31 is T, residue 43 is R, 54 is G, E, K, A, D, residue 55 is S, residue 57 is D, Y, N and/or residue 100 is I.

The family 2 or family 2-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In one aspect, the invention relates to an isolated binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (V_H) wherein said V_H domain comprises a family 3 or family 3-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said VH domain comprises a family 3 or family 3-like sequence. These include the V_H sequence of the parent clone (clone 3.1) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones or that are derived from the parent clone 3.1 through a process of optimization, for example as shown in Figure 3. CDR sequences and full length sequences of clones in family 3 are numbered according to table 3 as shown below.

Clone	CDR1 Seq ID No	CDR2 Seq ID No	CDR3 Seq ID No	FULL LENGTH Seq ID No
3.1	Seq ID No 1765	Seq ID No 1766	Seq ID No 1767	Seq ID No 1768
3.2	Seq ID No 1769	Seq ID No 1770	Seq ID No 1771	Seq ID No 1772
3.3	Seq ID No 1773	Seq ID No 1774	Seq ID No 1775	Seq ID No 1776
3.4	Seq ID No 1777	Seq ID No 1778	Seq ID No 1779	Seq ID No 1780
3.5	Seq ID No 1781	Seq ID No 1782	Seq ID No 1783	Seq ID No 1784
3.6	Seq ID No 1785	Seq ID No 1786	Seq ID No 1787	Seq ID No 1788
3.7	Seq ID No 1789	Seq ID No 1790	Seq ID No 1791	Seq ID No 1792
3.8	Seq ID No 1793	Seq ID No 1794	Seq ID No 1795	Seq ID No 1796
3.9	Seq ID No 1797	Seq ID No 1798	Seq ID No 1799	Seq ID No 1800
3.10	Seq ID No 1801	Seq ID No 1802	Seq ID No 1803	Seq ID No 1804
3.11	Seq ID No 1805	Seq ID No 1806	Seq ID No 1807	Seq ID No 1808
3.12	Seq ID No 1809	Seq ID No 1810	Seq ID No 1811	Seq ID No 1812
3.13	Seq ID No 1813	Seq ID No 1814	Seq ID No 1815	Seq ID No 1816
3.14	Seq ID No 1817	Seq ID No 1818	Seq ID No 1819	Seq ID No 1820
3.15	Seq ID No 1821	Seq ID No 1822	Seq ID No 1823	Seq ID No 1824
3.16	Seq ID No 1825	Seq ID No 1826	Seq ID No 1827	Seq ID No 1828
3.17	Seq ID No 1829	Seq ID No 1830	Seq ID No 1831	Seq ID No 1832
3.18	Seq ID No 1833	Seq ID No 1834	Seq ID No 1835	Seq ID No 1836
3.19	Seq ID No 1837	Seq ID No 1838	Seq ID No 1839	Seq ID No 1840
3.20	Seq ID No 1841	Seq ID No 1842	Seq ID No 1843	Seq ID No 1844
3.21	Seq ID No 1845	Seq ID No 1846	Seq ID No 1847	Seq ID No 1848
3.22	Seq ID No 1849	Seq ID No 1850	Seq ID No 1851	Seq ID No 1852
3.23	Seq ID No 1853	Seq ID No 1854	Seq ID No 1855	Seq ID No 1856
3.24	Seq ID No 1857	Seq ID No 1858	Seq ID No 1859	Seq ID No 1860
3.25	Seq ID No 1861	Seq ID No 1862	Seq ID No 1863	Seq ID No 1864
3.26	Seq ID No 1865	Seq ID No 1866	Seq ID No 1867	Seq ID No 1868
3.27	Seq ID No 1869	Seq ID No 1870	Seq ID No 1871	Seq ID No 1872
3.28	Seq ID No 1873	Seq ID No 1874	Seq ID No 1875	Seq ID No 1876
3.29	Seq ID No 1877	Seq ID No 1878	Seq ID No 1879	Seq ID No 1880
3.30	Seq ID No 1881	Seq ID No 1882	Seq ID No 1883	Seq ID No 1884
3.31	Seq ID No 1885	Seq ID No 1886	Seq ID No 1887	Seq ID No 1888
3.32	Seq ID No 1889	Seq ID No 1890	Seq ID No 1891	Seq ID No 1892
3.33	Seq ID No 1893	Seq ID No 1894	Seq ID No 1895	Seq ID No 1896
3.34	Seq ID No 1897	Seq ID No 1898	Seq ID No 1899	Seq ID No 1900
3.35	Seq ID No 1901	Seq ID No 1902	Seq ID No 1903	Seq ID No 1904
3.36	Seq ID No 1905	Seq ID No 1906	Seq ID No 1907	Seq ID No 1908

3.37	Seq ID No 1909	Seq ID No 1910	Seq ID No 1911	Seq ID No 1912
3.38	Seq ID No 1913	Seq ID No 1914	Seq ID No 1915	Seq ID No 1916
3.39	Seq ID No 1917	Seq ID No 1918	Seq ID No 1919	Seq ID No 1920
3.40	Seq ID No 1921	Seq ID No 1922	Seq ID No 1923	Seq ID No 1924
3.41	Seq ID No 1925	Seq ID No 1926	Seq ID No 1927	Seq ID No 1928
3.42	Seq ID No 1929	Seq ID No 1930	Seq ID No 1931	Seq ID No 1932
3.43	Seq ID No 1933	Seq ID No 1934	Seq ID No 1935	Seq ID No 1936
3.44	Seq ID No 1937	Seq ID No 1938	Seq ID No 1939	Seq ID No 1940
3.45	Seq ID No 1941	Seq ID No 1942	Seq ID No 1943	Seq ID No 1944
3.46	Seq ID No 1945	Seq ID No 1946	Seq ID No 1947	Seq ID No 1948
3.47	Seq ID No 1949	Seq ID No 1950	Seq ID No 1951	Seq ID No 1952
3.48	Seq ID No 1953	Seq ID No 1954	Seq ID No 1955	Seq ID No 1956
3.49	Seq ID No 1957	Seq ID No 1958	Seq ID No 1959	Seq ID No 1960
3.50	Seq ID No 1961	Seq ID No 1962	Seq ID No 1963	Seq ID No 1964
3.51	Seq ID No 1965	Seq ID No 1966	Seq ID No 1967	Seq ID No 1968
3.52	Seq ID No 1969	Seq ID No 1970	Seq ID No 1971	Seq ID No 1972
3.53	Seq ID No 1973	Seq ID No 1974	Seq ID No 1975	Seq ID No 1976
3.54	Seq ID No 1977	Seq ID No 1978	Seq ID No 1979	Seq ID No 1980
3.55	Seq ID No 1981	Seq ID No 1982	Seq ID No 1983	Seq ID No 1984
3.56	Seq ID No 1985	Seq ID No 1986	Seq ID No 1987	Seq ID No 1988
3.57	Seq ID No 1989	Seq ID No 1990	Seq ID No 1991	Seq ID No 1992
3.58	Seq ID No 1993	Seq ID No 1994	Seq ID No 1995	Seq ID No 1996
3.59	Seq ID No 1997	Seq ID No 1998	Seq ID No 1999	Seq ID No 2000
3.60	Seq ID No 2001	Seq ID No 2002	Seq ID No 2003	Seq ID No 2004
3.61	Seq ID No 2005	Seq ID No 2006	Seq ID No 2007	Seq ID No 2008
3.62	Seq ID No 2009	Seq ID No 2010	Seq ID No 2011	Seq ID No 2012
3.63	Seq ID No 2013	Seq ID No 2014	Seq ID No 2015	Seq ID No 2016
3.64	Seq ID No 2017	Seq ID No 2018	Seq ID No 2019	Seq ID No 2020
3.65	Seq ID No 2021	Seq ID No 2022	Seq ID No 2023	Seq ID No 2024
3.66	Seq ID No 2025	Seq ID No 2026	Seq ID No 2027	Seq ID No 2028
3.67	Seq ID No 2029	Seq ID No 2030	Seq ID No 2031	Seq ID No 2032
3.68	Seq ID No 2033	Seq ID No 2034	Seq ID No 2035	Seq ID No 2036
3.69	Seq ID No 2037	Seq ID No 2038	Seq ID No 2039	Seq ID No 2040
3.70	Seq ID No 2041	Seq ID No 2042	Seq ID No 2043	Seq ID No 2044
3.71	Seq ID No 2045	Seq ID No 2046	Seq ID No 2047	Seq ID No 2048
3.72	Seq ID No 2049	Seq ID No 2050	Seq ID No 2051	Seq ID No 2052
3.73	Seq ID No 2053	Seq ID No 2054	Seq ID No 2055	Seq ID No 2056
3.74	Seq ID No 2057	Seq ID No 2058	Seq ID No 2059	Seq ID No 2060

3.75	Seq ID No 2061	Seq ID No 2062	Seq ID No 2063	Seq ID No 2064
3.76	Seq ID No 2065	Seq ID No 2066	Seq ID No 2067	Seq ID No 2068
3.77	Seq ID No 2069	Seq ID No 2070	Seq ID No 2071	Seq ID No 2072
3.78	Seq ID No 2073	Seq ID No 2074	Seq ID No 2075	Seq ID No 2076
3.79	Seq ID No 2077	Seq ID No 2078	Seq ID No 2079	Seq ID No 2080
3.80	Seq ID No 2081	Seq ID No 2082	Seq ID No 2083	Seq ID No 2084
3.81	Seq ID No 2085	Seq ID No 2086	Seq ID No 2087	Seq ID No 2088
3.82	Seq ID No 2089	Seq ID No 2090	Seq ID No 2091	Seq ID No 2092
3.83	Seq ID No 2093	Seq ID No 2094	Seq ID No 2095	Seq ID No 2096
3.84	Seq ID No 2097	Seq ID No 2098	Seq ID No 2099	Seq ID No 2100
3.85	Seq ID No 2101	Seq ID No 2102	Seq ID No 2103	Seq ID No 2104
3.86	Seq ID No 2105	Seq ID No 2106	Seq ID No 2107	Seq ID No 2108
3.87	Seq ID No 2109	Seq ID No 2110	Seq ID No 2111	Seq ID No 2112
3.88	Seq ID No 2113	Seq ID No 2114	Seq ID No 2115	Seq ID No 2116
3.89	Seq ID No 2117	Seq ID No 2118	Seq ID No 2119	Seq ID No 2120
3.90	Seq ID No 2121	Seq ID No 2122	Seq ID No 2123	Seq ID No 2124
3.91	Seq ID No 2125	Seq ID No 2126	Seq ID No 2127	Seq ID No 2128

Table 3. This shows SEQ ID NOs of family 3-like CDR sequences and of family full length V_H sequences that are within the scope of the invention. Corresponding sequences are shown in Figure 3.

In one aspect, the invention relates to a family 3-like binding molecule comprises a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, the family 3 or family 3-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain and wherein said V_H comprises at least one antigen binding site comprising a CDR3 sequence having SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. In one embodiment, sequence homology is at least 90%.

In one embodiment, the CDR3 sequence is selected from one of the CDR3 sequences as shown in table 3 with reference to Fig 3. Thus, the CDR3 region comprises or consists of a sequence selected form SEQ ID Nos 1767, 1771, 1775, 1779, 1787, 1791, 1795, 1799, 1803, 1807, 1811, 1815, 1819, 1823, 1827, 1831, 1835, 1839, 1843,

1847, 1851, 1855, 1859, 1863, 1867, 1871, 1875, 1879, 1883, 1887, 1891, 1895, 1899, 1903, , 1907, 1911, 1915, 1919, 1923, 1927, 1931, 1935, 1939, 1943, 1947, 1951, 1955, 1963, 1967, 1971, 1975, 1979, 1983, 1987, 1991, 1995,, 1999, 2003, 2007, 2011, 2015, 2019, 2027, 2031, 2035, 2039, 2043, 2047, 2051, 2055, 2059, 2063, 2067, 2071, 2075, 2079, 2083, 2087, 2091, 2095, 2099, 2103, 2107, 2111, 2115, 2119, 2123 or 2127.

In one embodiment, the family 3-like sequence comprises at least one antigen binding site comprising hypervariable regions CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 1765 or a sequence with at least at least 70%, at least 80%, at least 90%, at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 1766 or a sequence with at least 70%, at least 80%, at least 90%, at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, at least 95% homology thereto. For example, the CDR sequence may be a sequence selected from those shown in figure 3.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 1765 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 1766 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 1767 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In one embodiment, CDR1 comprises or consists of one of the CDR1 amino acid sequence listed above in table 3 with reference to Fig. 3, CDR2 comprises or consists of one of the CDR2 amino acid sequence listed above in table 3 with reference to Fig. 3 and CDR3 comprises or consists of one of the CDR3 amino acid sequence listed above in table 3 with reference to Fig. 3. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 3.1 to 3.91 in Figure 3. In one embodiment, the binding molecule comprises a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 3.1 to 3.91 in Figure 3. In one

embodiment, the binding molecule has a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 3.1 in Figure 3.

In one embodiment, CDR1 is SEQ ID NO. 1765, CDR2 is SEQ ID No. 1766 and CDR3 is SEQ ID NO. 1767.

In one embodiment, the family 3 or family 3-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 1768 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. CDR sequences of such sequences are shown in Figure 3. For example, the V_H domain comprises or consists of one of the V_H amino acid sequences listed above for clones 3.1 to 3.91 in table 3 with reference to figure 3. In one embodiment, the V_H sequence is selected from 1768, 1772, 1776, 1780, 1784, 1788, 1792, 1796, 1800, 1804, 1808, 1812, 1816, 1820, 1824, 1828, 1832, 1836, 1840, 1844, 1848, 1852, 1856, 1860, 1864, 1868, 1876, 1880, 1884, 1888, 1892, 1896, 1900, 1904, 1908, 1912, 1916, 1920, 1924, 1928, 1932, 1936, 1940, 1944, 1948, 1956, 1964, 1968, 1972, 1976, 1980, 1984, 1988, 1992, 1996, 2000, 2004, 2008, 2012, 2016, 2020, 2024, 2028, 2032, 2036, 2040, 2044, 2048, 2052, 2056, 2060, 2064, 2068, 2072, 2084, 2088, 2092, 2096, 2100, 2104, 2108, 2112, 2116, 2120 or 2128.

In another embodiment, the V_H domain comprises a sequence selected from one of the sequences in the forgoing but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences. In one embodiment, the V_H domain comprises or consists of SEQ ID NO. 1767 or a sequence which comprises one or more amino acid substitutions, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions.

In another aspect, the invention relates to a binding molecule comprising or consisting of a V_H domain as shown in SEQ ID NO. 1768 or a variant thereof comprising amino acid substitutions compared to SEQ ID NO. 1768 as follows: residue 1 is Q, residue 31 is S, residue 36 is S, T, residue 51 is M, residue 52 is K, residue 53 is H, E, residue 59 is Q, N, residue 99 is A, residue 100 is W, residue 101 is S, residue 102 is G and/or residue 106 is D.

The family 3 or family 3-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In one aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 4 or family 4-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said V_H domain comprises a family 4 or family 4-like sequence. These include the V_H sequence of the parent clone (clone 4.1; Seq ID No 2132) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones or parts thereof that are derived from the parent clone 4.1 through a process of optimization, for example as shown in Figure 4. CDR sequences and full length sequences of clones in family 4 are numbered according to table 4 as shown below.

CLONE	CDR1	CDR2	CDR3	FULL LENGTH
4.1	Seq ID No 2129	Seq ID No 2130	Seq ID No 2131	Seq ID No 2132
4.2	Seq ID No 2133	Seq ID No 2134	Seq ID No 2135	Seq ID No 2136
4.3	Seq ID No 2137	Seq ID No 2138	Seq ID No 2139	Seq ID No 2140
4.4	Seq ID No 2141	Seq ID No 2142	Seq ID No 2143	Seq ID No 2144
4.5	Seq ID No 2145	Seq ID No 2146	Seq ID No 2147	Seq ID No 2148
4.6	Seq ID No 2149	Seq ID No 2150	Seq ID No 2151	Seq ID No 2152
4.7	Seq ID No 2153	Seq ID No 2154	Seq ID No 2155	Seq ID No 2156
4.8	Seq ID No 2157	Seq ID No 2158	Seq ID No 2159	Seq ID No 2160
4.9	Seq ID No 2161	Seq ID No 2162	Seq ID No 2163	Seq ID No 2164
4.10	Seq ID No 2165	Seq ID No 2166	Seq ID No 2167	Seq ID No 2168
4.11	Seq ID No 2169	Seq ID No 2170	Seq ID No 2171	Seq ID No 2172
4.12	Seq ID No 2173	Seq ID No 2174	Seq ID No 2175	Seq ID No 2176
4.13	Seq ID No 2177	Seq ID No 2178	Seq ID No 2179	Seq ID No 2180
4.14	Seq ID No 2181	Seq ID No 2182	Seq ID No 2183	Seq ID No 2184
4.15	Seq ID No 2185	Seq ID No 2186	Seq ID No 2187	Seq ID No 2188
4.16	Seq ID No 2189	Seq ID No 2190	Seq ID No 2191	Seq ID No 2192
4.17	Seq ID No 2193	Seq ID No 2194	Seq ID No 2195	Seq ID No 2196
4.18	Seq ID No 2197	Seq ID No 2198	Seq ID No 2199	Seq ID No 2200
4.19	Seq ID No 2201	Seq ID No 2202	Seq ID No 2203	Seq ID No 2204

4.20	Seq ID No 2205	Seq ID No 2206	Seq ID No 2207	Seq ID No 2208
4.21	Seq ID No 2209	Seq ID No 2210	Seq ID No 2211	Seq ID No 2212
4.22	Seq ID No 2213	Seq ID No 2214	Seq ID No 2215	Seq ID No 2216
4.23	Seq ID No 2217	Seq ID No 2218	Seq ID No 2219	Seq ID No 2220
4.24	Seq ID No 2221	Seq ID No 2222	Seq ID No 2223	Seq ID No 2224
4.25	Seq ID No 2225	Seq ID No 2226	Seq ID No 2227	Seq ID No 2228
4.26	Seq ID No 2229	Seq ID No 2230	Seq ID No 2231	Seq ID No 2232
4.27	Seq ID No 2233	Seq ID No 2234	Seq ID No 2235	Seq ID No 2236
4.28	Seq ID No 2237	Seq ID No 2238	Seq ID No 2239	Seq ID No 2240
4.29	Seq ID No 2241	Seq ID No 2242	Seq ID No 2243	Seq ID No 2244
4.30	Seq ID No 2245	Seq ID No 2246	Seq ID No 2247	Seq ID No 2248
4.31	Seq ID No 2249	Seq ID No 2250	Seq ID No 2251	Seq ID No 2252
4.32	Seq ID No 2253	Seq ID No 2254	Seq ID No 2255	Seq ID No 2256
4.33	Seq ID No 2257	Seq ID No 2258	Seq ID No 2259	Seq ID No 2260
4.34	Seq ID No 2261	Seq ID No 2262	Seq ID No 2263	Seq ID No 2264
4.35	Seq ID No 2265	Seq ID No 2266	Seq ID No 2267	Seq ID No 2268
4.36	Seq ID No 2269	Seq ID No 2270	Seq ID No 2271	Seq ID No 2272
4.37	Seq ID No 2273	Seq ID No 2274	Seq ID No 2275	Seq ID No 2276
4.38	Seq ID No 2277	Seq ID No 2278	Seq ID No 2279	Seq ID No 2280
4.39	Seq ID No 2281	Seq ID No 2282	Seq ID No 2283	Seq ID No 2284
4.40	Seq ID No 2285	Seq ID No 2286	Seq ID No 2287	Seq ID No 2288
4.41	Seq ID No 2289	Seq ID No 2290	Seq ID No 2291	Seq ID No 2292
4.42	Seq ID No 2293	Seq ID No 2294	Seq ID No 2295	Seq ID No 2296
4.43	Seq ID No 2297	Seq ID No 2298	Seq ID No 2299	Seq ID No 2300
4.44	Seq ID No 2301	Seq ID No 2302	Seq ID No 2303	Seq ID No 2304
4.45	Seq ID No 2305	Seq ID No 2306	Seq ID No 2307	Seq ID No 2308
4.46	Seq ID No 2309	Seq ID No 2310	Seq ID No 2311	Seq ID No 2312
4.47	Seq ID No 2313	Seq ID No 2314	Seq ID No 2315	Seq ID No 2316
4.48	Seq ID No 2317	Seq ID No 2318	Seq ID No 2319	Seq ID No 2320
4.49	Seq ID No 2321	Seq ID No 2322	Seq ID No 2323	Seq ID No 2324
4.50	Seq ID No 2325	Seq ID No 2326	Seq ID No 2327	Seq ID No 2328
4.51	Seq ID No 2329	Seq ID No 2330	Seq ID No 2331	Seq ID No 2332
4.52	Seq ID No 2333	Seq ID No 2334	Seq ID No 2335	Seq ID No 2336
4.53	Seq ID No 2337	Seq ID No 2338	Seq ID No 2339	Seq ID No 2340
4.54	Seq ID No 2341	Seq ID No 2342	Seq ID No 2343	Seq ID No 2344
4.55	Seq ID No 2345	Seq ID No 2346	Seq ID No 2347	Seq ID No 2348
4.56	Seq ID No 2349	Seq ID No 2350	Seq ID No 2351	Seq ID No 2352
4.57	Seq ID No 2353	Seq ID No 2354	Seq ID No 2355	Seq ID No 2356

4.58	Seq ID No 2357	Seq ID No 2358	Seq ID No 2359	Seq ID No 2360
4.59	Seq ID No 2361	Seq ID No 2362	Seq ID No 2363	Seq ID No 2364
4.60	Seq ID No 2365	Seq ID No 2366	Seq ID No 2367	Seq ID No 2368
4.61	Seq ID No 2369	Seq ID No 2370	Seq ID No 2371	Seq ID No 2372
4.62	Seq ID No 2373	Seq ID No 2374	Seq ID No 2375	Seq ID No 2376
4.63	Seq ID No 2377	Seq ID No 2378	Seq ID No 2379	Seq ID No 2380
4.64	Seq ID No 2381	Seq ID No 2382	Seq ID No 2383	Seq ID No 2384
4.65	Seq ID No 2385	Seq ID No 2386	Seq ID No 2387	Seq ID No 2388
4.66	Seq ID No 2389	Seq ID No 2390	Seq ID No 2391	Seq ID No 2392
4.67	Seq ID No 2393	Seq ID No 2394	Seq ID No 2395	Seq ID No 2396
4.68	Seq ID No 2397	Seq ID No 2398	Seq ID No 2399	Seq ID No 2400
4.69	Seq ID No 2401	Seq ID No 2402	Seq ID No 2403	Seq ID No 2404
4.70	Seq ID No 2405	Seq ID No 2406	Seq ID No 2407	Seq ID No 2408
4.71	Seq ID No 2409	Seq ID No 2410	Seq ID No 2411	Seq ID No 2412
4.72	Seq ID No 2413	Seq ID No 2414	Seq ID No 2415	Seq ID No 2416
4.73	Seq ID No 2417	Seq ID No 2418	Seq ID No 2419	Seq ID No 2420
4.74	Seq ID No 2421	Seq ID No 2422	Seq ID No 2423	Seq ID No 2424
4.75	Seq ID No 2425	Seq ID No 2426	Seq ID No 2427	Seq ID No 2428
4.76	Seq ID No 2429	Seq ID No 2430	Seq ID No 2431	Seq ID No 2432
4.77	Seq ID No 2433	Seq ID No 2434	Seq ID No 2435	Seq ID No 2436
4.78	Seq ID No 2437	Seq ID No 2438	Seq ID No 2439	Seq ID No 2440
4.79	Seq ID No 2441	Seq ID No 2442	Seq ID No 2443	Seq ID No 2444
4.80	Seq ID No 2445	Seq ID No 2446	Seq ID No 2447	Seq ID No 2448
4.81	Seq ID No 2449	Seq ID No 2450	Seq ID No 2451	Seq ID No 2452
4.82	Seq ID No 2453	Seq ID No 2454	Seq ID No 2455	Seq ID No 2456
4.83	Seq ID No 2457	Seq ID No 2458	Seq ID No 2459	Seq ID No 2460
4.84	Seq ID No 2461	Seq ID No 2462	Seq ID No 2463	Seq ID No 2464
4.85	Seq ID No 2465	Seq ID No 2466	Seq ID No 2467	Seq ID No 2468
4.86	Seq ID No 2469	Seq ID No 2470	Seq ID No 2471	Seq ID No 2472
4.87	Seq ID No 2473	Seq ID No 2474	Seq ID No 2475	Seq ID No 2476
4.88	Seq ID No 2477	Seq ID No 2478	Seq ID No 2479	Seq ID No 2480
4.89	Seq ID No 2481	Seq ID No 2482	Seq ID No 2483	Seq ID No 2484
4.90	Seq ID No 2485	Seq ID No 2486	Seq ID No 2487	Seq ID No 2488
4.91	Seq ID No 2489	Seq ID No 2490	Seq ID No 2491	Seq ID No 2492
4.92	Seq ID No 2493	Seq ID No 2494	Seq ID No 2495	Seq ID No 2496
4.93	Seq ID No 2497	Seq ID No 2498	Seq ID No 2499	Seq ID No 2500
4.94	Seq ID No 2501	Seq ID No 2502	Seq ID No 2503	Seq ID No 2504
4.95	Seq ID No 2505	Seq ID No 2506	Seq ID No 2507	Seq ID No 2508

4.96	Seq ID No 2509	Seq ID No 2510	Seq ID No 2511	Seq ID No 2512
4.97	Seq ID No 2513	Seq ID No 2514	Seq ID No 2515	Seq ID No 2516
4.98	Seq ID No 2517	Seq ID No 2518	Seq ID No 2519	Seq ID No 2520
4.99	Seq ID No 2521	Seq ID No 2522	Seq ID No 2523	Seq ID No 2524
4.100	Seq ID No 2525	Seq ID No 2526	Seq ID No 2527	Seq ID No 2528
4.101	Seq ID No 2529	Seq ID No 2530	Seq ID No 2531	Seq ID No 2532
4.102	Seq ID No 2533	Seq ID No 2534	Seq ID No 2535	Seq ID No 2536
4.103	Seq ID No 2537	Seq ID No 2538	Seq ID No 2539	Seq ID No 2540
4.104	Seq ID No 2541	Seq ID No 2542	Seq ID No 2543	Seq ID No 2544
4.105	Seq ID No 2545	Seq ID No 2546	Seq ID No 2547	Seq ID No 2548
4.106	Seq ID No 2549	Seq ID No 2550	Seq ID No 2551	Seq ID No 2552
4.107	Seq ID No 2553	Seq ID No 2554	Seq ID No 2555	Seq ID No 2556

Table 4. Family 4 CDR sequences and V_H sequences that are within the scope of the invention. Corresponding sequences are shown in figure 4.

In one aspect of the invention, the family 4 or family 4-like binding molecule comprises a human V_H domain comprising a hypervariable region CDR3 said CDR3 having the amino acid sequence SEQ ID NO. 2131, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2131.

In one embodiment, the family 4 or family 4-like binding molecule comprises a binding molecule comprising or consisting of at least one immunoglobulin single domain antibody directed against IL-17R wherein said domain is a human V_H domain and wherein said V_H domain comprises hypervariable region CDR3 said CDR3 having the amino acid sequence SEQ ID NO. 2131, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. In one embodiment, sequence homology is at least 90%.

In one embodiment, the CDR3 region is selected from one of the CDR3 sequence as shown in table 4 with reference to figure 4. Thus, the CDR3 sequence is selected from SEQ ID Nos: 2131, 2135, 2139, 2143, 2147, 2151, 2155, 2159, 2163, 2167, 2171, 2175, 2179, 2183, 2187, 2191, 2195, 2199, 2203, 2207, 2211, 2215, 2219, 2223, 2227, 2231, 2235, 2239, 2243, 2247, 2251, 2255, 2259, 2263, 2267, 2271, 2275, 2279, 2283, 2287, 2291, 2295, 2299, 2303, 2307, 2311, 2315, 2319, 2323, 2327, 2331, 2335, 2339, 2343, 2347, 2351, 2355, 2359, 2363, 2367, 2371, 2375, 2379, 2383, 2387, 2391, 2395, 2399, 2403, 2407, 2411, 2415, 2419, 2423, 2427, 2435, 2439, 2443, 2447, 2451, 2455,

2459, 2463, 2467, 2471, 2475, 2479, 2483, 2487, 2491, 2495, 2499, 2503, 2507, 2511, 2515, 2519, 2523, 2527, 2531, 2535, 2539, 2543, 2551 or 2555.

In one embodiment, the family 4 or family 4-like binding molecule comprises at least one antigen binding site comprising hypervariable regions CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2129 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2130 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2131, or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. For example, the CDR sequence may be a CDR sequence selected form those shown in Figure 4.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2129 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2130 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2131 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In one embodiment, CDR1 comprises or consists of one of the CDR1 amino acid sequence listed above in table 4 with reference to Fig. 4, CDR2 comprises or consists of one of the CDR2 amino acid sequence listed above in table 4 with reference to Fig. 4 and CDR3 comprises or consists of one of the CDR3 amino acid sequence listed above in table 4 with reference to Fig. 4. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 4.1 to 4.107 in Figure 4. In one embodiment, the binding molecule comprises a set of CDR1, CDR2 and CDR2 sequences of a V_H sequence as shown for clones 4.1 to 4.107 in Figure 4. In one embodiment, the binding molecule has a set of CDR1, CDR2 and CDR2 sequences of a V_H sequence as shown for clone 4.1 in Figure 4.

In one embodiment, the family 4 or family 4-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 2132 or a sequence with at least 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 96%, 97%, 98%, 99% homology thereto. CDR sequences of such V_H sequences are shown in Figure 4. For example, the V_H domain comprises or consists of one of the V_H amino acid sequences listed above for clones 41.1 to 4.107 in figure 4 and table 4. Thus, the V_H sequence comprises or consists of a V_H sequence selected from SEQ ID NOs. 2132, 2136, 2140, 2144, 2148, 2152, 2156, 2160, 2164, 2168, 2172, 2184, 2188, 2192, 2196, 2200, 2204, 2208, 2212, 2216, 2220, 2224, 2228, 2232, 2236, 2240, 2244, 2248, 2252, 2256, 2260,, 2264, 2268, 2272, 2276, 2280, 2284, 2288, 2292, 2300, 2304, 2308, 2312, 2316, , 2320, 2324, 2328, 2332, 2336, 2340, 2344, 2348, 2352, 2356, 2360, 2364, 2368, 2372, 2376, 2380, 2384, 2388, 2392, 2396, 2400, 2404, 2408, 2412, 2416, 2420, 2424, 2428, 2432, 2436, 2440, 2444, 2452, 2456, 2460, 2468, 2472, 2476, 2480, 2484, 2488, 2492, 2496, 2500, 2504, 2508, 2512, 2516, 2520, 2524, 2528, 2532, 2536, 2540, 2544, 2548, 2552 or 2556.

In another embodiment, the V_H domain comprises a sequence selected from one of the sequences in the forgoing, but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDR. In one embodiment, the amino acid substitutions are in the framework and CDR sequences. In one embodiment, the V_H domain comprises or consists of SEQ ID NO. 2132 or a sequence which comprises one or more amino acid substitutions, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions.

In another aspect, the invention relates to a binding molecule comprising or consisting of a V_H domain as shown in SEQ ID NO. 2132 or a variant thereof comprising amino acid substitutions compared to SEQ ID NO. 2132 as follows residue 5 is Q, residue 10 is G, residue 28 is T, residue 31 is S, G, residue 32 is H, residue 33 is I,G, V, residue 37 is V, M, residue 51 is I, residue 54 is N, K, E, residue 55 is N, residue 61 is S, T, residue 66 is D, residue 100 is D, residue 101 is S, F, residue 102 is G, residue 103 is S and/or residue 106 is Q, T.

The family 4 or family 4-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In one aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 5 or family 5-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said V_H domain comprises a family 5 or family 5-like sequence. These include the V_H sequence of the parent clone (clone 5.1; SEQ ID NO. 2560) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones that are derived from the parent clone 5.1 through a process of optimization, for example as shown in Figure 5.

CDR sequences and full length sequences of clones in family 5 are numbered according to table 5 as shown below.

Clone name	CDR1 SEQ ID NO.	CDR2 SEQ ID NO.	CDR3 SEQ ID NO.	Full length VH sequence SEQ ID NO.
5.1	SEQ ID NO. 2557	SEQ ID NO. 2558	SEQ ID NO. 2559	SEQ ID NO. 2560
5.2	SEQ ID NO. 2561	SEQ ID NO. 2562	SEQ ID NO. 2563	SEQ ID NO. 2564
5.3	SEQ ID NO. 2565	SEQ ID NO. 2566	SEQ ID NO. 2567	SEQ ID NO. 2568
5.4	SEQ ID NO. 2569	SEQ ID NO. 2570	SEQ ID NO. 2571	SEQ ID NO. 2572

Table 5: Family 5 CDR sequences and V_H sequences that are within the scope of the invention. Corresponding sequences are shown in figure 5.

In one aspect of the invention, the family 5 or family 5-like binding molecule comprises a human V_H domain comprising a CDR3 sequence comprising amino acid sequence SEQ ID NO. 2559, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, the family 5 or family 5-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17R wherein said domain is a human V_H domain and wherein said V_H comprises at least one antigen binding site comprising hypervariable region CDR3 said CDR3 having the amino acid

sequence SEQ ID NO. 2559, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, the homology is at least 90%.

In one embodiment, the CDR3 sequence is selected from one of the CDR3 sequences as shown in table 5 with reference to Figure 5. Thus, the CDR3 sequence is selected from 2559, 2563, 2567 or 2571.

In one embodiment, the family 5 or family 5-like sequence comprises a binding molecule comprising hypervariable regions CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2557 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2558 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2559, or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. For example, the CDR sequence may be a CDR sequence selected from those shown in Figure 5.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2557 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 96%, 97%, 98%, 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2558 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence as shown in SEQ ID NO. 2559 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In one embodiment, CDR1 comprises or consists of one of the CDR1 amino acid sequence listed above in table 5 with reference to Fig. 5, CDR2 comprises or consists of one of the CDR2 amino acid sequence listed above in table 5 with reference to Fig. 5 and CDR3 comprises or consists of one of the CDR3 amino acid sequence listed above in table 5 with reference to Fig. 5. In one embodiment, the binding molecule has combinations of CDR1, CDR2 and CDR3 as shown for clones 5.1 to 5.4 in Figure 5. In

one embodiment, the binding molecule comprises a set of CDR1, CDR2 and CDR3 sequences of a V_H sequence as shown for clones 5.1 to 5.4 in Figure 5.

In one embodiment, the family 5 or family 5-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 2560 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. Thus, the V_H comprises or consist of a V_H selected form SEQ ID Nos. 2560, 2564, 2568 or 2572. In another embodiment, the V_H domain comprises a sequence selected from one of the sequences in the forgoing but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences. In one embodiment, the V_H domain comprises or consists of SEQ ID NO. 2560 or a sequence which comprises one or more amino acid substitutions, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions.

In another aspect, the invention relates to a binding molecule comprising or consisting of a V_H domain as shown in SEQ ID NO. 2132 or a variant thereof comprising amino acid substitutions compared to SEQ ID NO. 2132 as follows residue 1 is Q, residue 32 is Y, residue 33 is Y, residue 52 is G, residue 53 is G, residue 56 is D, residue 57 is V, residue 103 is H, residue 104 is D and/or residue 106 is K.

The family 5 or family 5-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 6 or family 6-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human v domain and wherein said V_H domain comprises a family 6 or family 6-like sequence. These include the V_H sequence of the parent clone (clone 6.1; SEQ ID NO. 2576) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones or that are derived from the parent clone 6.1 through a process of optimization, for example as shown in Figure 6. CDR sequences

and full length sequences of clones in family 6 are numbered according to table 6 as shown below.

Clone name	CDR1	CDR2	CDR3	Full length sequence
6.1	SEQ ID NO. 2573	SEQ ID NO. 2574	SEQ ID NO. 2575	SEQ ID NO. 2576

Table 6: Family 6 CDR sequences and V_H sequences that are within the scope of the invention. Corresponding sequences are shown in figure 6.

In one aspect, the invention relates to a family 6 or family 6-like binding molecule comprises a human V_H domain comprising a CDR3 sequence CDR3 comprising the amino acid sequence SEQ ID NO. 2575, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, the family 6 or family 6-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17R comprising at least one antigen binding site comprising hypervariable region CDR3 said CDR3 having the amino acid sequence SEQ ID NO. 2575, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto. In one embodiment, the homology is at least 90%.

In one embodiment, the family 6 or family 6-like binding molecule comprises hypervariable regions CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2573 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2574 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2575, or a sequence with at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2573 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2574 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2575 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto.

In one embodiment, the family 6 or family 6-like binding molecule has a V_H domain that comprises or consists of SEQ ID NO. 2576 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% homology thereto.

In another embodiment, the V_H domain comprises SEQ ID NO. 2576, but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences.

The family 6 or family 6-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In another aspect, the invention relates to a binding molecule capable of binding human IL-17RA comprising a human V_H domain wherein said V_H domain comprises a family 7 or family 7-like sequence.

In one embodiment, the binding molecule comprises or consists of at least one immunoglobulin single domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and wherein said V_H domain comprises a family 7 or family 7-like sequence. These include the V_H sequence of the parent clone (clone 7.1; SEQ ID NO. 2580) or a part thereof, for example a CDR3 sequence, and V_H sequences of clones or parts thereof that are derived from the parent clone 7.1 through a process of optimization, for example as shown in Figure 7. CDR sequences and full length sequences of clones in family 7 are numbered according to table 7 as shown below.

Clone name	CDR1	CDR2	CDR3	Full length sequence
7.1	SEQ ID NO. 2577	SEQ ID NO. 2578	SEQ ID NO. 2579	SEQ ID NO. 2580

Table 7: Family 7 CDR sequences and V_H sequences that are within the scope of the invention. Corresponding sequences are shown in figure 7.

In one aspect, the invention relates to a family 7 or family 7-like binding molecule comprises a human V_H domain comprising a CDR3 sequence CDR3 comprising the amino acid sequence SEQ ID NO. 2579, or a sequence having at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, the family 7 or family 7-like binding molecule comprises at least one immunoglobulin single domain antibody directed against IL-17R comprising a human V_H domain comprising at least one antigen binding site comprising CDR1, CDR2 and CDR3, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2577 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2578 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto, and said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2579, or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

In one embodiment, said CDR1 comprises or consists of the amino acid sequence SEQ ID NO. 2577 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR2 comprises or consists of the amino acid sequence SEQ ID NO. 2578 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto. In one embodiment, said CDR3 comprises or consists of the amino acid sequence SEQ ID NO. 2579 or a sequence with at least 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto.

In one embodiment, the family 7 or family 7-like V_H has a V_H domain that comprises or consists of SEQ ID NO. 2580 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto.

In another embodiment, the V_H domain comprises SEQ ID NO. 2580, but comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In one embodiment, these are in the

framework region. In another embodiment, these are in the CDRs. In one embodiment, the amino acid substitutions are in the framework and CDR sequences.

The family 7 or family 7-like binding molecules have KD, Koff, KA, Kd and IC_{50} values as further described herein and as shown in the examples.

In one aspect, the binding molecule according to the invention comprises a CDR3 sequence selected from a family 1 or family 1-like, family 2 or family 2-like, family 3 or family 3-like, family 4 or family 4-like, family 5 or family 5-like, family 6 or family 6-like or family 7 or family 7-like CDR3 sequence combined with a CDR1 and CDR2 sequence from another family listed herein.

For example, the binding molecule according to the invention comprises a family 1 or family 1-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 2, 3, 4, 5, 6 or 7.

In another aspect, the binding molecule according to the invention comprises a family 2 or family 2-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 3, 4, 5, 6 or 7. Various combinations are possible as would be appreciated by a skilled person.

In another aspect, the binding molecule according to the invention comprises a family 3 or family 3-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 2, 4, 5, 6 or 7. Various combinations are possible as would be appreciated by a skilled person.

In another aspect, the binding molecule according to the invention comprises a family 4 or family 4-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 2, 3, 5, 6 or 7. Various combinations are possible as would be appreciated by a skilled person.

In another aspect, the binding molecule according to the invention comprises a family 5 or family 5-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 2, 3, 4, 6 or 7. Various combinations are possible as would be appreciated by a skilled person.

In another aspect, the binding molecule according to the invention comprises a family 6 or family 6-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 2, 3, 5 or 7. Various combinations are possible as would be appreciated by a skilled person.

In another aspect, the binding molecule according to the invention comprises a family 7 or family 7-like CDR3 sequence combined with a CDR1 and/or a CDR2 sequence from one or two other families as shown in Table 1, 2, 3, 5 or 6. Various combinations are possible as would be appreciated by a skilled person.

As mentioned above, also within the scope of the invention are V_H domains that comprise additional C or N terminal residues, for example linker residues introduced from the expression vector used (e.g., LEGGGS from phagemid vector or AA) and/or His tags, e.g. hexa-His (HHHHHH, SEQ ID NO: 2605).

A binding molecule described herein may be provided as a fusion protein with one or more additional protein moiety. For example, the binding molecule described herein may be provided as a fusion with a second moiety.

The second moiety may comprise a V_H domain that is also specific for human IL-17RA thus providing a bivalent binding molecule. In one embodiment, the binding molecule is biparatopic. Biparatopic binding molecules bind to different epitopes. Biparatopic binding molecules of the present invention can be constructed using methods known art.

For example, a family 1 binding molecule may be linked to a family 2, 3, 4, 5, 6 or 7 or family 2, 3, 4, 5, 6 or 7- like binding molecule.

In another embodiment, the second moiety comprises a V_H domain or another antibody fragment that is specific for a different antigen to provide a bispecific binding molecule. As used herein, the term "bispecific binding molecule" thus refers to a polypeptide that comprises a binding molecule as described herein which has a binding site that has binding specificity for IL17-RA, and a second polypeptide domain which has a binding site that has binding specificity for a second target, i.e., the agent has specificity for two targets. The first target and the second target are not the same, i.e. are different targets e.g., proteins, but are both present on a cell. Accordingly, a bispecific binding molecule

as described herein can selectively and specifically bind to a cell that expresses (or displays on its cell surface) the first target and the second target. In another embodiment, the binding molecule comprises more than two moieties.

In another embodiment, more than two moieties are joined together providing a multispecific binding molecule. A multispecific polypeptide agent as described herein can in addition bind one or more additional targets, i.e., a multispecific polypeptide can bind at least two, at least three, at least four, at least five, at least six, or more targets, wherein the multispecific polypeptide agent has at least two, at least, at least three, at least four, at least five, at least six, or more target binding sites respectively.

As used herein, the term "target" refers to a biological molecule (e.g., peptide, polypeptide, protein, lipid, carbohydrate) to which a polypeptide domain which has a binding site can selectively bind. The target can be, for example, an intracellular target (e.g. an intracellular protein target) or a cell surface target (e.g., a membrane protein, a receptor protein). Preferably, a target is a cell surface target, such as a cell surface protein. Preferably, the first cell surface target and second cell surface target are both present on a cell.

Multispecific antibodies of the present invention can be constructed using methods known art.

In biparatopic or multispecific binding molecules, the moieties are joined by a linker, for example a polypeptide linker. Suitable linkers, for example comprising linker including GS residues such as $(Gly_4Ser)_n$, where n=from 1 to 10, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 are known in the art.

If desired, bispecific or multispecific binding molecules can be linked to an antibody Fc region or a fragment thereof, comprising one or both of C_H2 and C_H3 domains, and optionally a hinge region. For example, vectors encoding bispecific or multispecific binding molecules linked as a single nucleotide sequence to an Fc region or a fragment thereof can be used to prepare such polypeptides.

Exemplary second antigen targets include leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD4, CD45, CD58, CD80, CD86 or their ligands; TNF, IL-1 IL-15, IL-23, IL-6 or CD20. This list is not limited to the agents mentioned.

In one embodiment, the second moiety may serve to prolong the half-life of the binding molecule. The second moiety or third may comprise a protein that binds a serum albumin, e.g., human serum albumin (HSA). The second moiety may comprise a V_H domain that binds serum albumin, e.g. human serum albumin (HSA). The second moiety may comprise a serum albumin, e.g. a human serum albumin (HSA) or a variant thereof such as C34S. Further provided is binding molecule as described herein comprising a V_H domain and an Fc domain or a fragment thereof, e.g., wherein the V_H domain is fused to an Fc domain or a fragment thereof. Further provided is a binding molecule that comprises a second variable domain that specifically binds a second antigen, where the second antigen is an antigen other than human IL-17R. The second antigen may be a cluster of differentiation (CD) molecule or a Major Histocompatibility Complex (MHC) Class II molecule.

The present invention further provides an isolated nucleic acid encoding a binding member of the present invention. Nucleic acid may include DNA and/or RNA. In one aspect, the present invention provides a nucleic acid that codes for a CDR, for example a CDR3, or set of CDRs, a V_H domain or binding molecule as defined above. In one aspect, the invention also relates to nucleic acid sequences encoding V_H domains of family 1, 2, 3, 4, 5, 6 or 7 as shown herein. Examples of such sequences encoding V_H sequences of specific clones are shown below.

1.1 SEQ ID NO. 2581

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGG
GTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAAT
AGTGGTAGGATGGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA
GACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACA
CGGCCATGTATTACTGTGCAAAAGAGAAGGGCCTAGGATTTTGTCGTGGTGGTAG
CTGTTCCTACTTTGACTATAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

1.2 SEQ ID NO. 2582

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGG
GTCCGACAAGCTCCAGGAAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAAT
AGTGGTAGGATGGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA
GACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACA
CGGCCTTATATTACTGTGCAAAGGAGAAGGGCCTAGGATATTGTCGTGGTGGTAG
CTGTTCCTACTTTGACTACAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

1.3 SEQ ID NO. 2583

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGCTGATTATGCCTTGCACTGG
GTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAAT
AGTGGTAGGAAGGACTATGCGGACACTGTGAAGGGCCGATTCACCATCTCCAGA
GACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACA
CGGCCATGTATTACTGTGCAAAAGAGAAGGGCCTAGGATTTTGTCGTGGTGGTAG
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1.4 SEQ ID NO. 2584

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGCTGATTATGCCTTGCACTGG
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GACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACA
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1.5 SEQ ID NO. 2585

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GACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACA
CGGCCTTATATTACTGTGCAAAGGAGAAGGGCCTAGGATATTGTCGTGGTGGTAG
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1.6 SEQ ID NO. 2586

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GACAATGCGAAAAATAGCCTGTATTTGCAGATGAACAGCCTGCGTGCGGAAGATA
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2.1 SEQ ID NO. 2587

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AGTGGTGACACAGTCTATGCACAGAAATTCCAGGGCAGAGTCACCATGACCAGGA

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2.2 SEQ ID NO. 2588

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ATACCTCCATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC
GGCCGTGTATTTTTGTGCGAGAGGCAGAAGGGATGACTGGAAGAACAATTATTGG
GGCCAGGGAACCCTGGTCACTGTCTCCTCA

2.3 SEQ ID NO. 2589

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ATACCTCCATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC
GGCCGTGTATTTTTGTGCGAGAGGCAGAAGGGATAACTGGAAGAACAATTATTGG
GGCCAGGGAACCCTGGTCACTGTCTCCTCA

3.1 SEQ ID NO. 2590

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ACAACGCCAAGAGTTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCTGTATATTACTGTGCGAGAGGGTGGGAGTCGGGGTGGTTCGAACCCTGGGG
CCAGGGAACCCTGGTCACCGTCTCCTCA

4.1 SEQ ID NO. 2591

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TGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAA
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GGCCAGGGCACCCTGGTCACCGTCTCCTCA

5.1 SEQ ID NO. 2592

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT
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GATAGTACCATATATTATAGAGACTCTGTGAAGGGCCGATTCACCATTTCCAGGGA
CAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACG
GCCGTGTATTACTGTTCGAGAAACGGGGCCCGGTATAACTGGAACTACGGGGAC
TTCCAGCACTGGGGCCAGGGCACCCTGGTCACTGTCTCCTCA

6.1 SEQ ID NO. 2593

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACGACTACATGAGCTGG
CTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGT
GGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGG
ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACTC
GGCCGTGTATTACTGTGCGAGAAAAGATATAACGAATATAGCAGTGGGCTCCCTC
GGCTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

7.1 SEQ ID NO. 2594

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGCCTCAGGATTCACCTTTAGTAACTATTGGATGAGCTGG
GTCCGCCAGGCTCGAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAGACCAGA
TGGAAGTGAGCGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA
GACAACGCCAAGAACTCATTGTATCTGCAGATGAGCAGCCTGAGAGCCGAGGAC
ACGGCTGTGTATTACTGTGCGAGATCGAGAGATTGGGGATCTCGGGCTTTTGATA
TCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA

Nucleic acid according to the present invention may comprise DNA or RNA and may be wholly or partially synthetic or recombinantly produced. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

Furthermore, the invention relates to a nucleic acid construct comprising at least one nucleic acid defined above. The construct may be in the form of plasmids, vectors, transcription or expression cassettes.

The invention also relates to an isolated recombinant host cell comprising one or more nucleic acid constructs as above.

The invention also relates to a binding agent capable of binding to IL-17RA that competes for binding to IL-17RA with a binding molecule of the invention as described above in a competitive assay.

The invention also relates to an isolated V_H domain comprising an amino acid product of or derived from a human V_H germline sequence, for example a human V_H 3-09, V_H1-08, V_H 3-07 or V_H 3-11 germline sequence.

The binding molecules of the invention have certain functional properties as described below and set out in the examples.

In particular, the binding molecules of the invention block the effects of IL-17RA on its target cells and are thus indicated for use in the treatment of IL-17RA-mediated diseases and disorders, for example as described herein.

These and other pharmacological activities of the binding molecules of the invention may be demonstrated in standard test methods for example as described in the art, e.g., “Neutralization of IL-17R dependent production of interleukin-6 by primary human fibroblasts: The production of IL-6 in primary human (dermal) fibroblasts is dependent on IL- 17” (Hwang SY *et al.*, (2004) Arthritis Res Ther; 6:R120-128)) and in the examples herein. Thus, as described in more detail in the examples, binding members according to the invention neutralize IL-17RA with high potency. The term "neutralizing" thus refers to neutralization of a biological activity of IL-17R when a binding protein specifically binds IL-17R. Inhibition of a biological activity of IL-17R by a neutralizing binding protein can be assessed by measuring one or more indicators of IL-17R biological activity well known in the art as described in the examples.

For example, neutralisation of IL-17R binding to its receptor may be measured as cellular release of a biological molecule, e.g., MMP13, PGE2 or a cytokine such as IL-6 or IL-8, in a biological assay, since IL-17RA binding to its receptor induces cellular release of these molecules, which can be determined using appropriate assays, e.g. in HT1080 cells, chondrocytes or other suitable cell or tissue types.

Inhibition of biological activity may be partial or total. In specific embodiments, binding members are provided that inhibit IL-17R biological activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the binding member. The degree to which a binding

member neutralises IL-17RA is referred to as its neutralising potency. Potency may be determined or measured using one or more assays known to the skilled person and/or as described or referred to herein. For example, potency may be assayed in:

- HTRF(R) (Homogeneous Time-Resolved Fluorescence) receptor-ligand binding assay
- HT1080 IL-6 release assay - HT1080 cell assay using synergised IL-6 release in response to IL-17 and TNFα
- Chondrocyte IL-6/IL-8/MMP13/PGE2-release assay IL-6 release assay in cartilage explants
- IL-6 release assay in synovial fibroblasts (e.g. from RA or OA patients), e.g. using synergised IL-6 response to IL-17 and TNFα.

Assays methods are described in detail in the examples.

Neutralising potency of a binding member as calculated in an assay using IL-17 from a first species (e.g. human) may be compared with neutralising potency of the binding member in the same assay using IL-17RA from a second species (e.g., cynomolgus), in order to assess the extent of cross-reactivity of the binding member for IL-17RA of the two species.

Potency is normally expressed as an IC_{50} value, in nM unless otherwise stated. In functional assays, IC_{50} is the concentration of a binding member that reduces a biological response by 50% of its maximum. IC_{50} may be calculated by plotting % of maximal biological response as a function of the log of the binding member concentration, and using a software program to fit a sigmoidal function to the data to generate IC_{50} values.

In another aspect, the invention thus relates to a binding molecule comprising at least one V_H domain directed against human IL-17A, or comprising or consisting of at least one immunoglobulin single V_H domain antibody directed against IL-17RA, preferably human IL-17RA, wherein said domain is a human V_H domain and has an IC_{50} for inhibition of IL-6 production of about 0.2 to about 500 nM or more, for example 0.2 to 400, 0.2 to 300, 0.2 to 200, 0.2 to 100, 0.2 to 50, 0.2 to 40, 0.2 to 30, 0.2 to 20, 0.2 to 10, 0.2 to 9, 0.2 to 8, 0.2 to 7, 0.2 to 6, 0.2 to 5, 0.2 to 4.0, 0.2 to , 0.2 to 2 or 0.2 to1 when tested as described in the examples, i.e. by measuring the ability of IL-17RA binding V_H to inhibit IL-17RA induced IL-6 release from the cell line HT1080. The binding molecules of the invention may have an IC_{50} for inhibition of IL-6 production of

less than about 500 nM, preferably less than about 100nM assessed by measuring the ability of IL-17RA binding V_H to inhibit IL-17RA induced IL-6 release from the cell line HT1080. This assay measures IL-6 release, a detailed method is given in the examples. The binding molecule, for example a V_H domain, having these binding characteristics may be selected from one of the sequences disclosed herein. In another embodiment, the V_H domain comprises a CDR3 sequence or V_H sequence as described herein.

In one embodiment, said IL-17RA binding molecule comprises a family 1 or family 1-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 2 or family 2-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 3 or family 3-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 4 or family 4-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 5 or family 5-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 6 or family 6-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 7 or family 7-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. Various embodiments of these sequences are detailed above.

Additionally, binding kinetics and affinity (expressed as the equilibrium dissociation constant, KD) of IL-17RA binding molecules of the invention for binding IL-17RA may be determined, e.g. using surface plasmon resonance such as BIAcore®, or KD may be estimated from pA2 analysis.

In another aspect, the invention relates to a binding molecule that has a KD (M) value of in the range of from about 1E-07 (1×10^{-7}) to about 6E-11 (6×10^{-11}), wherein said KD is calculated using BIAcore®. The term "KD" refers to the "equilibrium dissociation constant" and refers to the value obtained in a titration measurement at equilibrium, or by dividing the dissociation rate constant (Koff) by the association rate constant (Kon). In one embodiment, the KD may be as shown in the examples.

In one embodiment, said IL-17RA binding molecule comprises a family 1 or family 1-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 21 or family 2-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 3 or family 3-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 4 or family 4-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 5 or family 5-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 6 or family 6-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. In one embodiment, said IL-17RA binding molecule comprises a family 7 or family 7-like V_H sequence or part thereof, for example a CDR3 sequence, as described above. Various embodiments of these sequences are detailed above.

In one embodiment, the binding molecule has a KD as defined above and an IC_{50} for inhibition of IL-6 production as defined above.

A skilled person will know that there are different ways to identify and obtain the antigen binding molecules as described herein, including in vitro and in vivo expression libraries. This is further described in the examples. Optimisation techniques known in the art, such as display techniques (e.g., ribosome display and/or phage display) and / or mutagenesis techniques (e.g., error prone mutagenesis) can be used.

Methods for preparing or generating the polypeptides, nucleic acids, host cells, products and compositions described herein using *in vitro* expression libraries can comprise the steps of:

a) providing a set, collection or library of nucleic acid sequences encoding amino acid sequences; and
b) screening said set, collection or library of amino acid sequences for amino acid sequences that can bind to / have affinity for IL-17RA and
c) isolating the amino acid sequence(s) that can bind to / have affinity for IL-17RA.

In the above methods, the set, collection or library of sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to

facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) sequences will be clear to the person skilled in the art (see for example Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press; 1st edition (October 28, 1996) Brian K. Kay, Jill Winter, John McCafferty).

The binding molecules described herein comprising V_H domains, can be expressed in a transgenic rodent. The transgenic rodent, for example a mouse, has a reduced capacity to express endogenous antibody genes. Thus, in one embodiment, the rodent has a reduced capacity to express endogenous light and/or heavy chain antibody genes. The rodent may therefore comprise additional modifications to disrupt expression of endogenous light and/or heavy chain antibody genes so that no functional light and/or heavy chains are produced.

In one embodiment, the rodent is a mouse. The mouse may comprise a non-functional lambda light chain locus. Thus, the mouse does not make a functional endogenous lambda light chain. In one embodiment, the lambda light chain locus is deleted in part or completely or rendered non-functional through insertion, inversion, a recombination event, gene editing or gene silencing. For example, at least the constant region genes C1, C2 and C3 may be deleted or rendered non-functional through insertion. In one embodiment, the locus is functionally silenced so that mouse does not make a functional endogenous lambda light chain.

Furthermore, the mouse may comprise a non-functional kappa light chain locus. Thus, the mouse does not make a functional endogenous kappa light chain. In one embodiment, the kappa light chain locus is deleted in part or completely or rendered non-functional through insertion, inversion, a recombination event, gene editing or gene silencing. In one embodiment, the locus is functionally silenced so that the mouse does not make a functional endogenous kappa light chain.

The mouse having functionally silenced endogenous lambda and kappa L-chain loci may, for example, be made as disclosed in WO 2003/000737, which is hereby incorporated by reference in its entirety.

Furthermore, the mouse may comprise a non-functional heavy chain locus. Thus, the mouse does not make a functional endogenous heavy chain. In one embodiment, the heavy chain locus is deleted in part or completely or rendered non-functional through

insertion, inversion, a recombination event, gene editing or gene silencing. In one embodiment, the locus is functionally silenced so that the mouse does not make a functional endogenous heavy chain. In one embodiment, the locus is functionally silenced so that mouse does not make a functional endogenous heavy chain.

For example, as described in WO 2004/076618 (hereby incorporated by reference in its entirety), all 8 endogenous heavy chain constant region immunoglobulin genes (μ, δ, γ3, γ1, γ2a, γ2b, ε and α) are absent in the mouse, or partially absent to the extent that they are non-functional, or genes δ, γ3, γ1, γ2a, γ2b and ε are absent and the flanking genes μ and α are partially absent to the extent that they are rendered non-functional, or genes μ, δ, γ3, γ1, γ2a, γ2b and ε are absent and α is partially absent to the extent that it is rendered non-functional, or δ, γ3, γ1, γ2a, γ2b, ε and α are absent and μ is partially absent to the extent that it is rendered non-functional. By deletion in part is meant that the endogenous locus gene sequence has been deleted or disrupted, for example by an insertion, to the extent that no functional endogenous gene product is encoded by the locus, i.e. that no functional product is expressed from the locus. In another embodiment, the locus is functionally silenced.

In one embodiment, the mouse comprises a non-functional endogenous heavy chain locus, a non-functional endogenous lambda light chain locus and a non-functional endogenous kappa light chain locus. The mouse therefore does not produce any functional endogenous light or heavy chains. Thus, the mouse is a triple knockout (TKO) mouse.

The transgenic mouse may comprise a vector, for example a Yeast Artificial Chromosome (YAC) for expressing a heterologous heavy chain locus. YACs are vectors that can be employed for the cloning of very large DNA inserts in yeast. As well as comprising all three cis-acting structural elements essential for behaving like natural yeast chromosomes (an autonomously replicating sequence (ARS), a centromere (CEN) and two telomeres (TEL)), their capacity to accept large DNA inserts enables them to reach the minimum size (150 kb) required for chromosome-like stability and for fidelity of transmission in yeast cells. The construction and use of YACs is well known in the art (e.g. Bruschi, C.V. and Gjuracic, K. Yeast Artificial Chromosomes, ENCYCLOPEDIA OF LIFE SCIENCES 2002 Macmillan Publishers Ltd, Nature Publishing Group / www.els.net).

For example, the YAC may comprise a plethora of human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions. An example of such a YAC is provided in the example section.

Alternative methods known in the art may be used for deletion or inactivation of endogenous mouse or rat immunoglobulin genes and introduction of human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions

Transgenic mice can be created according to standard techniques as illustrated in the examples. The two most characterised routes for creating transgenic mice are via pronuclear microinjection of genetic material into freshly fertilised oocytes or via the introduction of stably transfected embryonic stem cells into morula or blastocyst stage embryos. Regardless of how the genetic material is introduced, the manipulated embryos are transferred to pseudo-pregnant female recipients where pregnancy continues and candidate transgenic pups are born.

The main differences between these broad methods are that ES clones can be screened extensively before their use to create a transgenic animal. In contrast, pronuclear microinjection relies on the genetic material integrating to the host genome after its introduction and, generally speaking, the successful incorporation of the transgene cannot be confirmed until after pups are born.

There are many methods known in the art to both assist with and determine whether successful integration of transgenes occurs. Transgenic animals can be generated by multiple means including random integration of the construct into the genome, site-specific integration, or homologous recombination. There are various tools and techniques that can be used to both drive and select for transgene integration and subsequent modification including the use of drug resistance markers (positive selection), recombinases, recombination-mediated cassette exchange, negative selection techniques, and nucleases to improve the efficiency of recombination. Most of these methods are commonly used in the modification of ES cells. However, some of the techniques may have utility for enhancing transgenesis mediated via pronuclear injection.

Further refinements can be used to give more efficient generation of the transgenic line within the desired background. As described above, in preferred embodiments, the endogenous mouse immunoglobulin expression is silenced to permit sole use of the introduced transgene for the expression of the heavy-chain only repertoire that can be exploited for drug discovery. Genetically-manipulated mice, for example TKO mice that are silenced for all endogenous immunoglobulin loci (mouse heavy chain, mouse kappa chain and mouse lambda chain) can be used as described above. The transfer of any introduced transgene to this TKO background can be achieved via breeding, (either conventional or with the inclusion of an IVF step to give efficient scaling of the process). However, it is also possible to include the TKO background during the transgenesis procedure. For example, for microinjection, the oocytes may be derived from TKO donors. Similarly, ES cells from TKO embryos can be derived for use in transgenesis.

The invention also relates to a method for producing a binding molecule comprising at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain said method comprising

a) immunising a transgenic mouse that expresses a nucleic acid construct comprising human heavy chain V genes and that is not capable of making functional endogenous light or heavy chains with an IL-17RA antigen,
b) generating a library from said mouse and
c) isolating V_H domains from said libraries.

Additional steps to optimize the sequences can be included.

The invention also relates to a binding molecule capable of binding human IL-17RA comprising a V_H domain obtained or obtainable from a mouse that is not capable of making functional endogenous light or heavy chains, for example through the method described above.

The binding molecule of the invention may be conjugated to another moiety. This can be selected from a toxin, enzyme, radioisotope, other detectable label, peptide, protein and chemical moiety of interest.

For example, the binding molecule of the invention may be labelled with a detectable or functional label. A label can be any molecule that produces or can be induced to produce a signal, including but not limited to fluorescers, radiolabels, enzymes, chemiluminescers or photosensitizers. Thus, binding may be detected and/or

measured by detecting fluorescence or luminescence, radioactivity, enzyme activity or light absorbance.

Half-life of the binding molecule of the invention can be increased by a chemical modification, especially by PEGylation, or by incorporation in a liposome or linking to another molecule, e.g. serum albumin or an anti-HSA binding molecule.

In one embodiment, a binding molecule of the invention is covalently modified. The term “covalently modified/covalent modification" includes modifications of a binding molecule according to the present invention, e.g. of a specified sequence; with an organic proteinaceous or non-proteinaceous derivatizing agent, fusions to heterologous polypeptide sequences, and post-translational modifications. Covalent modified polypeptides, e.g., of a specified sequence, still have the functional properties described herein, for example the ability to bind the human IL-17 or e.g. neutralize IL-6 production of IL-17 induced human dermal fibroblasts by crosslinking. Covalent modifications are generally introduced by reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected sides or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post- translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deaminated under mildly acidic conditions. Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl, tyrosine or threonyl residues, methylation of the [alpha]-amino groups of lysine, arginine, and histidine side chains. Covalent modifications e.g. include fusion proteins comprising a binding molecule according to the present invention, e.g. of a specified sequence and their amino acid sequence variants, such as immunoadhesins, and N-terminal fusions to heterologous signal sequences.

In another aspect of the present invention, there is provided a pharmaceutical composition comprising an IL-17RA binding molecule according to the present invention and a pharmaceutically acceptable carrier. The binding molecule of the present invention or a composition thereof can be administered by any convenient route and examples of the administration form of the binding molecule or composition of the present invention include without limitation topical, in particular dermal, parenteral, and intranasal. Parenteral administration includes subcutaneous injections,

intravenous, intramuscular, intrasternal injection or infusion techniques. Compositions can take the form of one or more dosage units.

The composition of the invention can be in the form of a liquid, e. g. a solution, emulsion or suspension. The liquid can be useful for delivery by dermal, topical or injection routes. The liquid compositions of the invention, whether they are solutions, suspensions or other like form, can also include one or more of the following: sterile diluents such as water, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides, polyethylene glycols, glycerin, or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; and agents for the adjustment of tonicity such as sodium chloride or dextrose. A composition can be enclosed in an ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material.

In specific embodiments, it can be desirable to administer a binding molecule of the present invention or composition thereof locally to the area in need of treatment.

Thus, in a preferred embodiment of all aspects of the invention, administration of the composition or binding molecule of the invention is by topical administration to healthy or diseased skin. The binding molecule is capable of penetrating at least the outer layer of the skin and can therefore be delivered dermally or transdermally. Accordingly, in one embodiment of the various aspects of the invention, topical delivery of the the composition or binding molecule of the invention to the skin is direct delivery into the skin for local non-systemic exposure. In another embodiment, topical delivery of the composition or binding molecule of the invention to the skin is direct delivery to the skin to provide systemic exposure as the $_H$ domain penetrates through all layers of the skin.

The skin that is treated may be diseased or healthy skin. In a preferred embodiment, the skin disease is psoriasis or atopic dermatitis.

Preferably, the surface area to which it is applied is 1%-30% of the body surface area, for example 1%-10% or 1-20%. Administration may thus be to 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29% or 30% of body surface area. In one embodiment, the disease state is mild. In another embodiment, the disease state is moderate. In another embodiment, the disease state is severe. For the treatment of psoriasis, administration is to areas affected, typically one or more affected area selected from elbows, knees, palms of hands, scalp, soles of feet, genitals, upper thighs, groin, buttocks, face and torso. For the treatment of atopic dermatitis

administration is to areas affected, typically one or more affected area selected from face, forearms and wrists.

Thus, the binding molecule can be applied directly to diseased or healthy skin in the form of cream, lotion, sprays, solution, gel, ointment, paste, plaster, patch, bioadhesive, suspension or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. In one embodiment, the binding molecule is applied directly to diseased skin in the form of a liquid (e.g. a spray), plaster, patch or bioadhesive. In one embodiment, the binding molecule is applied directly to diseased skin in the form of a microemulsion.

Microemulsions are generally defined as having a droplet diameter within the range of 2-500nm thus allowing effective delivery of actives into the skin. Microemulsions have been proposed for use in enhancing transdermal delivery of a range of compounds. This is described in US2007/0243132 incorporated herein in its entirety.

Specifically, as used herein, the term microemulsion refers to a formulation that comprises an oil phase, a water phase and a surfactant, wherein the microemulsion is suitable for transdermal delivery of a binding molecule, for example comprising a human V_H domain as described herein. Preferably, the microemulsion of the invention has a droplet diameter within the range of 2 - 500nm. In one embodiment, a microemulsion may further comprise a co-surfactant, a co-solvent, or a combination thereof.

The microemulsion of the present invention may be oil-in-water microemulsion, wherein the surfactant is preferentially soluble in water; water-in-oil microemulsion, wherein the surfactant is mainly in the oil phase; a three-phase microemulsion wherein a surfactant-rich middle phase coexists with water and oil phases; a bicontinuous monophase; a single phase micellar solution that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol); or a swollen micellar solution.

The microemulsion of the present invention may be produced by methods known in the art. In general, microemulsions are produced by emulsifying components under conditions including typically sufficient force or the required temperature to generate the required dispersion level, conductivity, viscosity, percolativity or other dispersion characteristics.

Microemulsion formation can be assessed using scattering and spectroscopic techniques such as neutron scattering, time-average scattering, quasi-electric light scattering i.e., high-resolution ultrasonic spectroscopy or photon correlation spectroscopy. The partition coefficients of microemulsions may also be measured chromatographically. The selection of particular formulations is based on a number of different paradigms depending upon the desired application. Illustrative paradigms include the hydrophilic-lipophilic balance, the phase-inversion temperature, or the cohesive-energy ratio. Microemulsions may be formulated using a wide range of immiscible liquids and other additional agents.

A microemulsion of the present invention may comprise an oil phase in the range of from 50 and 99% by weight, most preferably from 50 and 90% by weight; a water phase in the range of from 2 to 50% by weight, most preferably between 1 and 50% by weight; and surfactant in the range of from 0.1 to 90% by weight, preferably in the range of from 1 to 90% by weight surfactant. The microemulsion may further comprise from 0.1 to 90% by weight cosurfactant or cosolvent; preferably from 1 to 90% by weight cosurfactant or cosolvent.

The oil phase may comprise natural oils derived from plants or animals, such as vegetable oils, sunflower oils, coconut oils, almond oils; purified synthetic or natural di or triglycerides (such as Crodamol GTC® and Capmul MC®); phospholipids and their derivatives (such as lecithin or lysolecithin); fatty acid esters (such as isopropyl myristate, isopropyl palmitate, ethyl oleate, oleic acid ethyl ester); hydrocarbons (such as hexane, the n-decane through n-octadecane series); and/or glycerolysed fats and oils (such as glyceryl monooleate, glyceryl monocaprylate, glycerol monocaprate, propylene glycol monocaprylate, propyleme glycol monolaurate).

Other oil phase ingredients include, but are not limited to, Labrafil M 1944 CS™, benzene, tetrahydrofuran, and n-methyl pyrrolidone, or halogenated hydrocarbons, such as methylene chloride, or chloroform. In a particular embodiment, the oil phase comprises Crodamol GTCC® and Capmul MCM®, at 3:1 ratio. The oil component is either used alone or in combination with another oil component or components. Each oil or unique mixture of oils may require a different surfactant or mixture of surfactants or surfactants and co-surfactants to form a microemulsion with the water phase, as can routinely be determined by those of skill in the art. Water phase ingredients may comprise water and any water-soluble components in water, including one or more pharmaceutical agent.

The microemulsion of the present invention may further comprise solvents or other agents to enhance emulsion formation or stability. Other agents may be introduced to provide functions such as pH, ionic content, polymerisation, taste, smell, sterility, colour, viscosity, etc.

The microemulsions of the present invention may also be generated using any suitable synthetic plastic or polymeric, monomeric or hybrid colloidal material.

According to the methods and uses set out above, the binding molecule can be administered together with one or more chemical skin penetration enhancer. Examples of skin penetration enhancers are set out below.

In another embodiment, the binding molecule is administered using occlusion. In one embodiment, the binding molecule is administered to healthy or diseased skin together with a chemical skin penetration enhancer and using occlusion. In one embodiment, the binding molecule is administered to healthy or diseased skin as a microemulsion and using occlusion.

In another embodiment of the various aspects of the invention, administration may be improved using non-chemical skin penetration enhancers, for example phonophoresis, sonophoresis, electroporation or using the microneedle technique. This uses small needles (10–200 μm height and 10–50μm width) which are connected with the drug reservoir. The microneedle delivery device is applied to the skin surface without reaching the nerve endings of the upper dermis.

The binding molecule administered as set out above is capable of penetrating at least the outer layer of the skin and thus delivers an effective therapeutic amount of the binding molecule to treat the disease. The binding molecule administered as set out herein penetrates the skin in preferably 6 hours or less, for example 1 hour or less.

In one aspect, the invention relates to a pharmaceutical composition comprising a binding molecule of the invention and a skin penetration enhancer that facilitates or improves skin penetration. Unless otherwise specified, the term skin penetration enhancer as used herein refers to a chemical skin penetration enhancer. Numerous chemical penetration enhancers are known in the art and can be used in the composition of the invention. These include, but are not limited to: water, alcohols,

preferably alcohols with up to six carbon atoms, for example ethanol, glycols, for example alcohol diethylene glycol (Transcutol®), alkyl-N,N-disubstituted aminoacetates, for example dodecyl-N,N-dimethyl-aminoacetate, esters, for example ethylacetate, Azone® and derivatives, surfactants, for example sodium dodecyl sulphate, terpenes and terpenoids, for example d-Limonene, fatty acids, for example oleic acid, urea and derivatives, for example 1,3-Diphenyl-urea, pyrrolidones, for example N-Methyl-2-pyrrolidone, and 2-pyrrolidone- 5-carboxylic acid, cyclodextrins, for example beta-cyclodextrin, sulphoxides, for example dimethylsulphoxide. Other skin penetration enhancers are known to the skilled person. In one embodiment, the enhancer is not water. In one embodiment, the skin penetration enhancers are selected from one or more of Propylene Glycol, Isopropyl Myristate and Azone. Preferred penetration enhancers are DMSO, azone, Transcuto®, isopropyl myristate, oleic acid or combinations thereof, for example as set out in table 6 and in the examples.

In one embodiment, the penetration enhancer is not one or more of water, ethanol, polyethylene glycol derivatives, polyoxyethylene derivatives such as polysorbate, a fatty alcohol such as cetyl alcohol, stearyl alcohol, or cerostearyl alcohol, glycerol and propylene glycol.

The amount of the binding molecule of the present invention that is effective/active in the treatment of a particular disease will depend on the nature of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disease, and should be decided according to the judgment of the practitioner and each patient's circumstances.

Compositions of the invention comprise an effective amount of a binding molecule of the present invention such that a prophylactically- or therapeutically- effective dosage will be obtained. The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and its particular site, and the disease being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

Typically, this amount is at least about 0.01% of a binding molecule of the present invention by weight of the composition.

Preferred compositions of the present invention are prepared so that a parenteral dosage unit contains from about 0.01 % to about 2% by weight of the binding molecule of the present invention.

For intravenous administration, the composition can comprise from about typically about 0.1 mg/kg to about 250 mg/kg of the animal's body weight, preferably, between about 0.1 mg/kg and about 20 mg/kg of the animal's body weight, and more preferably about 1 mg/kg to about 10 mg/kg of the animal's body weight.

The present compositions can take the form of suitable carriers, such aerosols, sprays, suspensions, or any other form suitable for use. Other examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

Liposomes and micelles can also be used according to the invention.

Liposomes are microscopic vesicles having a lipid wall comprising a lipid bilayer, and, in the present context, encapsulate heavy chain only antibody or composition of the invention. Liposomal preparations herein include cationic (positively charged), anionic (negatively charged), and neutral preparations. Cationic liposomes are readily available. For example, N[1 -2,3- dioleyloxy)propyl]-N,N,N-triethyl-ammonium (DOTMA) liposomes are available under the tradename Lipofectin® (GIBCO BRL, Grand Island, NY). Similarly, anionic and neutral liposomes are readily available as well or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with DOTMA in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

Micelles are known in the art as comprised of surfactant molecules arranged so that their polar headgroups form an outer spherical shell, while the hydrophobic, hydrocarbon chains are oriented towards the center of the sphere, forming a core. Micelles form in an aqueous solution containing surfactant at a high enough concentration so that micelles naturally result. Surfactants useful for forming micelles include, but are not limited to, potassium laurate, sodium octane sulfonate, sodium

decane sulfonate, sodium dodecane sulfonate, sodium lauryl sulfate, docusate sodium, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethyl-ammonium chloride, dodecylammonium chloride, polyoxyl-8 dodecyl ether, polyoxyl-12 dodecyl ether, nonoxynol 10, and nonoxynol 30.

Microspheres, similarly, may be incorporated into the present formulations. Like liposomes and micelles, microspheres essentially encapsulate one or more components of the present formulations. They are generally although not necessarily formed from lipids, preferably charged lipids such as phospholipids. Preparation of lipidic microspheres is well known in the art and described in the pertinent texts and literature.

The pharmaceutical compositions can be prepared using methodology well known in the pharmaceutical art. For example, a composition can be prepared by combining a binding molecule of the present invention with water so as to form a solution. A surfactant can be added to facilitate the formation of a homogeneous solution or suspension.

The invention furthermore relates to a method for the prevention and/or treatment of a disease, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a binding molecule of the invention, and/or of a pharmaceutical composition of the invention. More in particular, the invention relates to a method for the prevention and/or treatment of a disease selected from the non-limiting group consisting of the diseases listed herein, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a binding molecule of the invention, and/or of a pharmaceutical composition of the invention. Examples of the immune related diseases that can be treated according to the invention will be clear to the skilled person based on the disclosure herein, and for example include autoimmune diseases, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.

The invention also relates to a binding molecule or pharmaceutical composition of the invention for use in the treatment of disease. In another aspect, the invention relates to a binding molecule of the invention for use in the treatment of a disease, for example

autoimmune diseases, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.

In another aspect, the invention relates to the use of a binding molecule of the invention in the manufacture of a medicament for the treatment of a disease, for example autoimmune diseases, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.

The disease according to the aspects set out above may be selected from the following non-limiting list: psoriasis, systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), transplantation associated diseases including graft rejection and graft-versus-host-disease.

In a preferred embodiment, the disease is selected from psoriasis, spondyloarthropathies, uveitis and atopic dermatitis. In another embodiment, the disease is asthma.

Binding molecules of the invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways. Binding molecules of the invention

are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by IL-17RA, or involve IL- 17RA production, or the promotion of TNF release by IL-17RA, e.g. acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS-related cachexia, e.g., associated with or consequential to HTV infection.

Binding molecules of the invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritis, and bone loss in general, including age-related bone loss, and in particular periodontal disease.

Binding molecules of the invention may be administered as the sole active ingredient or in combination with one or more other drug, e.g., immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g., for the treatment or prevention of diseases mentioned above. For example, the binding molecule of the invention maybe used in combination with immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40. CD45, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g., an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (e.g., designated ATCC 68629) or a mutant thereof, e.g., LEA29Y; adhesion molecule inhibitors, e.g., LFA-I antagonists, ICAM-I or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent, e.g., paclitaxel, gemcitabine, cisplatinum, doxorubicin or 5-fluorouracil; anti-TNF agents, e.g,. monoclonal antibodies to TNF, e.g., infliximab, adalimumab, CDP870, or receptor constructs to TNF-RI or TNF-RII, e.g., Etanercept™, PEG-TNF-RI; blockers of proinflammatory cytokines, IL-I blockers, e.g., Anakinra™ or IL-1 trap, AAL160, ACZ 885, IL-6 blockers; chemokines blockers, e.g., inhibitors or activators of proteases, e.g. metalloproteases, anti-IL-15 antibodies, anti-IL-6 antibodies, anti-CD20 antibodies, NSAIDs, such as aspirin or an anti-infectious agent. This list is not limited to the agents mentioned.

The binding molecule of pharmaceutical composition of the invention may administered at the same time or at a different time as the other drug. Administraiton may be simultaneously, sequentially or separately.

The invention also relates to methods for diagnosing a disease. Exemplary diseases are listed above. In one embodiment, the disease is psoriasis. The method comprises determining the level of IL-17RA expression by detecting binding of a binding molecule described herein in a sample and comparing the level of expression of IL-17RA in the test sample with the level of expression in a control sample from a non-psoriatic subject or with a standard value or standard value range for a non-psoriatic subject. An elevation in IL-17RA expression in the test sample relative to the control or standard indicates presence of the disease.

In another aspect, the invention provides a kit comprising a binding molecule of the invention useful for the treatment of a disease described above and optionally instructions for use.

The invention also relates to detection methods using the binding molecule of the invention. Given their ability to bind to human IL-17RA, the human-IL-17RA-binding molecules disclosed herein can be used to detect IL-17RA (e.g., in a biological sample, such as serum or plasma), using a conventional immunoassay, such as an enzyme linked immunosorbent assays (ELISA), a radioimmunoassay (RIA) or tissue immunohistochemistry. A method for detecting IL-17RA in a biological sample is provided comprising contacting a biological sample with a binding molecule disclosed herein and detecting either the binding molecule bound to IL-17RA or unbound binding molecule, to thereby detect IL-17RA in the biological sample. The binding molecule can be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound molecule. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials.

Alternative to labeling the binding molecule, human IL-17RA can be assayed in biological fluids by a competition immunoassay utilizing IL-17RA standards labeled with a detectable substance and an unlabeled human IL-17RA binding molecule. In this assay, the biological sample, the labeled IL-17RA standards and the human IL-17RA binding molecule are combined and the amount of labeled IL-17RA standard bound to the unlabeled binding molecule is determined. The amount of human IL-17RA in the

biological sample is inversely proportional to the amount of labeled IL-17RA standard bound to the IL-17RA binding molecule. Similarly, human IL-17RA can also be assayed in biological fluids by a competition immunoassay utilizing IL-17RA standards labeled with a detectable substance and an unlabeled human IL-17RA binding molecule.

As explained herein, binding molecules of the invention are capable of neutralizing IL-17RA activity, e.g., human IL-17RA activity, both *in vitro* and *in vivo*.

Accordingly, such binding molecules disclosed herein can be used to inhibit IL-17RA activity, e.g., in a cell culture containing IL-17RA, in human subjects or in other mammalian subjects having IL-17RA with which a binding molecule disclosed herein cross-reacts. In one embodiment, a method for inhibiting or increasing IL-17RA activity is provided comprising contacting IL-17RA with a binding molecule disclosed herein such that IL-17RA activity is inhibited or increased. For example, in a sample containing, or suspected of containing IL-17RA, a binding molecule disclosed herein can be added to the culture medium to inhibit IL-17RA activity in the sample.

Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. While the foregoing disclosure provides a general description of the subject matter encompassed within the scope of the present invention, including methods, as well as the best mode thereof, of making and using this invention, the following examples are provided to further enable those skilled in the art to practice this invention and to provide a complete written description thereof. However, those skilled in the art will appreciate that the specifics of these examples should not be read as limiting on the invention, the scope of which should be apprehended from the claims and equivalents thereof appended to this disclosure. Various further aspects and embodiments of the present invention will be apparent to those skilled in the art in view of the present disclosure.

All documents mentioned in this specification are incorporated herein by reference in their entirety, including references to gene accession numbers.

"and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example "A and/or B" is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein. Unless context dictates otherwise, the descriptions and

definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

The invention is further described in the non-limiting examples.

EXAMPLES

EXAMPLE 1. Construction of Tg/TKO mice

Mice carrying a heavy-chain antibody transgenic locus in germline configuration within a background that is silenced for endogenous heavy and light chain antibody expression (triple knock-out, or TKO) were created as previously described (WO2004/076618 and WO2003/000737, Ren *et al*. Genomics, 84, 686, 2004; Zou *et al*., J. Immunol., 170, 1354, 2003). Briefly, transgenic mice were derived following pronuclear microinjection of freshly fertilised oocytes with a yeast artificial chromosome (YAC) comprising a plethora of human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions. Yeast artificial chromosomes (YACs) are vectors that can be employed for the cloning of very large DNA inserts in yeast. As well as comprising all three cis-acting structural elements essential for behaving like natural yeast chromosomes (an autonomously replicating sequence (ARS), a centromere (CEN) and two telomeres (TEL)), their capacity to accept large DNA inserts enables them to reach the minimum size (150 kb) required for chromosome-like stability and for fidelity of transmission in yeast cells. The construction and use of YACs is well known in the art (e.g., Bruschi, C.V. and Gjuracic, K. Yeast Artificial Chromosomes, ENCYCLOPEDIA OF LIFE SCIENCES 2002 Macmillan Publishers Ltd, Nature Publishing Group / www.els.net).

The YAC used was about 340kb comprises 10 human heavy chain V genes in their natural configuration, human heavy chain D and J genes, a murine $C\gamma1$ gene and a murine 3' enhancer gene. It lacks the C_H1 exon. Specifically, the YAC comprised (from 5' to 3'): telomere-yeast *TRP1* marker gene-Centromere-10 human V genes- human D genes- human J genes-mouse μ enhancer and switch-mouse $C\gamma1$ ($C_H1\Delta$) gene-mouse 3' enhancer-Hygromycin resistant gene-yeast marker gene *HIS3*-telomere.

The transgenic founder mice were back-crossed with animals that lacked endogenous immunoglobulin expression to create the Tg/TKO lines used in the immunisation studies described.

EXAMPLE 2. Antigen for immunisation

The immunisations used recombinant purified protein. Recombinant human IL-17RA was purchased from R&D systems (177-IR-100).

EXAMPLE 3. Immunisation Protocol

In the present case, recombinant protein was administered to the Tg/TKO. Briefly, mice aged 8 – 12 weeks of age each received a total of 10ug of recombinant protein, emulsified in Complete Freund's Adjuvant and delivered subcutaneously, followed by boosts of 1 – 10ug of recombinant protein, emulsified in Incomplete Freund's Adjuvant, also administered subcutaneously, given at various intervals following the initial priming. A final dose of antigen was administered intraperitoneally, in phosphate buffered saline, in the absence of adjuvant.

Alternative immunisation routes and procedures can also be employed. For example, different adjuvants or immune potentiating procedures may be used instead of Freund's adjuvant. DNA immunisations are often delivered intramuscularly or via a Genegun. Transfected cells or membrane preparations from such cells are often, although not exclusively, administered intraperitoneally.

EXAMPLE 4. Serum ELISA

During and following immunisation, serum was collected from mice and checked for the presence of heavy-chain antibody responses to the immunogen by ELISA. Nunc Maxisorp plates (Nunc Cat. No. 443404) were coated overnight at 4°C with 50ul/well of a 5ug recombinant antigen/ml of PBS solution. Following decanting of the antigen solution, plates were washed using PBS (prepared from PBS tablets, Oxoid cat no. BR0014G) supplemented with 0.05% Tween™20 (sigma P1379), followed by washes with PBS without added Tween™. To block non-specific protein interactions, a solution of 3% skimmed milk powder (Marvel) in PBS was added to the wells and the plate was incubated for at least one hour at room temperature. Dilutions of serum in 3% Marvel/PBS were prepared in polypropylene tubes or plates and incubated for at least one hour at room temperature prior to transfer to the blocked ELISA plate where a further incubation of at least one hour took place. Unbound protein was then washed away using repetitive washes with PBS/Tween® followed by PBS. A solution of biotin-

conjugated, goat anti mouse IgG, Fcgamma subclass 1 specific antibody (Jackson 115-065-205), prepared in PBS/3% Marvel was then added to each well and a further incubation at room temperature for at least one hour took place. Unbound detection antibody was removed by repeated washing using PBS/Tween® and PBS. Neutravidin-HRP solution (Pierce 31030) in 3% Marvel/PBS was then added to the ELISA plates and allowed to bind for at least 30 minutes. Following further washing, the ELISA was developed using TMB substrate (Sigma cat. no. T0440) and the reaction was stopped after 10 minutes by the addition of 0.5M H_2SO_4 solution (Sigma cat. no. 320501). Absorbances were determined by reading at 450nm. Examples of Serum ELISA data are shown in Figure 8. Alternative assays, such as ELISPOT assays, may also be used to check for immunisation induced heavy-chain antibody responses.

EXAMPLE 5. Generation of Libraries from Immunised Mice

a. processing tissues, RNA extraction and cDNA manufacture

Spleen, inguinal and brachial lymph nodes were collected into RNAlater® from each immunised animal. For each animal, 1/3 of the spleen and 4 lymph nodes were processed separately. Initially, the tissues were homogenised; following transfer of tissues to Lysing matrix D bead tubes (MP Bio cat# 116913100), 600ul of RLT buffer containing β-mercaptoethanol (from Qiagen RNeasy® kit cat# 74104) was added before homogenisation in a MP Bio Fastprep homogeniser (cat # 116004500) using 6m/s 40 seconds cycles. The tubes containing the homogenised tissues were transferred to ice and debris was pelleted by microcentrifugation at 10g for 5 minutes. 400ul of the supernatant was removed and used for RT-PCR.

Initially, RNA was extracted using Qiagen RNeasy® kit cat# 74104 following the manufacturer's protocol. Each RNA sample was then used to make cDNA using Superscript III RT-PCR high-fidelity kit (Invitrogen cat # 12574-035). For each spleen and LN RNA sample, 5 RT-PCR reactions were performed, each with VH_J/F (long) primer in combination with a primer for V_H1, V_H2, V_H3, V_H4 or V_H6 family. Details of the primers are below in Table 8.

Table 8 Primers

V1a/pelB (long)	**GCCGCTGGATTGTTATTACTCGCGGCCCAGCCGGCCATGGCC**CAGG TBCAGCTGGTGCAGTCTGGGGCTGAGG SEQ ID NO 2595
V2/pelB(long)	**GCCGCTGGATTGTTATTACTCGCGGCCCAGCCGGCCATGGCC**CAGA TCACCTTGAAGGAGTCTGG SEQ ID NO 2596

V3/pelB(long)	**GCCGCTGGATTGTTATTACTCGCGGCCCAGCCGGCCATGGCC**SAGGTGCAGCTGGTGGAGTCTGGGGGAGG SEQ ID NO 2597
V4-4/pelB(long)	**GCCGCTGGATTGTTATTACTCGCGGCCCAGCCGGCCATGGCC**CAGGTGCAGCTGCAGGAGTCGGG SEQ ID NO 2598
V6/pelB(long)	**GCCGCTGGATTGTTATTACTCGCGGCCCAGCCGGCCATGGCC**CAGGTACAGCTGCAGCAGTCAGG SEQ ID NO 2599
VH_J/F(long)	**CCGTGGTGATGGTGGTGATGGCTACCGCCACCCTCGAG**TGARGAGACRGTGACC SEQ ID NO 2600

Residues in **bold** have homology with pUCG3

Mastermixes were prepared for the RT-PCR reactions, based on the following tube reaction components.

12.5µl 2x reaction mix
0.5µl forward primer (10uM)
0.5µl reverse primer (10uM)
0.5µl enzyme mix
500ng - 1µg RNA
Up to 25µl with water

The RT-PCR reactions were carried out in a thermal cycler using the following conditions;

50^0C 20min
94^0C 2min
35 cycles of 94^0C 15sec
58^0C 30sec
68^0C 30sec
68^0C 5min
Hold at 4^0C

Products in the range of 370bp were confirmed by gel electrophoresis.

For each mouse, the V_H products amplified for a given family from the 1/3 spleen and each of the 4 lymph nodes were then pooled for purification using Thermo/Fermentas GeneJet PCR purification kit (cat #K0702) which was used according to the Manufacturer's instructions, with the products eluted in 50ul of water.

b. Cloning into phagemid vector

The phagemid vector, pUCG3, was employed in these studies. As indicated, V_H may be cloned into pUCG3, using conventional methods involving restriction enzyme digestions with NcoI and XhoI, ligation and transformation. Alternatively, a PCR-based method may be used to construct the V_H phagemid libraries. Both of these procedures were used to generate libraries from the amplified V_H sequences. The former method is widely used in the art. For the PCR-based method, the following procedure was used:

A linearised version of pUCG3 was created using PCR; with the following primers:

pUCG3-F3 CTCGAGGGTGGCGGTAGCCATCACCACCATC SEQ ID NO. 2601

pUCG3-R3 TCCATGGCCATCGCCGGCTGGGCCGCGAG SEQ ID NO. 2602

Phusion High fidelity PCR master mix with GC buffer (cat # F532L, NEB) was used for the PCR reactions which comprised the following reagents;

Phusion GC 2x mix	25ul
pUCG3	5-10ng
Primers (10uM)	1.25µl of each
DMSO	1.5µl
Nuclease-free H_2O	to final volume of 50ul

The cycling conditions used were

98°C 30 seconds

10 cycles of

98 °C 10 seconds

58 °C 20 seconds

68 °C 2 minutes, 30 seconds

20 cycles of

98 °C 10 seconds

58 °C 20 seconds

68 °C 3 minutes

68 °C 5 minutes

4 °C hold

The PCR product (3152bp) was gel purified using Fermentas GeneJet Gel purification kit (cat # K0691), according to the manufacturer's instructions, with final elution in 40ul of elution buffer.

The purified V_H RT-PCR products were employed as megaprimers with the linearised pUCG3 to give phagemid products for transformation and library creation, based on the following reactions;

Phusion GC 2x mix	25µl
Linearised pUCG3	700ng
V_H PCR product	250ng
DMSO	1.5µl
Nuclease-free H_2O	to 50µl final volume

PCR was performed as follows;

98°C 30sec	
98°C 10sec	10 cycles
58°C 20sec	
72°C 2min	
72°C 5min	
Hold at 10°C	

The products of PCR were analysed on a 1% agarose gel.

The various family V_H/phagemid products were purified using Ferment as PCR purification kit (cat #K0702) according to the manufacturer's instructions with the final elution being in 25ul H_2O and used for transformations of TG1 *E. coli* (Lucigen, Cat: 60502-2) by electroporation using BioRad® 10 x 1 mm cuvettes (BioRad® cat # 165-2089, a Eppendorf™ Eporator and pre-warmed recovery medium (Lucigen, proprietary mix). 2ul of the purified products were added to 25ul of cells for the electroporation, with up to 10 electroporations being performed for each V_H/phagemid product at 1800v. Electroporated cells were pooled and recovered in 50ml Falcon tubes incubated for 1 hour at 37°C with shaking at 150rpm. A 10-fold dilution series of an aliquot of the transformations was performed and plated in petri dishes containing 2xTY agar supplemented with 2% (w/v) glucose and 100ug/ml ampicillin. Resulting colonies on these dishes were used to estimate the library size. The remainder of the transformation was plated on large format Bioassay dishes containing 2xTY agar supplemented with 2% (w/v) glucose and 100ug/ml ampicillin. All agar plates were incubated overnight at 30°C. 10ml of 2xTY broth was added to the large format bioassay dishes and colonies were scraped and OD600 measured (OD of 1.0 = 5 x 10^8 cells/ml). Aliquots were stored at -80°C in cryovials after addition of 50%v/v glycerol solution (50%) or used directly in a phage selection process.

In some instances, clones were picked directly and sequence was determined to give an estimate of the diversity of the library. Typically, for each mouse a phage display library with greater than 1e8 recombinants was constructed to fully capture the V_H diversity in that mouse.

EXAMPLE 6. Selection strategies for isolation of IL-17RA -binding V_H

Preparation of library phage stocks and phage display selections were performed according to published methods (Antibody Engineering, Edited by Benny Lo, chapter 8, p161-176, 2004). In most cases, phage display combined with a panning approach was used to isolate binding V_H domains. However, a variety of different selection methods may be employed, including (a) soluble selections; (b) selections performed under stress, where phage are heated at 70°C for 2 hours prior to selection; and (c) competitive selections, where excess antigen or antigen-reactive V_H domains are added as competition to encourage the recovery of high affinity V_H domains or to skew selections away from a particular epitope.

The IL-17RA antigen was expressed as a fusion with the Fc domain of human IgG1. Therefore, to minimise the isolation of unwanted antibodies to the Fc region of the fusion protein, human IgG1 was added to the phage display selections at 100ug/ml (approx 650nM) to compete or deselect for Fc binding V_H. For panning, antigen was immobilised onto maxisorb plates (Nunc 443404) in 50ul volumes at 0.1 - 10ug/ml in PBS. For the libraries from immunised mice, one round of selection was carried out.

EXAMPLE 7. Assays for target binding

V_H from the different selections were screened in one or more of the following assays to identify specific V_H with neutralising properties.

a) Binding ELISA

Following selections of the libraries, specific V_H antibodies were identified by phage ELISA following published methods (Antibody Engineering, Edited by Benny Lo, chapter 8, p161-176, 2004). Phage ELISAs were performed against target protein and an unrelated antigen as control. In some cases, purified or crude extracts of V_H domains were assayed by ELISA instead of using a phage ELISA. In these cases, bacterial periplasmic extracts or purified V_H were used.

Small-scale bacterial periplasmic extracts were prepared from 1ml cultures, grown in deep well plates. Starter cultures were used to inoculate 96-well deep well plates (Fisher, cat# MPA-600-030X) containing 2XTY broth (Melford, M2130), supplemented with 0.1% (w/v) glucose+ 100ug/ml ampicillin at 37°C with 250rpm shaking. When OD600 had achieved 0.6-1, V_H production was induced by adding 100ul of 2XTY, supplemented with IPTG (final concentration 1mM) and ampicillin and the cultures

were grown overnight at 30°C with shaking at 250rpm. *E. coli* were pelleted by centrifugation at 3200rpm for 10 mins and supernatants discarded. Cell pellets were resuspended in 30-100ul of ice cold extraction buffer (20% (w/v) sucrose, 1mM EDTA & 50mM Tris-HCl pH8.0) by gently pipetting. Cells were incubated on ice for 30 minutes and then centrifuged at 4500rpm for 15 mins at 4°C. Supernatants were transferred to polypropylene plates and used, following incubation in Marvel/PBS blocking solution, in the ELISA.

The purified V_H were obtained by using the V_H C-terminal 6xHIS tag for nickel-agarose affinity chromatographic purification of the periplasmic extracts. A starter culture of each V_H was grown overnight in 5ml 2XTY broth (Melford, M2103) supplemented with 2% (w/v) glucose + 100ug/ml ampicillin at 30°C with 250rpm shaking. 50ul of this overnight culture was then used to inoculate 50ml 2XTY supplemented with 2% (w/v) glucose + 100ug/ml ampicillin and incubated at 37°C with 250rpm shaking for approximately 6-8 hours (until OD600 = 0.6-1.0). Cultures were then centrifuged at 3200rpm for 10 mins and the cell pellets resuspended in 50ml fresh 2XTY broth containing 100ug/ml ampicillin + 1mM IPTG. Shake flasks were then incubated overnight at 30°C and 250rpm. Cultures were again centrifuged at 3200rpm for 10 mins and supernatants discarded. Cell pellets were resuspended in 1ml ice cold extraction buffer (20% (w/v) sucrose, 1mM EDTA & 50mM Tris-HCl pH8.0) by gently pipetting and then a further 1.5ml of 1:5 diluted ice cold extraction buffer added. Cells were incubated on ice for 30 minutes and then centrifuged at 4500rpm for 15 mins at 4°C. Supernatants were transferred to 50ml Falcon tubes containing imidazole (Sigma, I2399 - final concentration 10mM) and 0.5ml of nickel agarose beads (Qiagen, Ni-NTA 50% soln, 30210) pre- equilibrated with PBS buffer. V_H binding to the nickel agarose beads was allowed to proceed for 2 hours at 4°C with gentle shaking. The nickel agarose beads were then transferred to a polyprep column (BioRad™, 731-1550) and the supernatant discarded by gravity flow. The columns were then washed 3 times with 5ml of PBS+0.05% Tween™ followed by 3 washes with 5ml of PBS containing imidazole at a concentration of 20mM. V_H were then eluted from the columns by the addition of 250ul of PBS containing imidazole at a concentration of 250mM. Imidazole was then removed from the purified V_H preparations by buffer exchange with NAP-5 columns (GE Healthcare, 17-0853-01) and then eluting with 1ml of PBS. Yields of purified V_H were estimated spectrophotemetrically and purity was assessed using SDS PAGE.

The binding ELISA for crude or purified V_H was similar to the serum ELISA and phage ELISA, previously described, mostly differing in the final detection steps. Briefly, antigen was immobilised on maxisorb plates (Nunc 443404) by adding 50ul volumes at 0.1 - 1ug/ml in PBS and incubating at 4°C overnight. Following coating, the antigen solution was aspirated and the plates were washed using PBS (prepared from PBS tablets, Oxoid cat no. BR0014G) supplemented with 0.05% Tween® 20 (sigma P1379), followed by washes with PBS without added Tween®. To block non-specific protein interactions, a solution of 3% skimmed milk powder (Marvel) in PBS was added to the wells and the plate was incubated for at least one hour at room temperature. Dilutions of periplasmic extract or purified V_H in 3% Marvel/PBS were prepared in polypropylene tubes or plates and incubated for at least one hour at room temperature prior to transfer to the blocked ELISA plate where a further incubation of at least one hour took place. Unbound protein was then washed away using repetitive washes with PBS/Tween® followed by PBS. A solution of HRP-conjugated anti-His Ab (Miltenyi Biotec, 130-092-785), prepared at 1:1000 dilution in PBS/3% Marvel was then added to each well and a further incubation at room temperature for at least one hour took place. Unbound detection antibody was removed by repeated washing using PBS/Tween® and PBS. The ELISA was then developed using TMB substrate (Sigma cat. no. T0440) and the reaction was stopped after 10 minutes by the addition of 0.5M H_2SO_4 solution (Sigma cat. no. 320501). Absorbances were determined by reading at 450nm. Example ELISA data is shown in Figure 14.

b) R/L Biochemical Inhibition Assay

V_H, both purified and crude periplasmic extracts, were also tested for their ability to inhibit the interaction of IL-17A with recombinant IL-17RA-Fc. Maxisorb 96F well mictrotitre plates were incubated with 50ul solution of 2nM IL-17-RA (R & D systems, cat # 177-IR-100) and incubated overnight at 4°C. Following washing of excess coating antigen, as described above, the wells of the plate were incubated with 3%Marvel/PBS to block non-specific protein interactions. V_H preparations, crude periplasmic extracts or purified V_H, or suitable controls, were prepared with 1nM recombinant IL-17A (Peprotech, cat# AF-200-17) in 3% skimmed milk powder /PBS solution in polypropylene plates or tubes. The mixture was then transferred to the assay plate and incubated for 1 hour at room temperature. Excess protein was removed by washing and bound IL-17A was detected by incubation with biotinylated anti-IL-17A Mab (R & D Systems, cat BAF317) followed by the addition of neutravidin-HRP (Pierce, cat# 31030) and TMB substrate (Sigma, cat# T0440). The TMB reaction

was stopped by addition of 0.5M H_2SO_4 and absorbances were measured at 450nm in a plate reader.

Where appropriate, curve fitting in PRISM was used to determine the EC_{50} of inhibiting V_H. Example data illustrating inhibition of IL-17A responses in the biochemical assay are shown in Figure 10. V_H were expressed from phagemid vector and have the following C terminal extension LEGGGS HHHHHH (SEQ ID NO.2606).

c) R/L Cell Based Inhibition Assay

An assay was developed to measure the ability of IL-17RA -binding V_H to inhibit IL-17A-induced IL6 release from the cell line, HT1080 (ECACC cat #85111505). The cell line was maintained in exponential growth in MEM with Earles's salts, supplemented with non-essential amino acids, 10% FBS, 2mM L-Glutamine and penicillin/streptomycin and incubated in a humidified incubator at 37°C, 5% CO_2. For the assay, 50,000 cells/well were seeded into a 96 flat bottomed tissue culture plate and cultured overnight. Serial dilution of purified V_H were prepared and incubated at 37°C for 1 hour with culture medium/PBS supplemented with 10ng/ml IL-17A (Peprotech cat# AF200-17). Following incubation, the V_H/IL-17A mixture (or suitable controls) were transferred to the HT1080 cells (from which culture medium had been aspirated) and incubated for a further 5 hours in the CO_2 incubator. The cell culture supernatant was collected and assayed for IL6 using the IL-6 Duoset (R & D Systems, cat# DY206), following manufacturer's instructions. Example data illustrating inhibition of IL-17A responses in the cell based assay are shown in Figure 11. V_H were expressed from phagemid vector and have the following C terminal extension LEGGGS HHHHHH.

d) **Biacore®**.

Binding kinetics of anti-IL-17RA V_H antibodies were measured on a BIAcore® T200 instrument. For IL-17RA, first a protein G chip was prepared by diluting protein G to 20ug/ml in acetate buffer, pH 4 (BIAcore®, cat# BR-100-49) and then coupled 1200 RU to a CM5 Series S chip using amine coupling chemistry. This surface was then used to capture IL-17RA Fc fusion protein from solution: IL-17RA at 10ug/ml in HBS injected for 10 seconds at 30ul/min flow rate would capture approximately 100-150RU of IL-17RA onto the protein G surface.

Binding kinetics of anti-IL-17RA V_H antibodies were determined by single-cycle kinetics. V_H antibodies were prepared in dilution series (typically 1:3 dilution series starting with 100nM V_H at the highest concentration), and then injected over the antigen coated

surfaces and also a blank surface, starting with the lowest concentration of V_H and then working progressively up to the highest concentration. V_H binding kinetics were then determined from the (blank subtracted) sensorgram traces using 1:1 binding models and BIAevaluation software. Example BIAcore® binding traces are shown in Figure 12.

Following the above screening cascade, a number of V_H to IL-17R were identified that demonstrated inhibitory properties. These are summarised below in table 9. The clones are the parent clones for optimisation.

Table 9

		Clone name	CDR3 sequence	Biochem IC50 (nM)	Cell assay IC50 (nM)	BIAcore (Affinity) KD (M)
IL-17RA	Immunised mouse	2.1	GRRDDWKNNY SEQ ID NO1267	3.7	280	7.0E-09
		1.1	EKGLGFCRGGSCSY FDY SEQ ID NO 3	nd	4.7	6.3E-11
		5.1	NGARYNWNYGDFQH SEQ ID NO 2559	80	73	4.1E-08
		4.1	GGYNAWRTDY SEQ ID NO 2131	nd	282	4.5E-09
		3.1	GWESGWFEP SEQ ID NO 1767	11	Weak	9.6E-09
		6.1	KDITNIAVGSLGY SEQ ID NO 2575	nd	233	3.1E-08
		7.1	SRDWGSRAFDI SEQ ID NO 2579	nd	1840	3.7E-07

EXAMPLE 8. Optimisation of V_H

a. Optimisation of V_H Isolated from Immunised Mice

Where appropriate, a novel optimisation strategy was used to increase binding affinities of V_H isolated from immunised mice. Lead VH were aligned with other members of the

same lineage to identify somatic hypermutation hot-spots targeted during the immune response (Figure 13). The choice of amino acids at these positions formed the basis of a new recombination library approach, and led to the design of new libraries aimed at selecting higher affinity V_H with optimal amino acids at each mutation hot-spot.

As an example for IL-17RA, clone 2.1 was isolated directly from immunised TKO mouse. This V_H was shown to bind IL-17RA with high affinity Alignment of clone 2.1 with other members of the same lineage identified a number of amino acid positions that had been mutated during the immune response, and both V_H-CDRs and V_H-framework regions were affected. This information was then utilised to design a new clone 2.1 recombination library with the aim of identifying a higher affinity variant of clone 2.1. Following construction and phage display selection of a recombination library a new variant was isolated (2.2) that was improved in affinity by 10-fold.

Phusion High fidelity PCR master mix with HF buffer (cat # F531L, NEB) was used for the PCR reactions which were set up for each primer pairing as follows:

Phusion HF 2x mix	25μl
Primers (10uM)	1.25μl each (pairings as in table)
53F9 plasmid DNA (34ng/ul)	0.5μl
Nuclease-free H_2O	to 50ul final volume

PCR was performed as follows;

98°C 30sec	
98°C 10sec	31 cycles
58°C 20sec	
72°C 20sec	
72°C 10min	
Hold at 10°C	

The products of each PCR were analysed on a 1% agarose gel. Each product was then purified using Fermentas PCR purification kit (K0701) into 40ul elution buffer. Assembly PCRs were then set up to rebuild the full V_H sequence:

Phusion HF 2x mix	25μl
Purified PCR product 1	5 μl
Purified PCR product 2	5 μl
Purified PCR product 3	5 μl
Purified PCR product 4	5 μl
Purified PCR product 5	5 μl

PCR was performed as follows;

98°C 30sec
98°C 10sec
58°C 20sec } 5 cycles
72°C 20sec

Added 0.5ul of primers V3/pelB (long) and VH_J/F (long) (both 10uM) to the reaction and then continued for a further 10 PCR cycles at the above conditions. The PCR product was analysed on a 1% agarose gel and purified using Fermentas PCR purification kit into 40ul elution buffer. The PCR product was then used as a megaprimer for library construction as described above in Example 5, part b. Phage display selections and V_H screening was then performed as described in examples 7 and 8, following which several new variants of clone 2.1 were isolated with up to 10-fold improved affinities.

Following the lead optimisation steps, the potencies of improved V_H were as follows:

a) **Table 10** V_H produced following optimisation of anti-IL-17RA V_H family 2

V_H name	CDR3 sequence	Biochem IC50 (nM)	Cell assay IC50 (nM)	BIAcore (Affinity)		
				ka (1/Ms)	kd (1/s)	KD (M)
2.1	GRRDDWKNNY SEQ ID NO 1267	3.7	280	3.68E+05	2.63E-03	7.0E-09
2.3	GRRDNWKNNY SEQ ID NO 1275	1.3	118	5.55E+05	0.001368	2.50E-09
2.2	GRRDDWKNNY SEQ ID NO 1271	1.4	61	5.79E+05	7.99E-04	1.40E-09

Optimised V_H show improved affinities to IL-17R and improved potencies in the IL-17R cell based assay due to slower off-rates (Figure 15).

EXAMPLE 9 – Characterisation of V_H

a. Specificity of anti-IL-17A

The specificity of individual V_H for target antigen was confirmed by ELISA, following the methods described in Example 8(a). V_H were tested for binding to IL-17RA and shown not to cross-react with close relatives such as IL-17RB, IL-17RC and IL-17RD. (Figure 14).

b. **Epitope Mapping**

VH were shown to bind to unique epitopes of IL-17RA using a BIAcore T200 instrument. Manual sensorgrams were initiated at 30ul/min in HBS buffer and V_H injected as appropriate over the IL-17RA coupled CM5 chip coupled CM5 chip, plus a blank surface for reference subtraction (Figure 15).

For IL-17RA, IL-17RA-Fc fusion protein was first captured on a protein G chip by injecting IL-17RA-Fc at 10ug/ml in HBS buffer for 10 seconds. This surface was then used to measure binding and competition between different anti-IL-17RA V_H following the method described above. Epitope competition data is presented for 1.1 and 2.2 (Figure 15). V_H were expressed from phagemid vector and have the following C terminal extension LEGGGS HHHHHH (SEQ ID NO.2606).

c. HPLC Size Exclusion Chromatography

Purified V_H (clones 1.1, 1.2, 2.1) were subjected to size exclusion chromatography. Briefly, purified V_H were analysed using a Water® 2795 Separation Module with a Waters® 2487 Dual λ #absorbance Detector – (Detected at 280nM) and a TSKgel G2000SWXL (TOSOH) column. Samples were injected in 10-50ul volumes and run in mobile phases of either 10% isopropanol / 90% PBS or 100mM Phosphate buffer, pH 6.8, 150mM NaCl at a flow rate of 0.5ml/min – 0.7ml/min. Data were collected for up to 35 minutes and the size of the V_H fraction compared with known standards (see Figure 16). V_H were expressed from phagemid vector and have the following C terminal extension LEGGGS HHHHHH (SEQ ID NO.2606).

CLAIMS:

1. A binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (V_H) comprising a CDR3 sequence comprising SEQ ID NO. 3 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3.
2. A binding molecule according to claim 1 comprising at least one immunoglobulin single domain antibody.
3. A binding molecule according to claim 1 or 2 comprising a CDR1 sequence comprising SEQ ID NO. 1 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto and a CDR2 sequence comprising SEQ ID NO. 2 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.
4. A binding molecule according to claim 3 wherein said CDR1 sequence comprises or consists of SEQ ID NO. 1, 5, 9, 13, 17 or 21, said CDR2 sequence comprises or consists of SEQ ID NO. 2, 6, 10, 14, 18 or 22 and said CDR3 sequence comprises or consists of the amino acid sequence SEQ ID NO: 3, 7, 11, 15, 19 or 23.
5. A binding molecule according to a preceding claim wherein the binding molecule comprises a CDR1, CDR2 and CDR3 sequences as shown for a V_H sequence of any of clones 1.1 to 1.316 in Figure 1.
6. A binding molecule according to a preceding claim wherein said V_H domain comprises or consists of SEQ ID NO. 4 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
7. A binding molecule according to a preceding claim wherein said V_H domain comprises or consists of SEQ ID NO. 8, 12, 16, 20 or 24.
8. A binding molecule according to a preceding claim wherein the V_H domain is selected from a V_H domain as shown for clones 1.1 to 1.316 in Figure 1.
9. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1267 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1267.
10. A binding molecule according to claim 9 comprising at least one immunoglobulin single domain antibody.
11. A binding molecule according to claim 9 or 10 comprising a CDR1 sequence comprising SEQ ID NO. 1265 or a sequence with at least 70%, at least 80%, at

least 90%, or at least 95% homology thereto and a CDR2 sequence comprising SEQ ID NO. 1266 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.

12. A binding molecule according to any of claims 9 to 11 claim wherein the binding molecule comprises a CDR1, CDR2 and CDR3 sequence as shown for a V_H sequence of any of clones 2.1 to 2.125 in Figure 2.
13. A binding molecule according to any of claims 9 to 12 wherein in said the binding molecule CDR1 is SEQ ID NO. 1269, CDR2 is SEQ ID NO. 1270 and CDR3 is SEQ ID NO. 1271 or CDR1 is SEQ ID NO. 1273, CDR2 is SEQ ID NO. 1274 and CDR3 is SEQ ID NO. 1275.
14. A binding molecule according to any of claims 9 to 13 wherein said V_H domain comprises or consists of SEQ ID NO. 1268 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
15. A binding molecule according to any of claims 9 to 14 wherein the V_H domain is selected from a V_H domain as shown for clones 2.1 to 2.125 in Figure 2.
16. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 1767 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 1767.
17. A binding molecule according to claim 16 comprising an at least one immunoglobulin single domain antibody.
18. A binding molecule according to claim 16 or 17 comprising a CDR1 sequence having SEQ ID NO. 1765 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto and a CDR2 sequence having SEQ ID NO. 1766 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.
19. A binding molecule according to claim 18 wherein the binding molecule comprises CDR1, CDR2 and CDR3 sequences as shown for a V_H sequence of any of clones 3.1 to 3.91 in Figure 3.
20. A binding molecule according to claim 19 wherein said CDR1 comprises SEQ ID NO. 1765, said CDR2 comprises SEQ ID NO. 1766 and said CDR3 comprises SEQ ID NO. 1767.
21. A binding molecule according to any of claims 16 to 20 wherein said V_H domain comprises or consists of SEQ ID NO. 1768 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
22. A binding molecule according to any of claims 16 to 21 wherein the V_H domain is selected from a V_H domain as shown for clones 3.1 to 3.91 in Figure 3.

23. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2131 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2131.
24. A binding molecule according to claim 23 comprising at least one immunoglobulin single domain antibody.
25. A binding molecule according to claim 23 or 24 comprising a CDR1 sequence having SEQ ID NO. 2129 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto and a CDR2 sequence having SEQ ID NO. 2130 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto.
26. A binding molecule according to any of claims 23 to 25 wherein said binding molecule comprises a CDR1, CDR2 and CDR3 sequences as shown for a V_H sequence of any of clones 4.1 to 4.107 in Figure 4.
27. A binding molecule according to claim 26 wherein said CDR1 comprises SEQ ID NO. 2129, said CDR2 comprises SEQ ID NO. 2130 and said CDR3 comprises SEQ ID NO. 2131.
28. A binding molecule according to any of claims 23 to 27 wherein said V_H domain comprises or consists of SEQ ID NO. 2132 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
29. A binding molecule according to any of claims 23 to 28 wherein the V_H domain is selected from a V_H domain as shown for clones 4.1 to 4.107 in Figure 4.
30. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2559 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2559.
31. A binding molecule according to claim 30 comprising at least one immunoglobulin single domain antibody.
32. A binding molecule according to claim 30 or 31 comprising a CDR1 sequence having SEQ ID NO. 2557 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto and a CDR2 sequence having SEQ ID NO. 2558 or a sequence with at least 70% at least 80%, at least 90%, or at least 95% homology thereto.
33. A binding molecule according to any of claims 30 to 32 wherein the binding molecule has CDR1, CDR2 and CDR3 sequences as shown for a V_H sequence of any of clones 5.1 to 5.4 in Figure 5.

34. A binding molecule according to claim 33 wherein said CDR1 comprises SEQ ID NO. 2557, said CDR2 comprises SEQ ID NO. 2558 and said CDR3 comprises SEQ ID NO. 2559.
35. A binding molecule according to any of claims 30 to 34 wherein said V_H domain comprises or consists of SEQ ID NO. 2560 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
36. A binding molecule according to claim 35 wherein the V_H domain is selected from a V_H domain as shown for clones 5.1 to 5.4 in Figure 5.
37. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2575 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2575.
38. A binding molecule according to claim 37 comprising an immunoglobulin single domain antibody.
39. A binding molecule according to claim 37 or 38 comprising a CDR1 sequence having SEQ ID NO. 2573 or a sequence with at least 70%, at least 80%, at least 90%, at least 95% homology thereto and a CDR2 sequence having SEQ ID NO. 2574 or a sequence with at least 70% at least 80%, at least 90%, or at least 95% homology thereto.
40. A binding molecule according to any of claims 37 to 39 wherein said V_H domain comprises or consists of SEQ ID NO. 2576 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.
41. A binding molecule capable of binding human IL-17RA comprising a human V_H domain comprising a CDR3 sequence comprising SEQ ID NO. 2579 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 2579.
42. A binding molecule according to claim 41 comprising at least one immunoglobulin single domain antibody.
43. A binding molecule according to claim 41 or 42 comprising a CDR1 sequence comprising SEQ ID NO. 2577 or a sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology thereto and a CDR2 sequence comprising SEQ ID NO. 2578 or a sequence with at least 70% at least 80%, at least 90%, or at least 95% homology thereto.
44. A binding molecule according to any of claims 41 to 43 wherein said V_H domain comprises or consists of SEQ ID NO. 2580 or a sequence with at least 40%, 50%, 60%, 70%, 80%, 90% or 95% homology thereto.

45. A binding molecule according to a preceding claim wherein the binding molecule has an IC_{50} for inhibition of IL-6 production of about 0.2 to about 500 nM when tested as described in the examples, i.e. by measuring the ability of IL-17R-binding molecule to inhibit IL-17R induced IL-6 release from the cell line HT1080.
46. A binding molecule according to a preceding claim wherein said binding molecule has a KD (M) value in the range of from 6×10^{-11} to 3×10^{-7}, preferably in the range of from 1×10^{-9} to 6×10^{-11}, preferably when assessed by BIAcore®.
47. A binding molecule according to a preceding claim wherein said binding molecule comprises two or more V_H domains wherein at least one of the V_H domains binds specifically to IL-17RA.
48. A binding molecule according to a preceding claim wherein said binding molecule binds specifically to human IL-17RA.
49. A binding molecule according to a preceding claim wherein said binding molecule is conjugated to a toxin, enzyme or radioisotope or other chemical moiety.
50. A binding molecule according to a preceding claim obtained or obtainable from a transgenic mouse that does not produce any functional endogenous light or heavy chains.
51. A binding molecule that competes for binding to human IL-17R with a binding molecule of any one of claims 1 to 50.
52. A pharmaceutical composition comprising a binding molecule according to any preceding claim and a pharmaceutical carrier.
53. A pharmaceutical composition according to claim 52 comprising a chemical skin penetration enhancer.
54. A method for treating an disease selected from autoimmune diseases, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection, comprising administering an effective amount of a binding molecule according to any of claims 1 to 51 or a pharmaceutical composition according to claim 52 or 53.
55. A method according to claim 54 wherein the disease is selected from psoriasis, spondyloarthropathies, uveitis and atopic dermatitis.
56. A method according to claim 54 or 55 wherein the binding molecule or pharmaceutical composition is formulated for administration topically to the skin.
57. A binding molecule according to claims any of claims 1 to 51 or a pharmaceutical composition according to claim 52 or 53 for use as medicament.

58. A binding molecule according to any of claims 1 to 51 or a pharmaceutical composition according to claim 52 or 53 for use in the treatment of a disease selected from an autoimmune disease, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.
59. A binding molecule according to claim 58 wherein the disease is selected from psoriasis, spondyloarthropathies, uveitis and atopic dermatitis.
60. A binding molecule or pharmaceutical composition according to claim 58 or 59 wherein the binding molecule or pharmaceutical composition is formulated for administration topically to the skin.
61. Use of a binding molecule according to any of claims 1 to 51 or a pharmaceutical composition according to claim 52 or 53 in the manufacture of a medicament for the treatment of a disease selected from an autoimmune disease, inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, severe infections, and organ or tissue transplant rejection.
62. The use according to claim 61 wherein the disease is is selected from psoriasis, spondyloarthropathies, uveitis and atopic dermatitis.
63. The use according to claim 61 or 62 wherein the binding molecule or pharmaceutical composition is formulated for administration topically to the skin.
64. A method according to claims 54 to 56, a binding molecule according to claims 57 to 60, a use according to claims 61 to 63 wherein said disease is selected from the following non-limiting list: psoriasis, systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung

such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), transplantation associated diseases including graft rejection and graft-versus-host-disease.

65. An in vivo or in vitro method for reducing human IL-17RA activity comprising contacting human IL-17RA with a binding molecule according to any of claims 1 to 51.
66. A method for determining the presence of IL-17RA in a test sample by an immunoassay comprising contacting said sample with a binding molecule according to any of claims 1 to 51 and at least one detectable label.
67. A method of claim 66 wherein said method comprises diagnosing or assessing the efficacy of prophylactic or therapeutic treatment of a patient.
68. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a binding molecule according to any of claims 1 to 51.
69. A nucleic construct comprising a nucleic acid according to claim 68.
70. An isolated host cell comprising a nucleic acid according to claim 68 or a construct according to claim 69.
71. A method for producing a binding molecule according to any one of claims 1 to 51 comprising expressing a nucleic acid encoding said binding molecule in a host cell and isolating the binding molecule from the host cell culture.
72. A kit comprising a binding molecule according to any of claims 1 to 51 or a pharmaceutical composition according to claim 52 or 53.
73. A method for producing a binding molecule comprising at least one immunoglobulin single domain antibody directed against IL-17RA wherein said domain is a human V_H domain said method comprising
    d) immunising a transgenic mouse that expresses a nucleic acid construct comprising human heavy chain V genes and that is not capable of making functional endogenous light or heavy chains with an IL-17RA antigen,
    e) generating a library from said mouse and
    f) isolating V_H domains from said libraries.
74. A biparatopic, bivalent or multispecific binding molecule comprising a binding molecule as defined in any of claims 1 to 51.

Figure 1

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.1	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTAMYYCAK	**EKGLGFCRGGSCSYFDY**	RGQGTLVTVSS
1.2	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKGLGYCRGGSCSYFDY**	RGQGTLVTVSS
1.3	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYALH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADTVKG**	RFTISRDNAKKSLYLQMNSLRAEDTAMYYCAK	**EKGLGFCRGGSCSYFDY**	RGQGTLVTVSS
1.4	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYALH**	WVRQAPGKGLEWVS	**GISWNAGRKDYADTVKG**	RFTISRDNAKKSLYLQMNSLRAEDTAMYYCAK	**EKGLGFCRGGSCSYFDY**	RGQGTLVTVSS
1.5	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYALH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADTVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKGLGYCRGGSCSYFDY**	RGQGTLVTVSS
1.6	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYALH**	WVRQAPGKGLEWVS	**GISWNAGRKDYADTVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKGLGYCRGGSCSYFDY**	RVQGTLVTVSS
1.7	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.8	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.9	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.10	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.11	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.12	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.13	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.14	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.15	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.16	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.17	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.18	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.19	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.20	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.21	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.22	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRENAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.23	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRENAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.24	EVQLVESGGGLVQPGKSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISPENAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGALVTVSS
1.25	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.26	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.27	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKKCLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.28	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKKCLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.29	RVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKKCLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.30	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.31	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.32	EVQLVESGGGLVQPGRSLRLACAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.33	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.34	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.35	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.36	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.37	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.38	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAKKSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGSCSSFDY**	RGQGTLVTVSS
1.39	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRMGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSHFDY**	WGQGTLVTVSS
1.40	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.41	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSIGYCSGGSCSYFDY**	RGQGTLVTVSS
1.42	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.43	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.44	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.45	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.46	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.47	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.48	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.49	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.50	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.51	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.52	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.53	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ESSLGYCSGGTCSSFDY**	RGQGTLVTVSS
1.54	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.55	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNGGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DSSLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.56	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGYCSGGSCSTFDY**	RGQGTLVTVSS
1.57	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNSGRTGYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAMYYCAK	**DRGLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.58	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRGYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	**DRGLGYCSGGSCSSFDY**	WGQGTLVTVSS
1.59	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	**DRGLGYCSGGSCSYFDY**	WGQGTLVTVSS
1.60	QVRLVESGGGLVQPGKSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRTDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DPALGYCSGGSCSHFDY**	WGQGTLVTVSS
1.61	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRTDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DPSLGYCSGGSCSHFDY**	WGQGTLVTVSS
1.62	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DRGLGYCSGGSCSYFDY**	WGQGTLVTVSS
1.63	DVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DRGLGYCSGGSCSYFDY**	WGQGTLVTVSS
1.64	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ERGLGYCSGGSCSSLDY**	WGQGTLVTVSS
1.65	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.66	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.67	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.68	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.69	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNGNRRDYADPVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.70	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.71	EVQLVESGGGLVQPCRSLRLSCAASGFTFD	**DYAMH**	WVRQCPCKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQCTLVTVSS
1.72	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.73	QVQLVESGGGLVQPGRSLRLSCAASGLTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.74	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.75	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAN	**DSSLGYCSGGSCSNFDY**	WGQGTRVTVSS
1.76	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQGPGKGLEWVS	**GISWGNNRRDYADSVKG**	RFTISRDNAKNSLYLQINSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.77	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSKFDY**	WGQGTLVTVSS
1.78	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSKFDY**	WGQGTLVTVSS
1.79	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.80	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.81	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSKFDY**	WGQGTLVTVSS
1.82	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSKFDY**	WGQGTLVTVSS
1.83	QGQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAFGKGLEWVS	**GISWGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.84	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAFGKGLEWVS	**GISWGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.85	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DNAMH**	WVRQAFGKGLEWVS	**GISWNGNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.86	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNGNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.87	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNGNRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.88	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	**DSSLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.89	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQVPGKGPEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.90	KVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYFCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.91	KVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKSSLYLQMNSLRPEDTALYFCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS
1.92	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQTPGKGLEWVS	**GISWNSGRIDYADSVKG**	RFTISRDNAKSSLYLQMNSLRPEDTALYFCAK	**DSSLGYCSGGSCSYFDY**	RGQGTQVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.93	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DPSLGYCRGGSCSHFDY	WGQGTLVTVSS
1.94	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DPSLGYCRGGSCSHFDY	WGQGTLVTVSS
1.95	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRTEDTALYYCAK	EEGLGYCSGGSCSTFDY	RGQGTLVTVSS
1.96	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRTEDTALYYCAK	EEGLGYCSGGSCSTFDY	RGQGTLVTVSS
1.97	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLHLQMNSLRAEDTASYYCAK	DKGLGYCRGGSCSYFDY	RGQGTLVTVSS
1.98	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGNTDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKGLGYCRGGSCSLFDY	WGQGTLVTVSS
1.99	EVQLVESGGGLVQPGRSLXLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGSIDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKGLGYCRGGSCSLFDY	WGQGTLVTVSS
1.100	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQVPGKGPEQVS	GISWNSGRKDYVDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	ESSIGYCSGGSCSYFDY	RGQGTLVTVSS
1.101	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	DKGLGYCSGGSCSSFDY	WGQGTLVTVSS
1.102	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	DKGLGYCSGGSCSSFDY	WGQGTLVTVSS
1.103	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.104	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.105	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.106	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNARNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.107	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.108	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.109	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGQEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EMGLGYCSGGSCSYFDY	WGQGTLVTVSS
1.110	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQVPGKGPEWVS	GISWNSGRKDYVDSVKG	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	ESSIGYCSGGSCSYFDY	RGQGTLVTVSS
1.111	EVQLVESGGGLVQPGGSLRLSCAVSGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDSVKNSLYLQMNSLRAEDTALYYCAK	EGSLGYCRGGSCSHFDY	RGQGTLVTVSS
1.112	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFDY	GSQGTLVTVSS
1.113	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFDY	GSQGTLVTVSS
1.114	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFDY	GSQGTLVTVSS
1.115	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQTPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFEY	GGQGTLVTVSS
1.116	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFDY	GGNGTLVTVSS
1.117	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFSISRDNAKNSLYLQMNSLRTEDTAVYLCAK	ESSLGYCRGGSCSSFDY	GGRGTLVTVSS
1.118	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAK	ESSLGYCRGGSCSSFDY	WGQGTLVTVSS
1.119	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAK	ESSLGYCRGGSCSSFDY	WGQGTLVTVSS
1.120	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGTKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAK	ESSLGYCRGGSCSSFDY	WGQGTLVTVSS
1.121	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGTRDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAK	ESSLGYCRGGSCSSFDY	WGQGTLVTVSS
1.122	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQTPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	ESSIGYCSGGSCSNFDY	WGQGTLVTVSS
1.123	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMDYADSVKG	RFTISRDNARNSLYLQMNSLRPEDTALYYCAK	ESSIGYCSGGSCSNFDY	WGQGTLVTVSS
1.124	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DMGLGYCSGGSCSHFDH	WGQGTLVTVSS
1.125	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNGGSMDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	DRGLGYCRGGSCSSLDY	WGQGTLVTVSS
1.126	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNGGSMDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DRGLGYCRGGTCSSLDY	WGQGTLVTVSS
1.127	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRTGYADSVKG	RFTISRDNAKNSLYLQMNSLRTEDTALYYCAK	DASLGFCSGGSCSHFDY	RGQGIQVTVSS
1.128	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.129	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.130	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.131	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.132	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.133	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.134	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.135	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.136	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.137	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.138	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS
1.139	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	EYAMH	WVRQAPGKGLEWVS	GISWNSGRLGYADSVKG	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	ESSLGYCSGGSCSHFDY	RGQGTLVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.140	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.141	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.142	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.143	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.44	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.145	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.146	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADFVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.147	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.148	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRVEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.49	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRVEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.150	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.151	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**XYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.152	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDAAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.153	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDAAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.154	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRQDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ETSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.155	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.157	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.158	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.159	QVQLVESGGGLVQPGRSLRLSCVASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRVEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.160	QVQLVESGGGLVQPGRSLRLSCVASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRVEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.161	QVQLVESGGGLVQPGRSLRLSCVASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLRVEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.162	QVQLVESGGGLVQPGRSLRLSCVASGFPFD	**EYAMH**	WARQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.163	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WARQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.164	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WARQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.165	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WARQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.166	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTPVTVSS
1.167	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTPVTVSS
1.168	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLGYADSVKG**	RFTISRDNAKKSLHLQMNSLKTEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTPVTVSS
1.169	QVQLVESGGGLVQPGRSLRLSCAASGFPFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLSAEDTAMYYCAK	**ESSLGYCNGGTCHFDY**	RGQGTLVTVSS
1.170	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGRLDYADSVKG**	RFTISRDNAKKSLHLQMNSLRAEDTAMYYCAK	**ESSLGYCSGGSCHFDY**	RGQGTLVTVSS
1.171	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVA	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRSEDTALYYCAK	**EEGLGYCSGGSCSTFDY**	RGQGTLVTVSS
1.172	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRIGYADSVKG**	RFTISRDNAENSLYLQMNSLRAEDTALYYCAK	**EEGLGYCSGGSCSTFDQ**	RGQGTLVTVSS
1.173	QVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSTGYADSVKG**	RFTISRDNAENSLYLQMNSLRAEDTALYYCAK	**EEGLGYCRGGSCSTFDY**	RGQGTLVTVSS
1.174	EVQLVESGGGLVQPGRSLRLSCEASGFTFD	**DYSMH**	WVRQAPGKGLEWVS	**GISWNSGRMGYADSVRG**	RFTISRDNAENSLYLQMNSLRPEDTALYYCAK	**DRGLGYCHGGSCSSFDY**	WGQGTLVTVSS
1.175	EVQLVESGGGLVQPGRSLRLSCAASGFTFA	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNGKNSLYLQMNSLRAEDTAMYYCAK	**EEGLGYCSGGSCTFDQ**	RGQGTLVTVSS
1.176	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNGKNSLYLQMNSLRAEDTAMYYCAK	**EEGLGYCSGGSCTFDQ**	RGQGTLVTVSS
1.177	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WIRQTPGKGLEWVS	**GISWNSGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYHCAK	**EPSLGFCRGGSCSSFDY**	WGQGTLVTVSS
1.178	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WIRQTPGKGLEWVS	**GISWNSGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAVYHCAK	**EPSLGFCRGGSCSSFDY**	WGQGTLVTVSS
1.179	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WIRQTPGKGLEWVS	**GISWNSGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTAVYHCAK	**ESSLGYCRGGSCSSFDY**	WGQGTLVTVSS
1.180	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTAVYHCAK	**ESSLGYCRGGSCSSFDY**	WGRGTLVTVSS
1.181	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTAVYHCAK	**ESSLGYCRGGSCSSFDY**	WGRGTLVTVSS
1.182	EVQLVESGBGSVQPGRSLRLSCAASGFTFD	**DYTMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DKGLGYCSGGSCSNFDY**	WGQGTLVTVSS
1.183	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMY**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCHFDY**	WGQGTLVTVSS
1.184	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCHFDY**	WGQGTLVTVSS
1.185	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCHFDY**	WGQGTLVTVSS
1.186	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCHFDY**	WGQGTLVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.187	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCSHFDY**	WGQGTLVTVSS
1.188	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGYCRGGSCSHFDY**	WGQGTLVTVSS
1.189	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGYCRGGSCSHFDY**	WGQGTLVTVSS
1.190	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGGCSHFDY**	WGQGTLVTVSS
1.191	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGQEWVS	**GISWNGGTKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGGCSHFDY**	WGQGTLVTVSS
1.192	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNSGSKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**DQGLGFCRGGSCSHFDY**	WGQGTLVTVSS
1.193	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNGGTIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.194	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNGGTIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.195	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGTMDYADSVKG**	RFTISRDNVKNSLYLQMNSLRAEDTALYFCAK	**DSSIGYCRGGSCSNFDY**	WGQGTLVTVSS
1.196	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGTMDYADSVKG**	RFTISRDNVKNSLYLQMNSLRAEDTALYFCAK	**DSSIGYCRGGSCSNFDY**	WGQGTLVTVSS
1.197	EVQLVESGGGLVQPGRSLRLSCVASGFAFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DRAIGYCSGGSCSDFDY**	RGQGTLVTVSS
1.198	QVQLVESGGGLVQPGRSLRLSCVASGFAFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DRAIGYCSGGSCSDFDY**	RGQGTLVTVSS
1.199	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNSGSIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKGLGYCSGGTCGDLDN**	WGQGTLVTVSS
1.200	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNSGRRGYADSVBG**	RFTISRDNAKNSLYLEMNSLRVEDTALYYCAK	**ESSLGYCDGGSCSSFDH**	WGQGTLVTVSS
1.201	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRGYADSVBG**	RFTISRDNAKNSLYLEMNSLRVEDTALYYCAK	**ESSLGYCDGGSCSSFDH**	WGQGTLVTVSS
1.202	EVQLVESGGGLVQPGRSLRLSCAASGFAFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRTEDTALYYCAK	**DSSIGYCRGGSCSNFDY**	WGQGTRVTVSS
1.203	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DFAMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLFLQMTSLRVEDTALYFCAK	**ESSLGYCTGGSCSHFDY**	WGQGTLVTVSS
1.204	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DFAMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLFLQMTSLRVEDTALYFCAK	**ESSLGYCTGGSCSHFDY**	WGQGTLVTVSS
1.205	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DFAMH**	WVRQAPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLFLQMTSLRVEDTALYFCAK	**ESSLGYCTGGSCSHFDY**	WGQGTLVTVSS
1.206	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGNIDYTDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTALYFCAK	**DKGLGYCRGGSCSSFDY**	WGQGTLVTVSS
1.207	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNGNRMDYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAK	**DKGLGYCSGGSCSDFDY**	WGQGTLVTVSS
1.208	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRRDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCVK	**ETGLGYCSGGGCSDFDY**	RGQGTLVTVSS
1.209	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSIDYADSVKG**	RFSISRDNAKNSLYLQMNSLRPEDTALYYCAK	**EKSLGFCRGGSCSGFDI**	WGQGTMVTVSS
1.210	QVQLQESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGSIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**DMGLGYCRGGSCSHFDY**	WGQGTMVTVSS
1.211	EVQLVESGGGLVEPGRSLRLSCAASGFNFD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGKNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.212	EVQLVESGGGLVEPGRSLRLSCAASGFNFD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGKNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.213	EVQLVESGGGLVEPGRSLRLSCAASGFNFD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGKNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.214	EVQLVESGGGLVEPGRSLRLSCAASGFNLD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGKNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.215	QVQLVESGGGLVEPGRSLRLSCAASGFNFD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGKNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGFCRGGSCSTFDY**	WGQGTLVTVSS
1.216	EVQLVESGGELVEPGRSLRLSCAASGFNFD	**EYAMH**	WVRQCPGKGQEWVS	**GISWNGDNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EEGLGYCRGGSCSTFDY**	WGQGTLVTVSS
1.217	QVQLVESGGGLVEPGRSLRLSCAASGFNFD	**DYAMH**	WVRQGPGKGQEWVS	**GISWNGDNVDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAR	**EEGLGYCRGGSCSTFDY**	WGQGTLVTVSS
1.218	QVQLVESGGGLVQPGRSLRLSCAASGFSLD	**DYAMH**	WVRQAFGKGLEWVS	**GISWNGGSLDYADSVKG**	RFTISRDNAKNSLYLEMKSLRDEDTALYYCAK	**EKGLGYCRGGSCSSFDY**	WGQGTLVTVSS
1.219	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.220	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.221	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.222	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.223	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEBVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.224	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCGGGFCSTFDS**	RGQGIVVTVSS
1.225	QVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCGGGFCSTFDS**	RGQGIVVTVSS
1.226	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.227	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.228	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.229	EVQLVESGGGLVQPGRSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSDRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.230	QVQLVESGGGLVKPGGSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.231	QVQLVESGGGLVKPGGSLKLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.232	EVQLVESGGGLVKPGGSLRLSCAASGFTFD	**DYAMH**	WVRQVPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYFCAK	**EEGLGYCSGGFCSTFDS**	RGQGIVVTVSS
1.233	QVQLQESGGGLVQPGRSLRLSCVASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRLDCADSVKG**	RFTISRDNAKNSLYLQMNSLRPEDTAVYYCAK	**ERGLGYCSGGSCSSLEH**	GGQGTLVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.234	EVBLVESGGGLVQPGRSLRLSCAASGFPFV	DYTMH	WVRQAPGKGLEWVA	AISWNSGRKSIADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DGAIGYCSGGSCSDFDY	WGQGTLVTVSS
1.235	EVBLVESGGGLVQPGRSLRLSCAASGFPFV	DYTMH	WVRQAPGKGLEWVA	AISWNSGRKSIADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DGAIGYCSGGSCSDFDY	WGQGTLVTVSS
1.236	EVBLVESGGGLVQPGRSLRLSCAASGFPFV	DYTMH	WVRQAPGKGLEWVA	AISWNSGRKSYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	DGAIGYCSGGSCSDFDY	WGQGTLVTVSS
1.237	EVQLVEFGGGLVBPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRLDYADSVKG	RFTISRDNAKDSLYLEMNSLRTEDTALYYCAK	ERGLGYCSGTTCSDLDY	WGQGTLVTVSS
1.238	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRRVPGKGLEWVS	GISWNGGSLDYADSVKA	RFIISRDNAKDSLYLQMNSLRAEDTALYYCVK	EEGLGFCRGGSCSTFDF	WGQGTLVTVSS
1.239	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.240	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.241	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.242	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.243	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.244	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.245	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.246	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.247	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGREGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.248	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.249	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.250	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.251	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.252	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.253	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.254	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.255	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.256	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQGPGKGLEWVS	GISWNSGRKDYADSVKG	RFTISRDNAKNSLYLQMDSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.257	QVQLVESGGGLVBPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.258	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKSSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.259	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.260	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.261	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.262	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.263	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.264	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.265	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.266	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.267	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.268	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.269	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.270	EVQLVESGGGLVQPGGSLRLSCAASGFTFE	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLYLQMNSLRADDTALYYCAK	EKSLGYCSSGPCSDAFDI	WGQGTMVTVSS
1.271	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRTGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGSCSDAFDI	WGQGTMVTVSS
1.272	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	EKSLGYCSSGSCSDAFDI	WGQGTMVTVSS
1.273	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.274	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.275	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.276	EVQLVESGGGWVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNGGRIGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.277	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.278	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRKGYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.279	EVQLVESGGGLVQPGGSLRLSCAASGFTFA	DYAMH	WVRQAPGKGLEWVS	GISWNSGRMGYADSVKG	RFTISRDNAKNSLSLQMNSLRAEDTALYYCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS
1.280	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	GISWNSGRIEYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTALYFCTK	EKSLGYCSGGTCSDAFDI	WGQGTMVTVSS

Figure 1 (continued)

Clone	FR1	CDR	FR2	CDR2	FR3	CDR3	FR4
1.281	QVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDI**	WGQGTMVTVSS
1.282	QVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDI**	WGQGTMVTVSS
1.283	QVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDI**	WGQGTMVTVSS
1.284	EVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDI**	WGQGTMVTVSS
1.285	EVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDI**	WGQGTMVTVSS
1.286	EVQLVESGGGLVQPGRSLRLSCAASGFSFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EKSLGYCSGGSCSDGFDM**	WGQGTMVTVSS
1.287	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GITWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	**EKSLGYCSGGTCSNAFDI**	WGQGTMVTVSS
1.288	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GITWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCTK	**EKSLGYCSGGTCSNAFDI**	WGQGTMVTVSS
1.289	QVQLVESGGGLVQPGRSLRLSCAASGFTFE	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGSCSDAFDI**	WGQGAMVTVSS
1.290	EVQLVESGGGLVQPGRSLRLSCAASGFTFE	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGSCSDAFDI**	WGQGTMVTVSS
1.291	QVQLVESGGGLVQPGRSLRLSCAASGFTVD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGSCSDAFDI**	WGQGTMVTVSS
1.292	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQGPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGSCSDAFDI**	WGQGAMVTVSS
1.293	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGSCSDAFDI**	WGQGAMVTVSS
1.294	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTVSRDNAKNSLFLQMNSLRAEDTALYYCVK	**EKSLGYCSGGTCSDAFDI**	WGQGTMVTVSS
1.295	EVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ERSLGYCSGGTCADAFDI**	WGQGTMVTVSS
1.296	QVQLVESGGGLVQPGGSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**SISWNSGRMGYADSVKG**	RFTISRDNAKNSLSLQMNSLRAEDTALYYCAK	**EKSLGYCSGGTCSDGFDI**	WGQGTMVTVSS
1.297	EVQLVESGGGLVQPGRSLRLSCAASGFPFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRTDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	**DPSLGYCSGGSCSDVFDI**	WGQGTMVTVSS
1.298	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQPPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAMYYCVK	**DPSLVYCSGGTCSDSFDI**	RGQGTMVTVSS
1.299	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQPPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAMYYCVK	**DPSLVYCSGGTCSDSFDI**	RGQGTMVTVSS
1.300	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQFPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNTLYLQMNSLRAEDTAMYYCVK	**DPSLVYCSGGTCSDSFDI**	RGQGTMVTVSS
1.301	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAML**	WVRQPPGKGLEWVS	**GISWNSGRMDYADSVKG**	RFTISRDNAKNSLYLQMNSLRTEDTAMYYCVK	**DPSLGYCSGGTCSDSFDI**	RGQGTMVTVSS
1.302	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAMYYCVK	**DPSLGYCSGGSCSDSFDI**	RGQGTMVTVSS
1.303	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGSIGYADSVKG**	RFTISRDNAKNSLYLQMNSLRVEDTAMYYCVK	**DPSLGYCSGGSCSDSFDI**	RGQGTMVTVSS
1.304	QVQLVESGGGLVQPGGSLRLSCAASGFSFD	**DYTMH**	WVRQAPGKGLEWVS	**GISWNSGRKGYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**EPSLGYCSGGTCSDAFDI**	WGQGTMVTVSS
1.305	EVQLVESGGGLVQPGRSLRLSCAASGFAFA	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRKDYADSVKG**	RFTISRDNAKNSLFLQMNSLRPEDTALYHCAK	**ERSLGYCSGGTCSDAFDI**	WGQGTMVTVSS
1.306	QVQLVESGGGLVQPGRSLRLSCAASGFSFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNSGRVDYVDTVKG**	RFTISRDNAKNSLYLQMNSLRAEDTALYYCAK	**ERSLGYCRGGSCSDGFDI**	WGQGTMVTVSS
1.307	EVQLVESGGGLVQPGRSLRLSCAASGFTFG	**DYAMH**	WVRQPPGKGLEWVS	**GISWNGGRIDYADSLKG**	RFTISRDNANNSLYLQMNSLRAEDTAMYYCVK	**DPSLGYCSGGTCSDSFDI**	RGQGTMVTVSS
1.308	QVQLVESGGGLVQPGRSLRLSCAASGFTFG	**DYAMH**	WVRQPPGKGLEWVS	**GISWNGGRIDYADSLKG**	RFTISRDNANNSLYLQMNSLRAEDTAMYYCVK	**DPSLGYCSGGTCSDSFDI**	RGQGTMVTVSS
1.309	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GITWNSGRIDYADSVKG**	RFTISRDNAKNSLYLQMNSLRTEDTALYYCVK	**ERSLGYCRGGPCSDAFDI**	WGQGTMVTVSS
1.310	EVQLVESGGGLVQPGRSLRLSCAASGFNFD	**EYAMH**	WVRQAPGKGLEWVS	**GISWNGGRVGYAEPVKG**	RFTISRDNAKNSLYLQMNSLRVEDTALYYCAK	**ERSLGYCSGGSCSDGFDI**	WDQGTLVTVSS
1.311	QVQLVESGGGLVQPGRSLRLSCAASGFNFD	**EYAMH**	WVRQPPGKGLEWVS	**GISWNGGRVDYVDTVKG**	RFTISRDNAKNSLYLQTNSLRVEDTAMYYCAK	**ERSLGFCRGGSCSDGFDI**	WGQGTMVTVSS
1.312	QVQLVESGGGLVQPGRSLRLSCAASGFSFD	**DYAMH**	WVRQAPGKGLEWVS	**GITWNSGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRSEDTALYYCVK	**ERSLGYCRGGTCSEPFHI**	WGQGTMVTVSS
1.313	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GITWNGGRMDYADSVKG**	RFTISRDNAKNSLYLQMHSLRTEDTALYYCTK	**ERSLGYCGGDSCSDAFDI**	WGQGTMVTVSS
1.314	QVQLVESGGGLVRPGRSLRLSCTASGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGAMDYADSVKG**	RFTISRDNAKNSLYLQMNSLRSEDTALYYCIK	**EKSLGYCRGGSCSDAFDI**	WGQGTMVTVSS
1.315	EVQLVESGGGLVQPGRSLRLSCTAGGFTFD	**DYAMH**	WVRQAPGKGLEWVS	**GISWNGGAMDYADSVKG**	RFTISRDNANNSLYLQMNSLRSEDTALYYCIK	**EKSLGYCRGGSCSDAFDI**	WGQGTMVTVSS
1.316	EVQLVESGGGLVQPGRSLRLSCAASGFSFD	**DYAMH**	WVRQPPGKGLEWVS	**GITWNGGRKDYADSVKG**	RFTISRDNAKNSLYLQMNSLRAEDAALYYCVK	**GIRDDWKNNYWGQGILVTVSS**	

Figure 2

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
2.1	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**SYDIN**	WVRQATGQSLEWMG	**WMNPNSGDTVYAQKFQG**	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	**GRRDDWKNNY**WGQGTLVTVSS	
2.2	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**SYDIN**	WVRQATGRSLEWMG	**WMNPTNGNTVYAQKFQD**	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	**GRRDDWKNNY**WGQGTLVTVSS	
2.3	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**SYDIN**	WVRQATGRSLEWMG	**WMNPTSGDTVYAQKFQD**	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	**GRRDDWKNNY**WGQGTLVTVSS	
2.4	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**TYDIN**	WVRQATGRSLEWMG	**WMNPTNGNTVYAQKFQD**	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	**GRRDDWKNNY**WGQGTLVTVSS	
2.5	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**SYDIN**	WVRQATGRSLEWMG	**WMNPKNGNTVYAQKFQD**	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	**GIRDDWKNNY**WGQGILVTVSS	

Figure 2 (continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
3.4	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.5	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.6	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.7	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NMNHDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.8	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NMNHDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.9	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.10	EVQLVESGGGLVKPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.11	QVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.12	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.13	EVQLVESGGGLVHPGGSLRLSCTASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.14	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.15	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.16	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.17	EVQLVESGGGLVQPGGSLRLSCAASGFNFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGTEKYYVDSVKG**	RFTISRDNAENSLNLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTQVTVSS
3.18	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMR**	WLRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.19	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMS**	WLRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.20	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.21	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.22	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMY**	WVRQAPGKGLEWVA	**NIKQDGSERNYVDSVKG**	RFTISRDNAKNSLSLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.23	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMT**	WIRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.24	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.25	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEIQYVDSVKG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.26	EVQLVESGGGLVQPGRSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NIKQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.27	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMS**	WLRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.28	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDVKNSMYLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.29	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMS**	WVRQAPGKGVEWVA	**NIKEDGSEKQYVDSVKG**	RFTISRDNAKNSVYLQMNSLRAEDTAVYYCAR	**AYSSGWFDP**	WGQGTLVTVSS
3.30	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.31	QVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.32	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVFFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.33	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NINEDGSEKYYVDSVKG**	RFTISRDNAKNSVYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.34	QVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINEDGSEKYYVDSVKG**	RFTISRDNAMDSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTPVTVSS
3.35	EVQLVESGGGLVQPGGSLKLSCAASGFPFS	**TYWMT**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRADDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.36	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.37	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAMNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.38	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.39	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.40	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.41	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.42	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WLRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS

Figure 2 (continued)

2.49	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.50	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPTSGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.51	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.52	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQAIGRSLEWMGWMNPESGDTVYAQKFQDRVIMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGILVTVSS
2.53	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPNNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.54	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDDWKNNYWGQGTLVTVSS
2.55	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPESGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDDWKNNYWGQGTLVTVSS
2.56	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.57	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.58	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGQSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.59	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWCQGTLVTVSS
2.60	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.61	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQATGRSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.62	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.63	QVQLVQSGAEVKKPGASVKVSFTTYDINWVRQAIGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.64	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYDINWVRQATGRSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.65	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGQSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.66	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGQSLEWMGWMNPTNGYTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.67	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.68	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQAIGRSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.69	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQATGRSLEWMGWMNPGSGYTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDNWKNNYWGQGTLVTVSS
2.70	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDIAVYFCARGIRDNWKNNYWGQGTLVTVSS
2.71	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPTNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDNWKNNYWGQGTLVTVSS
2.72	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQATGRSLEWMGWMNPESGDTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.73	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYDINWVRQAIGRSLEWMGWMNPRNGYTVYAQKFQGRVTMTRNISISTAYMELSSLRSEDIAVYFCARGRDDWKNNYWGQGTLVTVSS
2.74	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYDINWVRQATGRSLEWMGWMNPTNGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.75	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPGSGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTIVTVSS
2.76	QVQLVESGAEVKKPGASVKVSCKASGYPFTTSDINWVRQATGRSLEWMGWMNPGSGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.77	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQATGRSLEWMGWMNPESGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.78	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPASGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.79	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQATGQSLEWMGWMNPRSGNTVYAQKFQGRVIMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDDWKNNYWGQGTLVTVSS
2.80	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPESGNTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDDWKNNYWGQGTLVTVSS
2.81	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYDINWVRQATGQSLEWMGWMNPTNGNTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.82	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQSLEWMGWMNPKNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDDWKNNYWGQGTLVTVSS
2.83	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTYDINWVRQAIGQSLEWMGWMNPTSGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.84	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGQSLEWMGWMNPTSGDTVYAQKFQGRVIMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDNWKNNYWGQGTLVTVSS
2.85	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPTSGDTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.86	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQAIGRSLEWMGWMNPNNGNTVYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.87	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYDINWVRQAIGQSLEWMGWMNPNNGNTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFFARGRDDWKNNYWGQGTLVTVSS
2.88	QVQLVQSGAEVKKPGASVKVSCKASGYPFTTSDINWVRQAIGQSLEWMGWMNPNSGYTVYAQKFQDRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGIRDNWKNNYWGQGTLVTVSS
2.89	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPKNGNTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.90	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGRSLEWMGWMNPNSGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS
2.91	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYDINWVRQATGQSLEWMGWMNPNSGDTVYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYFCARGRDDWKNNYWGQGTLVTVSS

Figure 2 (continued)

2.92	QVQLVQSGAEVKKPGASVKVSCKASGYPFT**TYDIN**WVRQATGQGLEWMG**WMNPNSGDTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.93	QVQLVQSGAEVKRPGASVKVSCKASGYPFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGNTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.94	QVQLVQSGAEVKKPGASVKVSCKASGYPFT**SYDIN**WVRQAAGQSLEWMG**WMNPNSGNTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.95	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGDTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.96	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGNTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.97	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPDSGYTVYAQKFQD**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GIRDDWKNNY**WGQGTLVTVSS
2.98	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPDSGYTVYAQKFQD**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.99	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPSSGYTVYAQKFQD**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.100	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNNGNTVYAQKFQG**RVTMTRNTSISTAYMELSSLTSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.101	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGDTVYAQKFQG**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GIRDDWKNNY**WGQGTLVTVSS
2.102	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGDTVYAQKFQG**RVTMTRNTSISTAYMELSNLRSEDTAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.103	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGDTVYAQKFQG**RVTMTRNTSISTAYMELSSLTSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.104	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGDTVYAQKFQG**RVTMTRNISISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.105	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGDTVYAQKFQG**RVAMTRNTSISTAYMELSSLRSEDIAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.106	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SFDIN**WVRQATGQSLEWMG**WMNPNSGDTVYAQKFQG**RVTMTRNTSISTAYMELTSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.107	QVQLVQSGAEVKKPGASVKVSCKAFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGYTVYAQKFQD**RVTMTRNISISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.108	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGYTVYAQKFQD**RVTMTRNISISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.109	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPSGYTVYAQKFQD**RVTMTRNISISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.110	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPSSGYTVYAQKFQD**RVTMTRNISISTAYMELSSLRSEDTAIYFCAR**GRRGDWKNNY**WGQGTLVTVSS
2.111	QVQLVQSGAEVKKPGASVKVSCKASGYSFT**SYDIN**WVRQATGQSLEWMG**WMNPNNGNTVYAQQFQG**RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR**GRRDDWKNNY**WGQGTLVTVSS
2.112	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNNGNAVYAQKFQG**RVTMTRNTSISTAYMELRSLTSEDTAVYYCAR**GRRDDWKNNY**WGQGTLVTVSS
2.113	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNNGNTVYAQKFQG**RVTMTRNISTAYMELISLTSEDTAVYYCAR**GRRDNWKNNY**WGQGTLVTVSS
2.114	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGRSLEWMG**WMNPDSGYTVYAQKFQD**RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.115	QVQLVQSGAEVKKPGASVIVSCKASGYTFT**SYDIN**WVRQATGRSLEWMG**WMNPNSGDTVYAQKFQG**RVTMTRNISTAYMELSSLRSEDTAVYFCAR**GRRDDWKNNY**WGQGTLVTVSS
2.116	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SFDIN**WVRQATGQSLEWMG**WMNPNSGNTVYAQKFQD**RVTMTRNTSISTAYMELSNLRSEDTAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.117	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGNTVYAQKFQD**RVTMTRNTSISTAYMELSNLRSEDTAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.118	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPTSGNTVYAQKFQD**RVTMTRNTSISTAYMELSNLRSEDIAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.119	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGNTVYAQKFQD**RVTMTRNISISTAYMELSNLRSEDTAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.120	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGNTVYAQKFQG**RVTMTRNTSLSTAYMELSSLRSEDIAVYFCAR**GIRDNWKNNY**WGQGTLVIVSS
2.121	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPKSGNTVYAQKFQG**RVTMTRNTSLSTAYMELSSLRSEDTAVFFCAR**GIRDNWKNNY**WGQGTTVTVSS
2.122	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPSSGYTVYAQKFQG**RVTMTRNTSLSTAYMELSSLRSEDIAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.123	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYDIN**WVRQATGQSLEWMG**WMNPNSGYTVYAQKFQD**RVTMTRNISISTAYMELRNLRSEDTAVFFCAR**GIRDDWKNNY**WGQGTLVTVSS
2.124	QVQLVQSGAEVKKPGASVKVSCKASGYPFT**SYDIN**WVRQATGQSLEWMG**WMNPESGYTVYAQKFQG**RVAMTRNTSLCTAYMELSNLRSEDIAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS
2.125	QVQLVQSGAEVKKPGASVKVSCKASGYPFS**TYDIN**WVRQATGQSLEWMG**WMNPKSGYTVYAQKFQG**RVAMTRNTSLSTAYMELSNLRSEDTAVYYCAR**GIRDDWKNNY**WGQGTLVTVSS

Figure 3

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
3.1	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.2	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.3	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS

Figure 3(continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
3.4	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.5	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.6	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTTSRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.7	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NMNHDGSEKYYVDSVKG**	RFTTSRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.8	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NMNHDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.9	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.10	EVQLVESGGGLVKPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.11	QVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.12	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.13	EVQLVESGGGLVHPGGSLRLSCTASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.14	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVS
3.15	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.16	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.17	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGTEKYYVDSVKG**	RFTISRDNAENSLNLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTQVTVSS
3.18	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMR**	WLRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.19	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMS**	WLRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.20	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.21	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.22	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMY**	WVRQAPGKGLEWVA	**NIKQDGSERNYVDSVKG**	RFTTSRDNAKNSLSLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.23	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMT**	WIRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTTSRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.24	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.25	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEIQYVDSVKG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.26	EVQLVESGGGLVQPGRSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NIKQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.27	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMS**	WLRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.28	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNVKNSMYLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.29	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMS**	WVRQAPGKGVEWVA	**NIKEDGSEKQYVDSVKG**	RFTISRDNAKNSVYLQMNSLRAEDTAVYYCAR	**AYSSGWFDP**	WGQGTLVTVSS
3.30	EVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.31	QVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.32	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NINHDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYFCAR	**GYSGGWFEP**	WGQGTLVTVSS
3.33	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NINEDGSEKYYVDSVKG**	RFTISRDNAKNSVYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.34	QVQLVESGGGLVQPGGSLRLSCAASGFTFT	**TYWMT**	WVRQAPGKGLEWVA	**NINEDGSEKYYVDSVKG**	RFTISRDNAMDSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTPVTVSS
3.35	EVQLVESGGGLVQPGGSLKLSCAASGFPFS	**TYWMT**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.36	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.37	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAMNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.38	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.39	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.40	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.41	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMTSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.42	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NINHDGSEIQYVDSVRG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS

Figure 3(continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
3.43	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WLRQAPGKGLEWVA	**NINHDGSEIQYVDSVKG**	RFTISRDNANNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGQGTRVTVSS
3.44	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.45	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.46	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVNVSS
3.47	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAMNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVNVSS
3.48	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.49	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.50	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKSSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.51	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.52	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.53	EVQLVESGGGLVQPGGSLSLSCAASGFSLS	**TYWMR**	WLRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.54	QVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.55	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.56	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.57	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.58	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.59	EVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTLSS
3.60	QVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WLRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGILVTVSS
3.61	QVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WLRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGILVTVSS
3.62	QVQLVESGGGLVQPGGSLRLSCEASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.63	QVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.64	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.65	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.66	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.67	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.68	EVQLVESGGGLVQPGGSLRLSCTASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTMVTVSS
3.69	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.70	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.71	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.72	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMS**	RLRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFDP**	WGKGTLVTVSS
3.73	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.74	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.75	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLYLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.76	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.77	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMS**	WVRQAPGKGLEWVA	**NIKQDGSEKYYVDSVKG**	RFTISRDNAKDSLFLQMNSLRAEDTAVYYCAR	**GWESGWFEP**	WGQGTLVTVSS
3.78	EVQLVESGGGLVHPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDAAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.79	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.80	EVQLVESGGGLVHPGGSLRLSCTASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEKQYVDSVKG**	RFTISRDNAKNSLFLQMISLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.81	EVQLVESGGGLVQPGGSLRLSCAASGFPFS	**TYWMT**	WVRQAPGKGLDWVA	**NINQDGTEKQYVDSVKG**	RFTISRDNAKNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFDP**	WGQGTLVTVSS

Figure 3 (continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
3.82	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINHDGSEQYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.83	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEQYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAR	**GYSNGWFDP**	WGQGTLVTVSS
3.84	EVQLVESGGGLVQPGRSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEEYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYHCAR	**GYSSGWFDP**	WGQGTLVTVSS
3.85	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEQYYVDSVEG**	RFTISRDNAKNSLYLQMNSLRAEDTALYHCAR	**GYSNGWFDP**	WGQGTLVTVSS
3.86	EVQLVESGGGLVQPGRSLRLSCAASGFTFS	**TYWMT**	WIRQAPGKGLEWVA	**NMNQDGSEKHYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.87	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFTISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.88	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NMNQDGSEKYYVDSVKG**	RFAISRDNARNSLFLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.89	QVQLVESGGGLVQPGGSLSLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEHQYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.90	EVQLVESGGGLVQPGGSLSLSCAASGFTFS	**TYWMT**	WVRQAPGKGLEWVA	**NINQDGSEHQYVDSVKG**	RFTISRDNAKNSLYLQMNNLRAEDTAVYYCAR	**GYSSGWFEP**	WGQGTLVTVSS
3.91	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	**SYWMS**	WVRQAPGKGLEWVA	**NIKEDGSEKYYVDSVKG**	RFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR	**GYSSGWFEP**	WGQGTLVTVSS

Figure 4

Clone	FR1	CDR1	FR2	CDR2	FR3	CD3	FR4
4.1	QVQLVQSGAEVKKPGASVKVSCKASGYPFT	**NYDIS**	WIRQATGQSLEWMG	**WMNPDSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.2	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAIYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.3	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAIYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.4	QVQLVQSGAGVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTDYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.5	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.6	QVQLQQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.7	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.8	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**SYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.9	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**SYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.10	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**SYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.11	QVQLVQSGAEVKNPGASVKVSCKASGYTFS	**NYDIS**	WVRQATGRSLEYMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.12	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEWMG	**WMNPKSGNTGYSQKFQG**	RVTMTRNTSISTAYMELSSLSSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVTVSS
4.13	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGRSLEWMG	**WMNPKSGNTGYSQKFQG**	RVTMTRNTSISTAYMELSSLSSEDTAVYYCAR	**GDSGSWREDY**	WGQGTLVAVSS
4.14	QVQLVQSGAEVKKPGASVKVSCKASGYTFI	**NYDIS**	WVRQATGRSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSTSTAYMELSSLTSEDTAVYYCAR	**GDFGSWREDY**	WGQGTLVTVSS

Figure 4(continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CD3	FR4
4.15	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGRSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GNSGSWREDY	WGQGTLVTVSS
4.16	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WMRQATGRSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GDRGNWRQDY	WGQGTLVTVSS
4.17	QVQLQQSGAEVKNPGASVKVSCKASGYTFS	NYGIS	WVRQATGRSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GDSGSWREDY	WGQGTLVTVSS
4.18	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.19	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.20	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.21	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.22	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.23	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.24	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.25	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SHDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLSSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.26	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSNLRSEDTAVYYCAR	GDSGSWREDY	WGQGTLVTVSS
4.27	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.28	QVQLQQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.29	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.30	QVQLQQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.31	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMALSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.32	QITLKESGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.33	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.34	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WINPNSGKTVYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GDSGTWREDY	WGQGTLVTVSS
4.35	QVQLVQSGAEVKNPGASVKVSCKASGYTFT	SYDIS	WVRQATGRSLEYMG	WMNPNSGKTVYAQKFQG	RVTMTRNTSITTAYMELSSLRSEDTAVYYCAR	GDSGTWREDY	WGQGTLVTVSS
4.36	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGRSLEYMG	WMNPNSGNTVYAQKFHG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GDSGSWREDY	WGQGTLVTVSS
4.37	QVQLVQSGAEVREPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYSQKFQG	RVTMTRNTSISTAYMELNSLRSEDSAVYYCAR	GGEKEWRRDY	WGQGTLVTVSS
4.	QVQLVQSGAEVKKPGASVKVSCKASGYSFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNAGYAQKFQG	RVTMTRNTSISTAYMELRGLRSEDTAVYFCAR	GGFSAWRTDY	WGQGTLVTVSS

Figure 4(continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CD3	FR4
38							
4.39	QVQLVQSGAEVKKPGASVKVSCKASGYSFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNAGYAQKFQG	RVTMTRNTSISTAYMELRGLRSEDTAVYFCAR	GGFSAWRTDY	WGQGTLVTVSS
4.40	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGRSLEYMG	WMNPNSGKTVYTQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GDSGTWRDDY	WGQGTLVTVSS
4.41	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQRLEWMG	WMNPKSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTYEDTAVYFCAR	GDFGSWRDDY	WGQGTLVTVSS
4.42	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQRLEWMG	WMNPKSGNTGYSQKFQG	RVTMTRNTSISTAYMELSNLTYEDTATYFCAR	GDFGSWRDDY	WGQGTLVTVSS
4.43	QVQLVQSGAEVRYPGASVKVSCKASGYTFT	SYDIS	WVRQATGQRLEWMG	WMNPKSGNTGYAQKFQG	RVTMTRNTSINTAYMELNNLGYEDTAVYFCAR	GDFGSWRDDY	WGQGTLVTVSS
4.44	QVQLVQSCAEVRYPGASVKVSCKASGYTFT	SYDIS	WVRQATGQRLEWMG	WMNPKSGNTGYAQKFQG	RVTMTRNTSINTAYMELSNLGYEDTAVYFCAR	GDFGSWRDDY	WGQGTLVTVSS
4.45	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	NYDIS	WVRQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.46	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEYMG	WMNPNSGNTNYAQKFQG	RVTMTRNISISTAYMELSSLRSEDTAVYYCAR	GNSGNWRDDY	WGQGTLVTVSS
4.47	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEYMG	WMNPNSGNTNYAQKFQG	RVTMTRNISISTAYMELSSLRSEDTAVYYCAR	GNSGNWRDDY	WGQGTLVTVSS
4.48	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPDSGNTGYSQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYFCAR	GGEKEWRRDY	WGQGTLVTVSS
4.49	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	GYDIS	WVRQATGQSLEWMG	WMNPNNGNTGYSQKFQG	RVTMTRNISISTAYMELSSLTSEDTAVYYCAR	GGEKEWRRDY	WGQGTLVTVSS
4.50	QVQLVQSGAEVRKPGASVKVSCKASGYTFT	SYIIS	WVRQATGQSLEYMG	WMNPENGNTDYTQKFQG	RITMTMDPSLNTAYMELGSLKSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.51	QVQLVQSGAEVRKPGASVKVSCKASGYTFT	SYVIS	WVRQATGQSLEYMG	WMNPKSGNTDYTQKFQG	RITMTMDPSINTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.52	QVQLVQSGAEVKMPGASVKVSCKASGYTFT	NYNIS	WVRQPTGQSLEWMG	WMNPDNGNTGYSQKFQG	RVTMTRNTSISTAYMELSSLRSDDTAVYFCAR	GGEKEWRRDY	WGQGTLVTVSS
4.53	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.54	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	NYDIS	WVRQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.55	QVQLQQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGITEWRRDY	WGQGTLVTVSS
4.56	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.57	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.58	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.59	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGQGTLVTVSS
4.60	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQGLEYMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.61	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQGLEYMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS

Figure 4(continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CD3	FR4
4.62	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.63	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.64	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.65	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.66	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.67	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.68	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQSLEWMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.69	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	NYDIS	WVRQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.70	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	NYDIS	WVRQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.71	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYIIS	WVSQATGQSLEYMG	WMNPENGNTDYTQKFQG	RITMTMDPSLNTAYMELGSLKSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.72	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVRQATGQGLEYMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.73	QVQLVQSGAEVKKPGASVRVSCKASGYTFT	SYDIS	WVSQATGQGLEYMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.74	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQSLEYMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYFCAR	GGSSAWRTDY	WGRGTLVTVSS
4.75	QVQLVQSGAEVKKPGASVKVSCKASGYAFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.76	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SHDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.77	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYDIS	WIRQATGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.78	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIS	WVRQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.79	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	NYDIS	WVSQPSGQSLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRDTSINTAYMELSSLRSEDTAVYYCAR	GGYSDWRTDY	WGQGTLVTVSS
4.80	QVQLVQSGAEVRKPGASVKVSCKASGYTFT	SYVIS	WVRQATGQSLEYMG	WMNPKSGNTDYVQKFQG	RITMTMDPSISTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.81	QVQLVQSGAEVRKPGASVKVSCKASGYTFT	SYVIS	WVSQATGQSLEYMG	WMNPKSGNTDYAQKFQG	RITMTMDPSISTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.82	QVQLVQSGAEVRKPGASVKVSCKASGYTFT	SYVIS	WVRQATGQSLEYMG	WMNPKSGNTDYTQKFQG	RITMTMDPSISTAYMELSSLRSEDTAVYYCAR	GGSSAWRTDY	WGQGTLVTVSS
4.83	CVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIS	WVRQATGQGLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.84	QVQLVQSGAEAKKPGASVKVSCKASGYTFT	SYDIS	WVRQATGQGLEYMG	WMNPNSGNTGYAQKFQD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GGSSDWRTDY	WGQGTLVTVSS
4.	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIS	WIRQATGQSLEWMG	WMNPDSGNTGYAQKFQG	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	GGYNAWRTDY	WGQGTLVTVSS

Figure 4 (continued)

Clone	FR1	CDR1	FR2	CDR2	FR3	CD3	FR4
85							
4.86	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WIRQATGQSLEWMG	**WMNPDSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.87	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WIRQATGQSLEWMG	**WMNPDSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.88	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WMNPASGNTGYAQKFQG**	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.89	QVQLVQSGAEVKKPGASVKVSCKATGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WMNPDSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.90	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WMNPDSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSDLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.91	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**SYDIS**	WIRQATGQSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSISTAYMELSSLTSEDTAVYYCAR	**GNSSGWRTDY**	WGQGTLVTVSS
4.92	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	**SYDIS**	WVRQATGQRLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGYSDWRTDY**	WGQGTLVTVSS
4.93	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	**SYDIS**	WVRQATGQRLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGYSDWRTDY**	WGQGTLVTVSS
4.94	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	**SYDIS**	WVRQATGQRLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGYSDWRTDY**	WGQGTLVTVSS
4.95	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	**SYDIS**	WVRQATGQRLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGYSDWRTDY**	WGQGTLVTVSS
4.96	QVQLVQSGAEVKKPGATVKVSCKASGYTFT	**SYDIS**	WVRQATGQSLEWMG	**WMNPNSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGYSDWRTDY**	WGQGTLVTVSS
4.97	QVQLVQSGAEVKKPGASVKVSCKASGYIFT	**SYDIS**	WVRQATGQGLEYMG	**WMNPKSGNTGYVQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGSSDWRTDY**	WGQGTLVTVSS
4.98	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**SYDIS**	WVRQATGQGLEYMG	**WMNPKSGNTGYVQKFQG**	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	**GGSSDWRTDY**	WGQGTLVTVSS
4.99	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WMNPDTGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.100	QVQLVQSGAEVKKPGASVKVSCKASGYIFT	**NYDIS**	WVRQATGQSLEWMG	**WMNPDTGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS
4.101	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WINPDSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYHAWRTDY**	WGQGTLVTVSS
4.102	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WINPDSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYHAWRTDY**	WGQGTLVTVSS
4.103	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WINPDSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYHAWRTDY**	WGQGTLVTVSS
4.104	QVQLVQSGAEVKKPGASVKVSCKASGYIFT	**NYDIS**	WVRQATGQSLEWMG	**WINPDSGNTGYAQKFQG**	RVTMTRNTSINTAYMELSGLRSEDTAVYFCAR	**GGYHAWRTDY**	WGQGTLVTVSS
4.105	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIS**	WVRQATGQSLEWMG	**WMXPXXGNTGYAQKFQX**	RVTMTRNTSISTAYMELSDLRSEDTAVYFCAR	**GGYNAWRTDY**	WGQGTLVTVSS

Figure 4 (continued)

Clone	FR1	**CDR1**	FR2	**CDR2**	FR3	**CD3**	FR4
4.106	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**SYDIS**	WVRQATGQSLEYMG	**WMNPKSNYTDYTQKFQG**	RITMTVDPSISTAYMELSSLRSEDTAVYYCAR	**GGSSAWRTDY**	WGQGTLVTVSS
4.107	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	**NYDIT**	WVRQATGQSLEWMG	**WINPNSGNTGYAEKFQG**	RVTMTRNTSISTAYMELVSLRSEDTAIYFCAR	**GNSSTWRTDY**	WGQGTPVTVSS

Figure 5

Clone	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
5.1	EVQLVESGGGLVKPGGSLRLSCEASGFTFS	DFDMS	WIRQAPGKGLEWVA	YISSSDSTIYYRDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCSR	NGARYNWNYGDFQH	WGQGTLVTVSS
5.2	EVQLVESGGGLVKPGGSLRLSCEASGFTFS	DFDMS	WIRQAPGKGLEWVA	YISSSDSTIYYRDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCSR	NGARYNWNYGDFQH	WGQGTLVTVSS
5.3	QVQLVESGGGLVKPGGSLRLSCAASGFAFS	DYYMS	WIRQAPGKGLEWVS	YIGGSDDVIYYRDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	NGARHDWKYGDFQH	WGQGTLVTVSS
5.4	QVQLVESGGGLVKPGGSLRLSCAASGFTFS	DYYMS	WIRQAPGKGLEWVS	YIGGSDDVIYYRDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK	NGARHDWKYGDFQH	WGQGTLVTVSS

CLONE 6.1

Figure 6

FR1 **CDR1** FR2 **CDR2** FR3

EVQLVESGGGLVKPGGSLRLSCAASGFTFS**DDYMS**WLRQAPGKGLEWVS**YISSSGSTIYYADSVKG**RFTISRDNAKNSLYLQMNSLRAEDSA

CDR3 FR4

VYYCAR**KDITNIAVGSLGY**WGQGTLVTVSS

CLONE 7.1

Figure 7

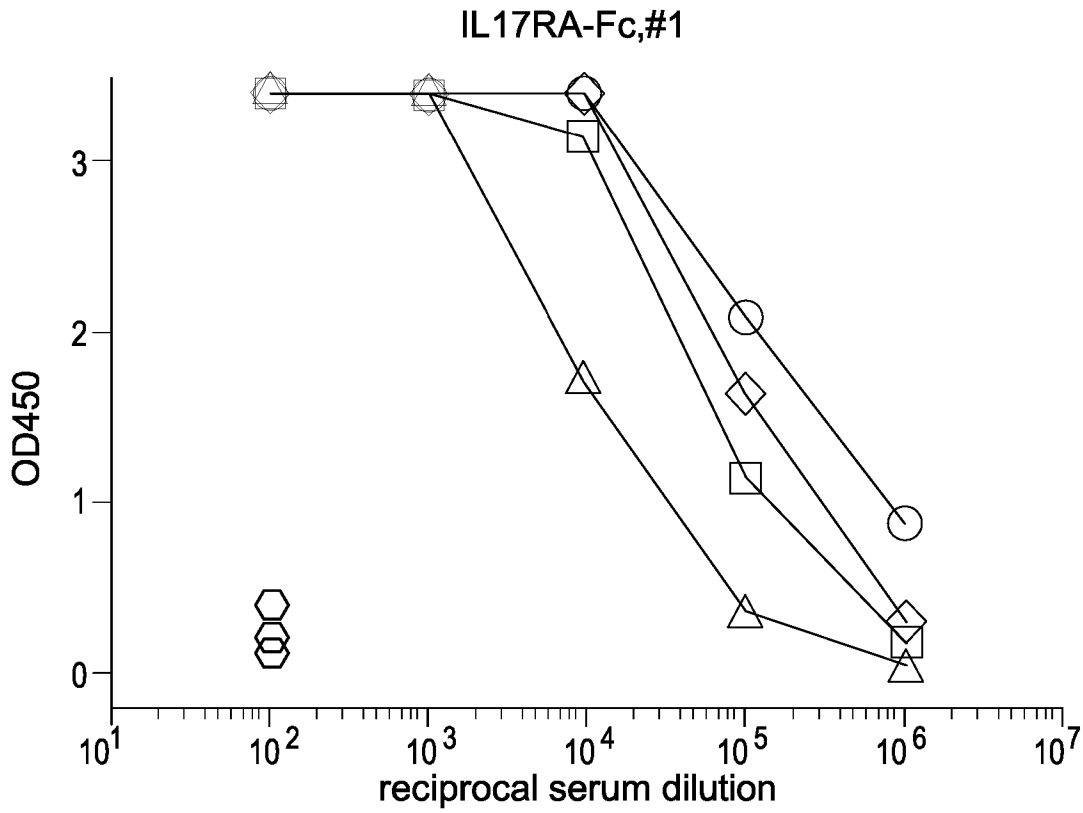
FR1 **CDR1** FR2 **CDR2** FR3

EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYWMS**WVRQARGKGLEWVA**NIRPDGSERYYVDSVKG**RFTISRDNAKNSLYLQMSSLRAEDT

CDR3 FR4

AVYYCAR**SRDWGSRAFDI**WGQGTMVTVSS

Figure 8


IL17RA-Fc,#1
OD450
0
1
2
3
10^1
10^2
10^3
10^4
10^5
10^6
10^7
reciprocal serum dilution

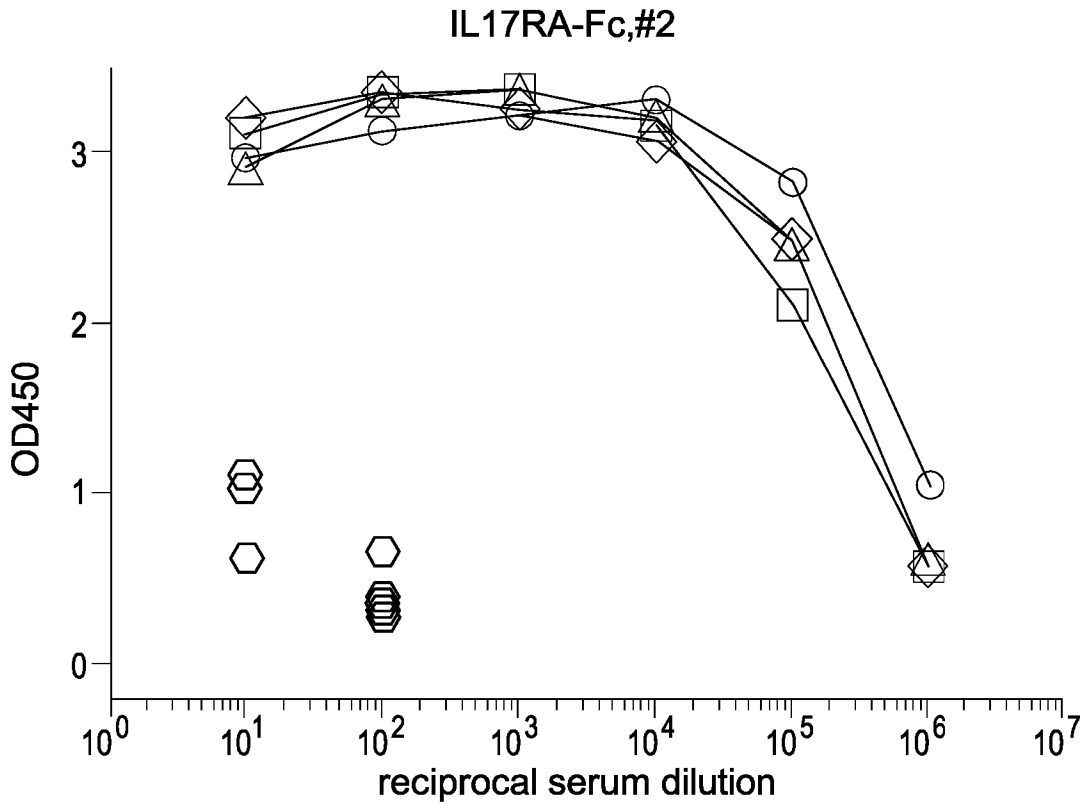

IL17RA-Fc,#2
OD450
0
1
2
3
10^0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
reciprocal serum dilution

Figure 9

A

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.066	0.065	0.222	0.2	0.065	0.172	0.271	0.215	0.067	0.086	0.089	0.085
B	0.255	0.298	0.21	0.166	0.084	0.084	0.372	0.084	2.106	0.201	0.165	0.093
C	0.22	0.061	0.28	0.058	0.127	0.349	1.902	0.328	0.202	0.063	0.229	1.283
D	0.093	2.862	0.22	0.373	0.061	0.058	0.291	0.295	0.274	0.066	0.179	1.127
E	0.238	0.173	0.196	0.063	0.223	0.362	0.058	0.257	0.265	1.263	0.161	0.437
F	0.061	0.345	0.218	0.06	0.312	0.361	0.058	0.288	0.062	0.065	0.067	0.246
G	0.047	0.146	0.208	0.305	0.289	0.054	0.261	0.059	0.468	0.505	0.07	0.041
H	1.54	0.296	0.212	0.511	0.07	0.069	0.059	0.256	0.345	0.061	0.065	0.071

B

	1	2	3	4	5	6	7	8	9	10	11	12
A	1.507	1.7	1.347	0.581	0.046	0.916	1.358	1.12	0.232	1.666	1.653	0.046
B	1.375	1.515	1.14	1.425	0.617	1.525	1.379	1.573	0.568	1.432	0.999	1.73
C	1.457	0.044	1.261	0.237	1.325	1.279	0.488	1.117	1.354	0.188	1.322	0.04
D	0.055	0.429	1.319	1.447	1.69	0.696	1.393	1.5	1.501	1.04	1.483	0.043
E	1.378	1.388	1.467	1.692	1.42	1.371	0.041	1.341	1.368	0.956	1.494	1.397
F	1.707	1.418	1.177	0.045	1.524	0.15	0.039	1.427	1.493	0.04	1.491	1.387
G	0.026	1.376	1.482	1.48	1.441	1.662	1.341	1.485	1.248	1.49	1.239	0.042
H	0.521	1.37	1.238	1.688	1.498	0.043	0.757	1.279	1.376	1.677	1.477	0.045

C

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.041	0.669	0.046	0.044	0.046	0.043	0.042	0.045	0.056	0.057	0.054	0.047
B	0.06	0.06	0.066	0.925	0.058	0.057	0.057	0.06	0.057	0.06	0.062	0.061
C	0.045	0.055	0.046	0.043	0.584	0.04	0.045	0.039	0.042	0.038	0.039	0.04
D	0.049	0.106	0.043	0.046	0.043	0.04	0.041	0.045	0.049	0.044	0.042	0.042
E	0.042	0.044	0.041	0.041	0.048	0.039	0.039	0.039	0.048	0.039	1.366	0.041
F	0.053	0.043	0.044	0.043	0.043	0.041	0.04	0.042	0.044	0.043	0.044	0.044
G	0.031	0.031	0.027	0.023	0.031	0.026	0.027	0.037	0.029	0.024	0.487	0.025
H	0.05	0.071	0.065	1.362	0.055	0.043	0.046	0.042	0.043	0.044	0.04	0.038

Figure 10

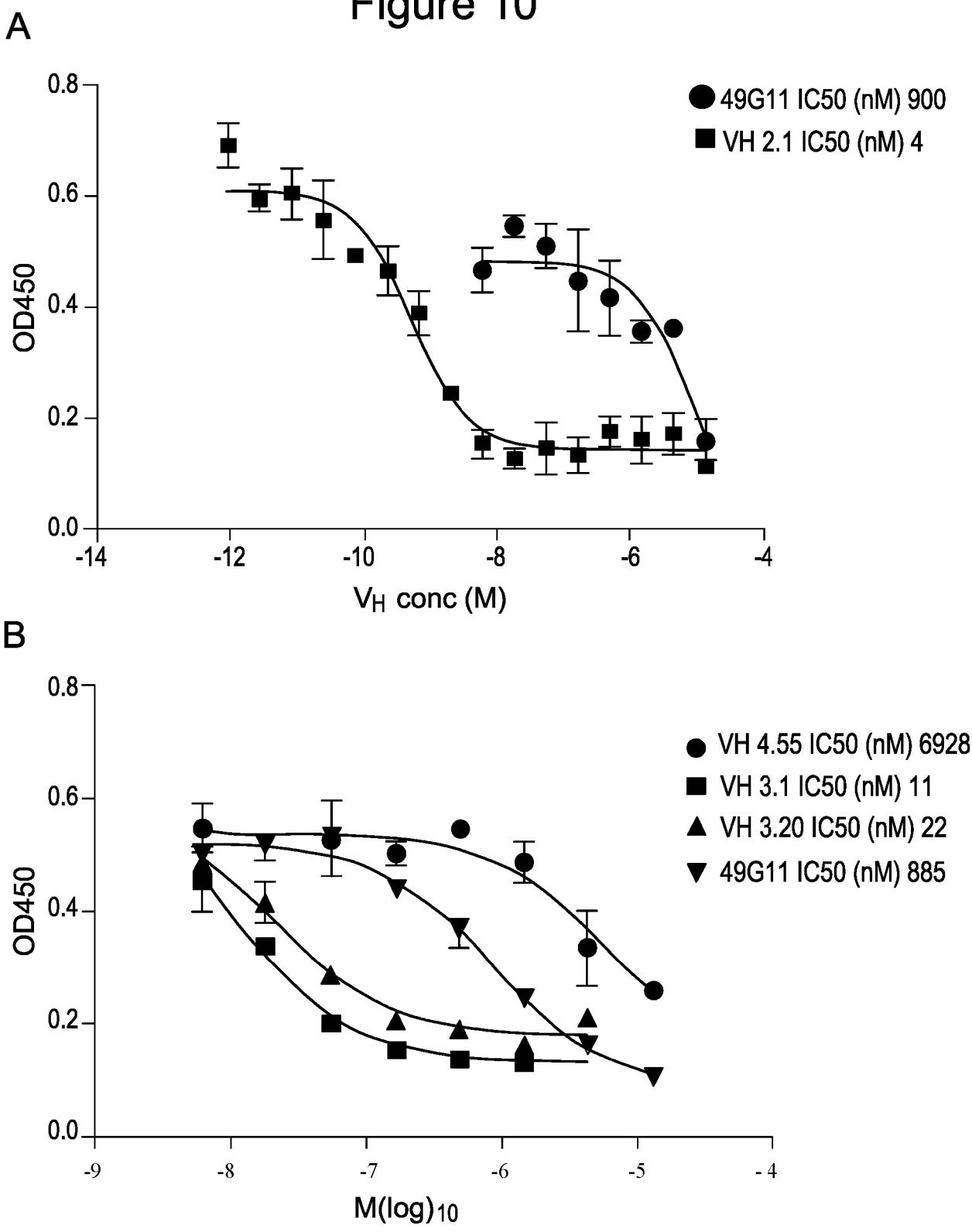

A
0.8
0.6
0.4
0.2
0.0
OD450
-14
-12
-10
-8
-6
-4
V_H conc (M)
49G11 IC50 (nM) 900
VH 2.1 IC50 (nM) 4
B
0.8
0.6
0.4
0.2
0.0
OD450
-9
-8
-7
-6
-5
- 4
M(log)10
VH 4.55 IC50 (nM) 6928
VH 3.1 IC50 (nM) 11
VH 3.20 IC50 (nM) 22
49G11 IC50 (nM) 885

Figure 11

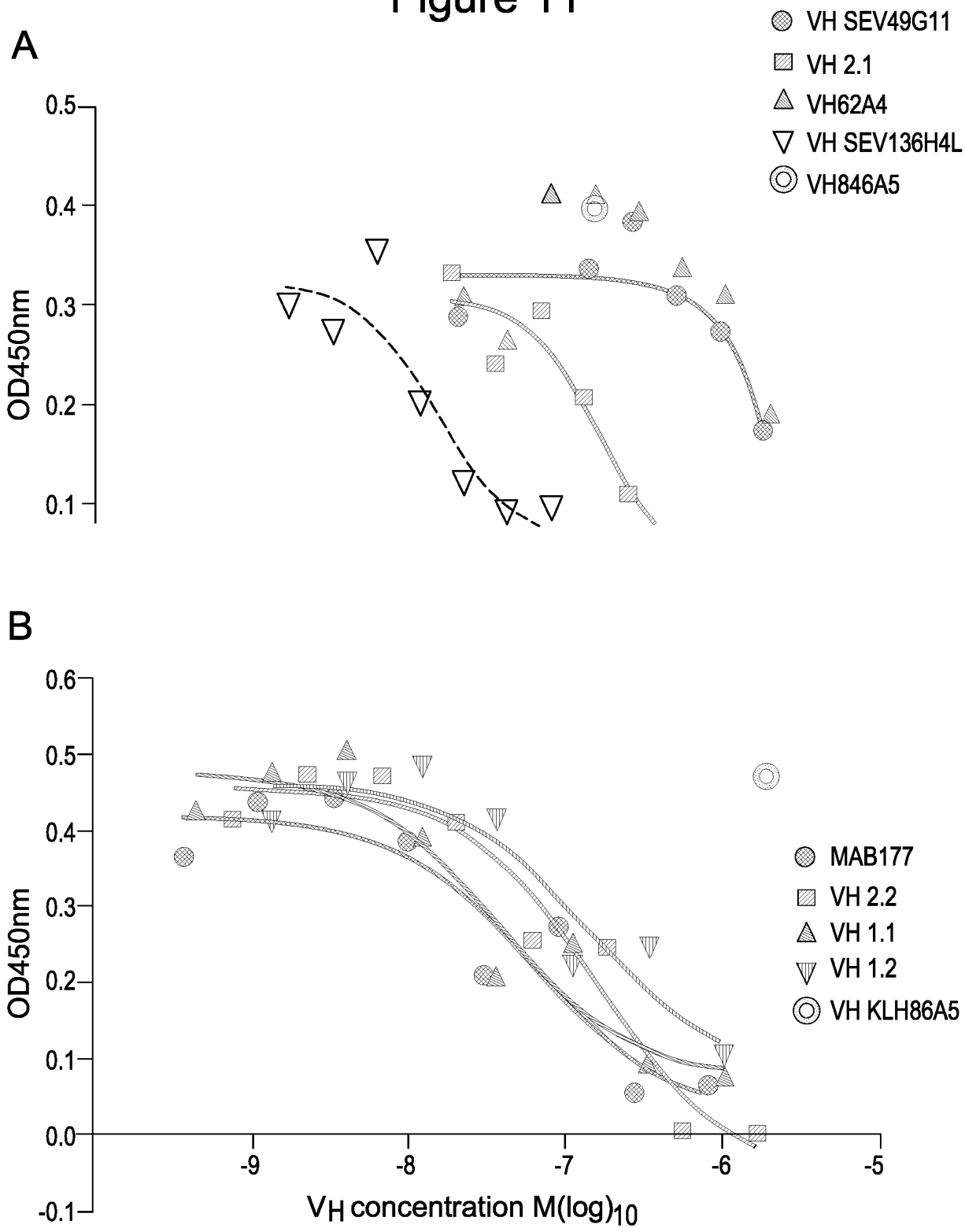
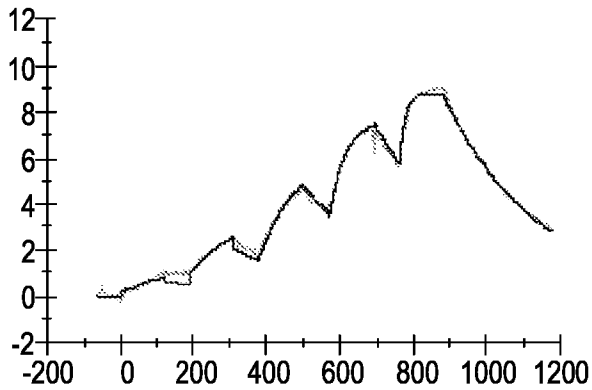

A
VH SEV49G11
VH 2.1
VH62A4
VH SEV136H4L
VH846A5
OD450nm
0.5
0.4
0.3
0.2
0.1
B
MAB177
VH 2.2
VH 1.1
VH 1.2
VH KLH86A5
OD450nm
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-9
-8
-7
-6
-5
VH concentration M(log)10

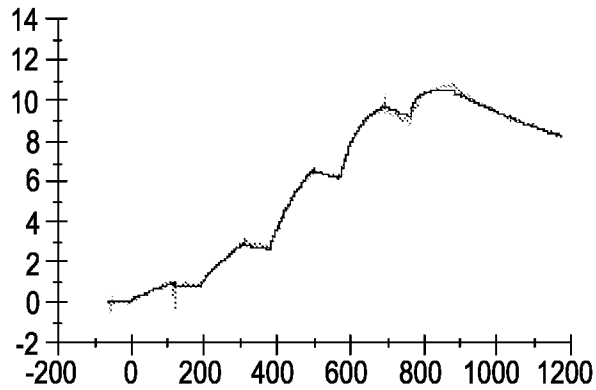
Figure 12

A. 2.1



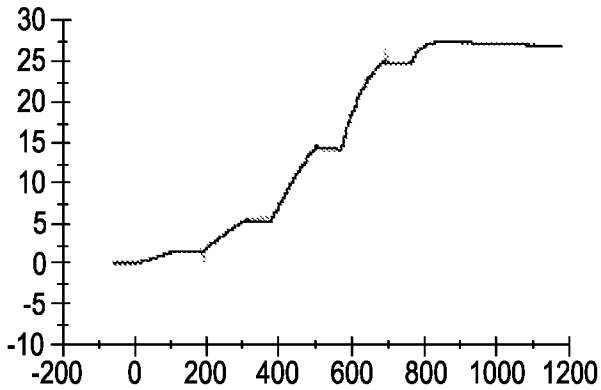
Fit:	1:1 Binding
ka (1/Ms):	6.374E+5
kd (1/Ms):	0.003838

B. 2.2



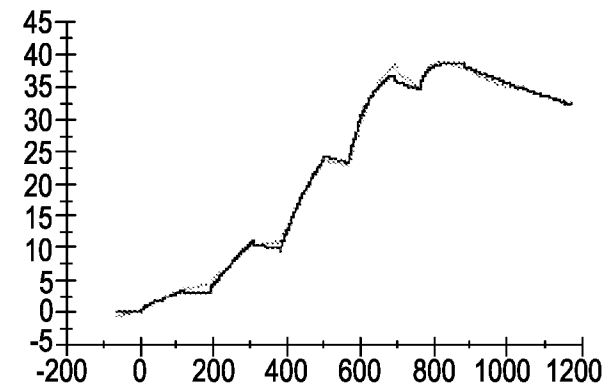
Fit:	1:1 Binding
ka (1/Ms):	5.785E+5
kd (1/Ms):	7.988E-4

C. 1.1



Fit:	1:1 Binding
ka (1/Ms):	1.306E+6
kd (1/Ms):	5.834E-5

D. 1.2



Fit:	1:1 Binding
ka (1/Ms):	1.718E+6
kd (1/Ms):	5.795E-5

Figure 13

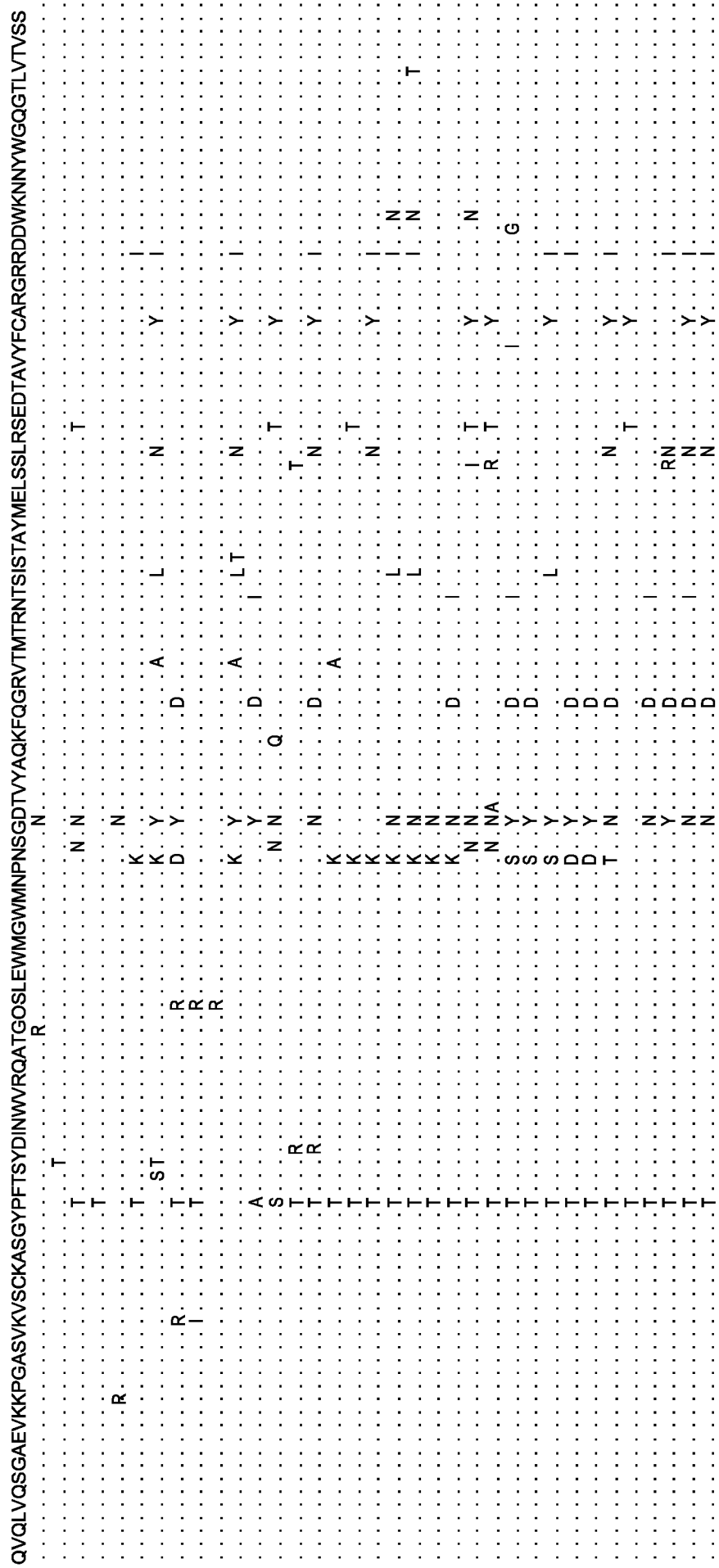

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Figure 14

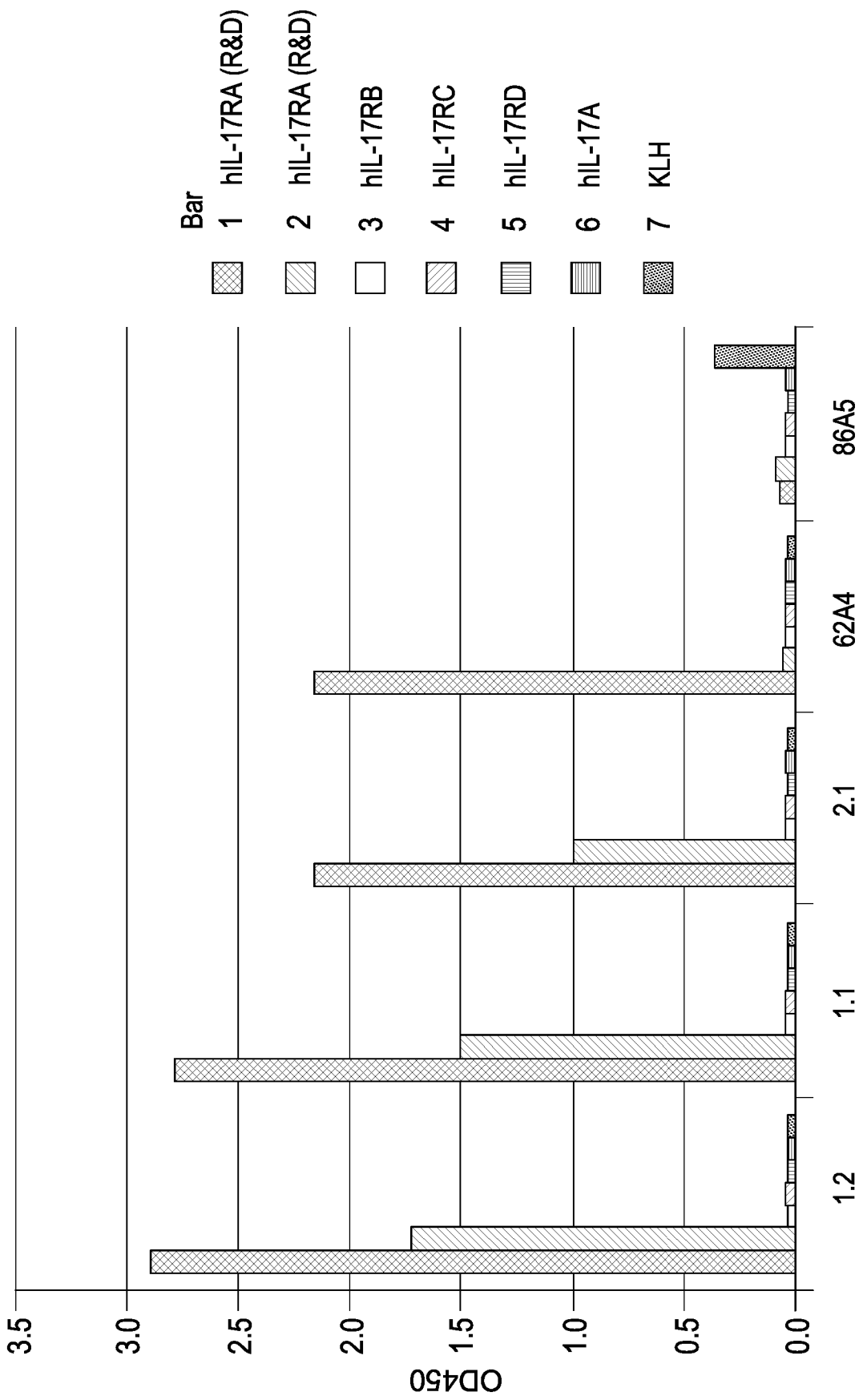

Bar
1 hIL-17RA (R&D)
2 hIL-17RA (R&D)
3 hIL-17RB
4 hIL-17RC
5 hIL-17RD
6 hIL-17A
7 KLH
OD450
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.2
1.1
2.1
62A4
86A5

Figure 15

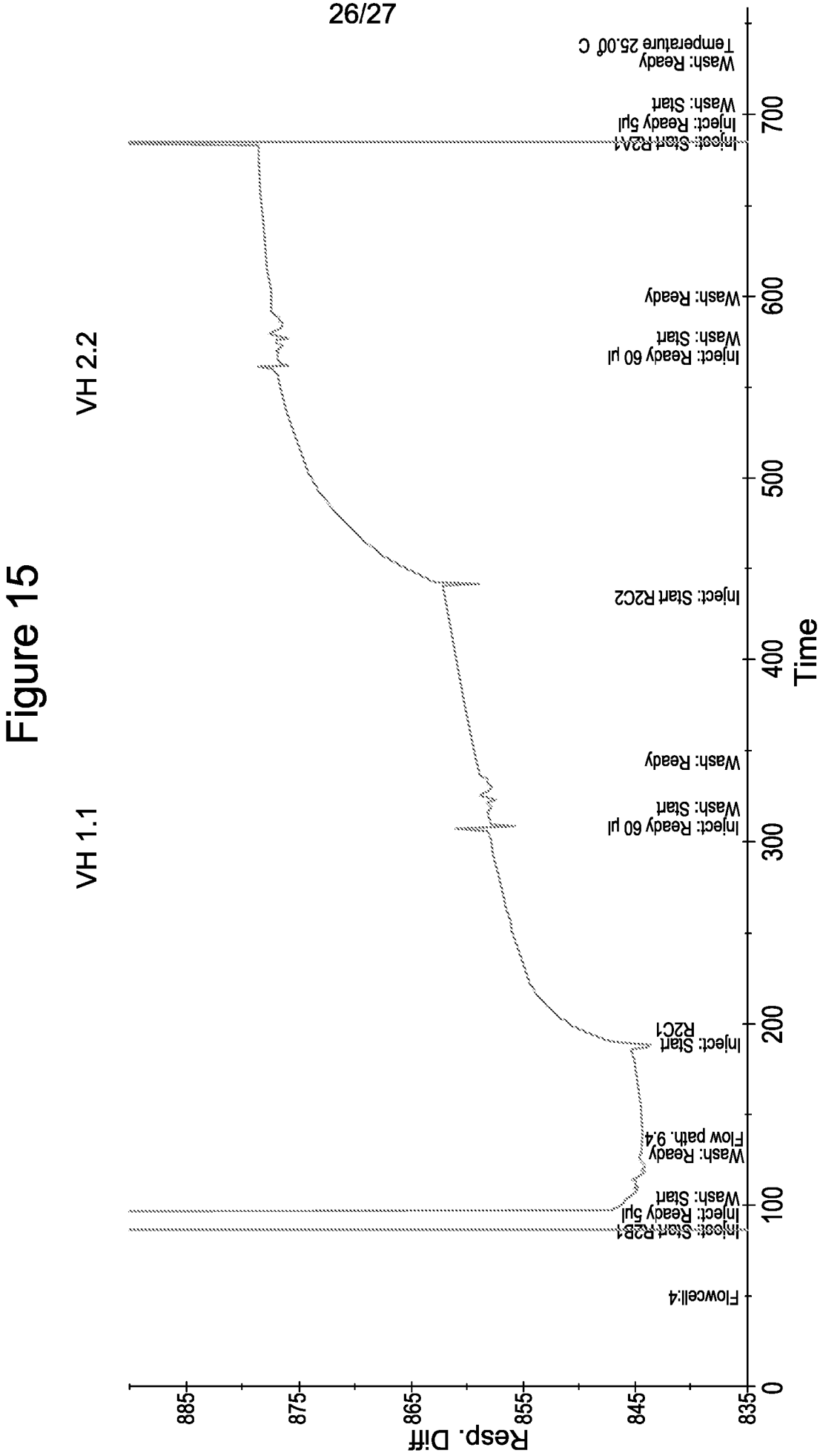
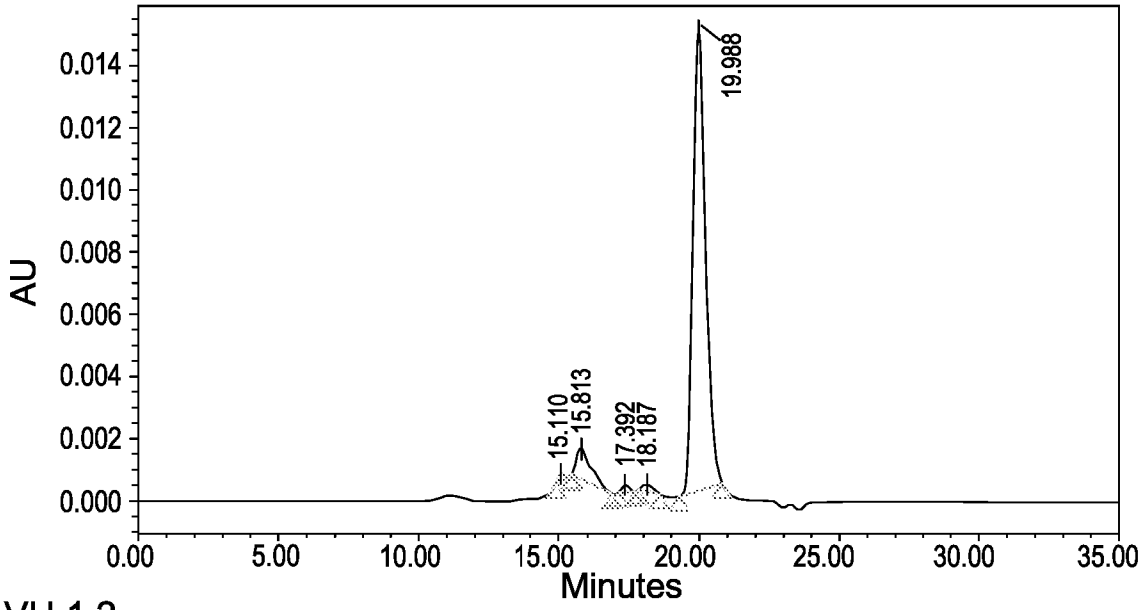
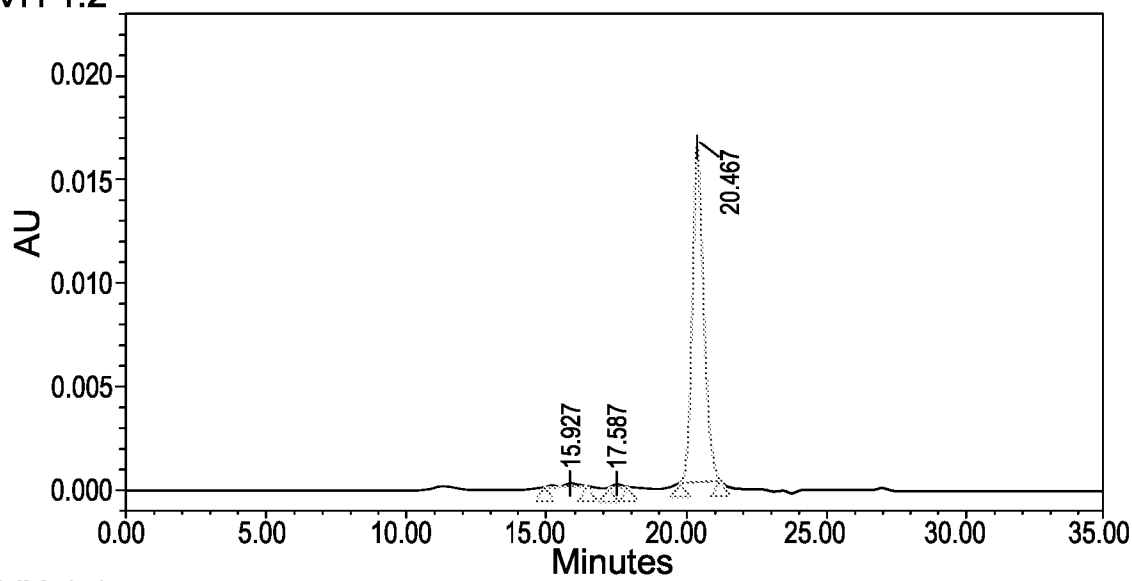

VH 1.1
VH 2.2
Resp. Diff
Time
835
845
855
865
875
885
0
100
200
300
400
500
600
700
Flowcell:4
Inject: Start R2B1
Inject: Ready 5ul
Wash: Start
Wash: Ready
Flow path. 9.4
Inject: Start R2C1
Wash: Ready
Inject: Ready 60 ul
Wash: Start
Inject: Start R2C2
Wash: Ready
Inject: Ready 60 ul
Wash: Start
Inject: Start R2A1
Inject: Ready 5ul
Wash: Start
Wash: Ready
Temperature 25.0∫ C

Figure 16

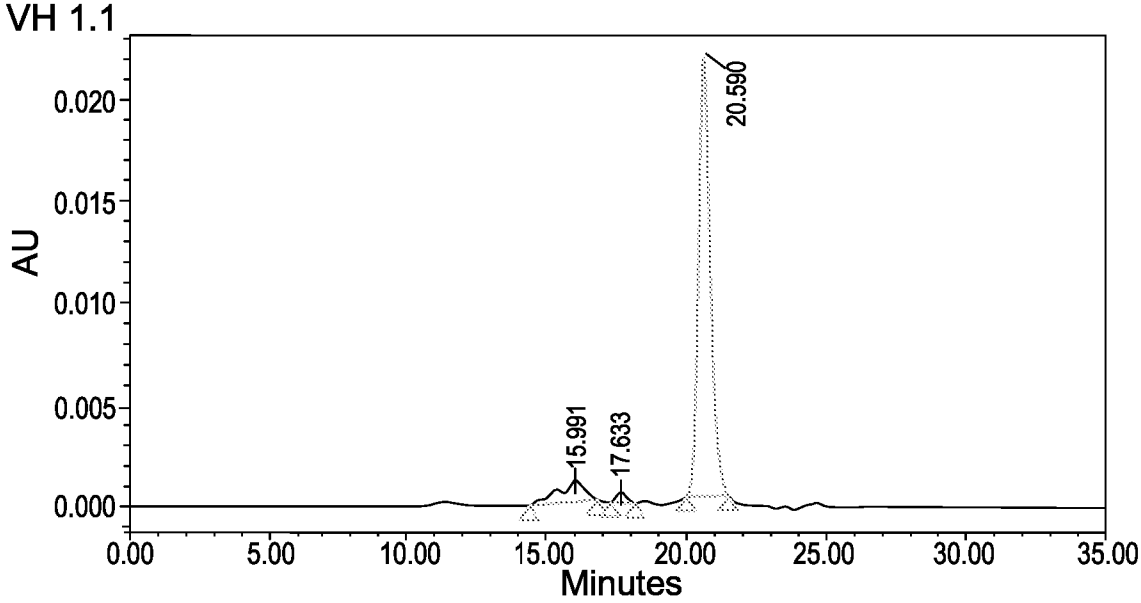
A. VH 2.1



B. VH 1.2



C. VH 1.1



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/050067

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A01K67/027 C12N15/85
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A01K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/054603 A2 (AMGEN INC [US]; TOCKER JOEL [US]; PESCHON JACQUES J [US]; FITZPATRICK) 8 May 2008 (2008-05-08) claim 1; Tab 8; p 174, l 13 ff; p 50, l 27 ff; p 54, par 1, l 33	1-8, 45-74
X	WO 2010/142551 A2 (ABLYNX NV [BE]; HULTBERG ANNA [NL]; MAASSEN BRAM [NL]; SAUNDERS MICHAE) 16 December 2010 (2010-12-16) claims 1-3; Tab AA-2	1-8, 45-74
X	AU 2011 203 098 A1 (AMGEN INC) 14 July 2011 (2011-07-14) claim 1, example 7	1-8, 45-74

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2016	25/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lechner, Oskar

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Matthew Roe: "Superior human single domain VH antibody fragments from a transgenic mouse", biopharmadealmakers, 12 April 2013 (2013-04-12), page B23, XP055254756, Retrieved from the Internet: URL:http://www.crescendobiologics.com/uploads/news/id11/Nature Biopharma Dealmakers April 2013.pdf [retrieved on 2016-03-02] the whole document	1-8, 45-74
X	US 2010/122358 A1 (BRUEGGEMANN MARIANNE [GB] ET AL) 13 May 2010 (2010-05-13) claim 1	1-8, 45-74
A	KIM A. PAPP ET AL: "Anti-IL-17 Receptor Antibody AMG 827 Leads to Rapid Clinical Response in Subjects with Moderate to Severe Psoriasis: Results from a Phase I, Randomized, Placebo-Controlled Trial", JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 132, no. 10, 1 October 2012 (2012-10-01), pages 2466-2469, XP055254737, US ISSN: 0022-202X, DOI: 10.1038/jid.2012.163 abstract	1-8, 45-74
A	SUSANA COIMBRA ET AL: "Brodalumab: an evidence-based review of its potential in the treatment of moderate-to-severe psoriasis", CORE EVIDENCE, 1 July 2014 (2014-07-01), page 89, XP055254753, DOI: 10.2147/CE.S33940 abstract	1-8, 45-74
A	RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436, ISSN: 0027-8424, DOI: 10.1073/PNAS.79.6.1979 the whole document	1-8, 45-74

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/050067

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YEE WAH WONG ET AL: "Structural Requirements for a Specificity Switch and for Maintenance of Affinity Using Mutational Analysis of a Phage-Displayed Anti-Arsonate Antibody of Fab Heavy Chain First Complementarity-Determining Region", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 160, 1 January 1998 (1998-01-01), pages 5990-5997, XP007916801, ISSN: 0022-1767 the whole document -----	1-8, 45-74
A	JEFFEREY R JACKSON: "In Vitro Antibody Maturation Improvement of a High Affinity, Neutralizing Antibody Against IL-1 beta", THE JOURNAL OF IMMUNOLOGY, vol. 154, 1 January 1995 (1995-01-01), pages 3310-3319, XP055033979, the whole document -----	1-8, 45-74

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2016/050067

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8, 45-74(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8, 45-74(all partially)

A binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (VH) comprising a CDR3 sequence comprising SEQ ID NO. 3 = Seq 11 = Seq 15 excluding any other CDR3 sequence specifically disclosed in the application (i.e. identified by SeqID No). The binding molecule further comprising CDR2 acc. to Seq 2 (= 6) and CDR1 acc. to Seq 1 (= Seq 5).

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2. claims: 1-8, 45-74(all partially)

A binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (VH) comprising a CDR3 sequence with at least 70%, at least 80%, at least 90%, or at least 95% homology to SEQ ID NO. 3 = 11 = 15 excluding any other CDR3 sequence specifically disclosed in the application (i.e. identified by SeqID No).
The binding molecule further comprising CDR2 acc. to Seq 2 (= 6) and CDR1 acc. to Seq 1 (= Seq 5).

3-6. claims: 1-8, 45-74(all partially)

A binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (VH) comprising a CDR3 sequence with at least 70%, at least 80%, at least 90%, at least 95% or 100% homology to SEQ ID NO. 3 = 11 = 15 excluding any other CDR3 sequence specifically disclosed in the application (i.e. identified by SeqID No).
invention 3: The binding molecule further comprising CDR2 acc. to Seq 10 (= Seq 18) and CDR1 acc. to Seq 1 (= Seq 5).
invention 4: The binding molecule further comprising CDR2 acc. to Seq 14 (= Seq 22) and CDR1 acc. to Seq 1 (= Seq 5).
invention 5: The binding molecule further comprising CDR2 acc. to Seq 10 (= Seq 18) and CDR1 acc. to Seq 9 (= Seq 13 = Seq 17 = Seq 21).
invention 6: The binding molecule further comprising CDR2 acc. to Seq 14 (= Seq 22) and CDR1 acc. to Seq 9 (= Seq 13 = Seq 17 = Seq 21).

7-12. claims: 9-74(partially)

A binding molecule capable of binding human IL-17RA comprising a human VH domain comprising a CDR3 sequence comprising SEQ ID NO. 1267 (invention 3), 1767 (invention 4), 2131 (invention 5), 2559 (invention 6), 2575 (invention 7), 2579 (invention 8) or a sequence with at least 70%, at

least 80%, at least 90%, or at least 95% homology to one of the above sequences, the particular invention excluding any higher invention, excluding any other CDR3 sequence specifically disclosed in the application (i.e. identified by SeqID No).

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13. claims: 1-8, 45-74(all partially)

A binding molecule capable of binding human IL-17RA comprising a human heavy chain variable immunoglobulin domain (VH) comprising a CDR3 sequence comprising SEQ ID NO. 3 or a sequence with at least 70% homology to SEQ ID NO. 7 = 19 = 23 excluding any other CDR3 sequence specifically disclosed in the application (i.e. identified by SeqID No).

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14. claims: 1-74(partially)

Other inventions in the claims not covered by the above mentioned ones - to be specified by the applicant on the basis of the present set of claims.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2016/050067

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008054603 A2	08-05-2008	AR 063090 A1	23-12-2008
		AU 2007314519 A1	08-05-2008
		AU 2010219370 A1	30-09-2010
		BR PI0719762 A2	28-01-2014
		CA 2663537 A1	08-05-2008
		CL 2007002800 A1	23-05-2008
		CN 103214576 A	24-07-2013
		CR 10760 A	27-05-2009
		DK 2076541 T3	30-03-2015
		EA 200900514 A1	30-10-2009
		EP 2076541 A2	08-07-2009
		EP 2487188 A2	15-08-2012
		EP 2518085 A1	31-10-2012
		ES 2533352 T3	09-04-2015
		JP 5013383 B2	29-08-2012
		JP 2010505416 A	25-02-2010
		KR 20090088870 A	20-08-2009
		KR 20120098953 A	05-09-2012
		NZ 575631 A	27-04-2012
		PE 08322012 A1	11-08-2012
		PE 16252008 A1	11-01-2009
		PT 2076541 E	31-03-2015
		SI 2076541 T1	29-05-2015
		TW 200821326 A	16-05-2008
		US 2008219979 A1	11-09-2008
		US 2008220479 A1	11-09-2008
		US 2008221307 A1	11-09-2008
		US 2009074758 A1	19-03-2009
		US 2010028345 A1	04-02-2010
		US 2010292442 A1	18-11-2010
		US 2011008841 A1	13-01-2011
		US 2011081339 A1	07-04-2011
		US 2011166331 A1	07-07-2011
		US 2012251547 A1	04-10-2012
		US 2014356355 A1	04-12-2014
		WO 2008054603 A2	08-05-2008
WO 2010142551 A2	16-12-2010	NONE	
AU 2011203098 A1	14-07-2011	AU 2011203098 A1	14-07-2011
		AU 2013202561 A1	02-05-2013
		AU 2016201892 A1	21-04-2016
US 2010122358 A1	13-05-2010	NONE	